厚生労働行政推進調査事業費補助金

医薬品・医療機器等レギュラトリーサイエンス総合研究事業

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究（20KC2005）

令和２年度総括・分担研究報告書

研究代表者　日ノ下　文彦

令和３（2021）年３月

目　次

Ⅰ．はじめに　・・・

厚生労働行政推進調査事業費補助金
医薬品・医療機器等レギュラトリーサイエンス総合研究事業
令和２年度総括・分担研究報告書

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究

(20KC2005)

Ⅰ．はじめに

研究代表者　　日ノ下　文彦　　国立国際医療研究センター病院腎臓内科　診療科長

厚生労働省により組織されたサリドマイド胎芽症（以下、サ症）に関する研究班は、この班で第４次研究班となり、第 1 次研究班から数えると既に10年が経過した。サ症に取り組む研究班としては、直面している問題に取り組み、今後必要となる研究や活動、支援について思いを馳せながらも、これまでの活動や業績について真摯に反省し総括もしなければならない時期だと考えられる。

というのも、一般的に、どんな事業も研究も 10 年という長い期間があれば、それなりの成果が出ていて然るべきである。また、サリドマイド薬禍者にとって 10 年というのは、人生の中でそれなりに長い時間である。「人生 100 年時代」と言われて久しいが、仮に人生が 100 年だとしたら、その 1/10 なのだからとても長い歳月だと言える。当然、その間に、健康状態が変化することも多々あろうし、目に見えて老化が進むこともあろう。大抵のサリドマイド薬禍者は 50 歳代後半である為、不幸にしてお亡くなりになる方さえいる。さらに、研究班にとっても 10 年という長い期間には、班員の入れ替わりも含め様々な変化を経験した。つまり端的に言うと、本年度は第４次研究班の初年ではあるが、いろいろな意味で研究班の節目だと言える。

さらに本年度の特徴として、新型コロナウイルス感染症（COVID-19）が流行し、様々な社会的活動に制約が生じた為、事前に計画していた活動の一部が中止となったり、先送りになってしまったのも特筆すべきことである。例えば、欧州での学会発表や出張を企画していたが、海外渡航が事実上禁止されたので、少なくとも計画通りには実現しなかった。また、例年実施している人間ドック健診も応募予定の２割も希望者が集まらなかった。コロナ禍にあっては、それも致し方ないことだと考えるが、思うように事業計画を進められなかったものもあるが、Proceedings や成書の編集・発行など相当なボリュームのデスクワークを 1 年でやり遂げたものもある。

というわけで、過去 10 年の研究班の歴史をしっかりと振り返りつつ、本年度の活動や研究を総括していくことにする。

Ⅱ．総括報告

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究

研究代表者　　日ノ下　文彦　　国立国際医療研究センター病院腎臓内科

１．日帰り人間ドック、健康診断

研究代表者	日ノ下　文彦	国立国際医療研究センター病院腎臓内科　診療科長
研究分担者	田上　哲也	国立病院機構京都医療センター健診センター　健診センター長
研究分担者	長瀬　洋之	帝京大学医学部内科学講座呼吸器・アレルギー学　教授
研究分担者	田嶋　強	国立国際医療研究センター病院放射線診断科　放射線診療部門長
研究協力者	田山　二朗	国立国際医療研究センター病院耳鼻咽喉科　診療科長

研究協力者　丸岡　豊　国立国際医療研究センター病院歯科・口腔外科　診療科長
研究協力者　堤内　亮博　国立国際医療研究センター病院耳鼻咽喉科　医師
研究協力者　田山　道太　国立国際医療研究センター病院歯科・口腔外科　医師
研究協力者　片桐　大輔　国立国際医療研究センター病院腎臓内科　医師
研究協力者　坂本　絵美　国立国際医療研究センター病院腎臓内科　フェロー
研究協力者　島　伸子　国立病院機構京都医療センター健診センター　副健診センター長
研究協力者　難波　綾　同上　医師
研究協力者　前川　高天　同上　医師

研究要旨

国立研究開発法人国立国際医療研究センター病院、（独）国立病院機構京都医療センター、帝京大学医学部附属病院にてサリドマイド胎芽症（以下、サ症）者 24 名の日帰り人間ドック（リピーターも含む）を計画していたが、新型コロナウイルス感染症（COVID-19）の影響で、計 3 名しか受診しなかった。

A. 研究の背景と目的

第 1 次研究班のアイデアで創始され、その後、10 年近くにわたって継続してきた人間ドック健診は研究班の臨床活動の柱であり、2020 年 2 月以降、新型コロナウイルス感染症（COVID-19）が本邦で拡がり始めてはいたが、サリドマイド胎芽症（以下、サ症）者の健康管理を重視して本年度もドック健診を継続することにした。

対象者のリクルートは例年通り公益財団法人いしずえを通じて行うこととし、24 名（初回症例以外の受診も容認）を目標とした。

B. 研究方法

国立国際医療研究センター病院（以下、当センター病院）、（独）国立病院機構京都医療センター（以下、京都医療センター）、帝京大学医学部附属病院（以下、帝京大病院）において、希望したサ症者に日帰りドックの形で健診を行うこととした。健診項目の内容は、原則、3 施設の人間ドックの内容に準ずるものである。主な健診項目を下に列挙する。

1）身長、体重、年齢、性別、障害区分
2）腹囲、BMI、血圧測定（上下肢）
3）生化学検査（T-chol, HDL-C, TG, LDL-C, FBS, HbA1c, UA, Cr, etc）
4）血算、検尿
5）胸部レントゲン、ECG、腹部超音波検査、上部消化管内視鏡検査、体脂肪率

当センター病院における健診は、研究代表者の日ノ下が立ち会い、数名の研究協力者、病院医師・スタッフの協力を得て実施されたほか、京都医療センターでは田上、前川、島、難波らにより実施された。

C. 研究結果

結局、人間ドック受診者は当センター病院 1 名、京都医療センター2 名にとどまったので、健診結果を分析するのは控えることにした。

D. 考察と今後の展望

例年、少なくとも 20 名程度が受診していたが、今年度 3 名と少なかったのは、COVID-19 の影響だと思われる。まず、令和 2 年度だけで 3 回も緊急事態宣言が発出されており、その時期に人間ドックを受けるのは、サ症者にとっても憚られることだったのではなかろうか。実際、サ症者は病院に来て不要不急の人間ドックで得られるメリットよりも、人込みに混じって病院に出向くことや病院で長時間滞在することによるリスクを強く感じ、積極的にドックに応募しなかったのではなかろうか。

次年度の下半期には、COVID-19 のワクチン接種がかなり行きわたることが予想され、COVID-19 の終息とともに、サ症者向けの人間ドック健診が活発になることを祈っている。また、少なくとも次年度上半期は COVID-19 の蔓延、オリンピック・パラリンピック開催によるいろいろな制限などから、人間ドック健診の募集をしないのが賢明であろう。

E. 健康危険情報

なし

F. 研究発表

・著書

Hinoshita F, Kayamori R, et al. 2020 Guide for

the Management of Thalidomide Embryopathy. Hinoshita F (eds), The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan, Tokyo, 2021

日ノ下文彦. 老い楽のすゝめ. 文芸社, 東京, 2021

・総説

なし

・研究会/講演会

なし

G. 知的財産権の出願・登録状況

1.特許取得

2.実用新案登録

3.その他

なし

２．" 2020 Guide for the Management of Thalidomide Embryopathy " の編集、発行

研究代表者	日ノ下　文彦	国立国際医療研究センター病院腎臓内科
研究分担者	田嶋　強	国立国際医療研究センター病院放射線診断科
研究分担者	田上　哲也	国立病院機構京都医療センター健診センター
研究分担者	芳賀　信彦	東京大学大学院医学系研究科リハビリテーション医学分野
研究分担者	長瀬　洋之	帝京大学医学部内科学講座（呼吸器・アレルギー学）
研究協力者	栢森　良二	帝京平成大学健康メディカル学部理学療法科
研究協力者	志賀　智子	東京女子医科大学予防医学科・総合診療科
研究協力者	島　伸子	国立病院機構京都医療センター健診センター
研究協力者	前川　高天	同上
研究協力者	前原　康宏	国立国際医療研究センター病院麻酔科
研究協力者	小林　毅	日本医療科学大学保健医療学部リハビリテーション学科
研究協力者	藤谷　順子	国立国際医療研究センター病院リハビリテーション科
研究協力者	辻村　裕次	滋賀医科大学社会医学講座衛生学部門
研究協力者	白星　伸一	佛教大学保健医療技術学部
研究協力者	皆川　梓	国立国際医療研究センター病院放射線診療部門
研究協力者	篠﨑　雅史	国立がん研究センター東病院放射線技術部
研究協力者	原田　潤	国立国際医療研究センター病院放射線診療部門
研究協力者	田山　二朗	国立国際医療研究センター病院耳鼻咽喉科
研究協力者	丸岡　豊	国立国際医療研究センター病院歯科・口腔外科
研究協力者	永原　幸	国立国際医療研究センター病院眼科
研究協力者	加藤　温	国立国際医療研究センター病院精神科
研究協力者	大友　健	同上
研究協力者	曽根　英恵	同上
研究協力者	中野　友貴	同上
その他	伊藤　拓水	東京医科大学ケミカルバイオロジー講座
	半田　宏	同上
	山口　雄輝	東京工業大学生命理工学院
	田中　敬子	国立国際医療研究センター病院看護部
	久下　智佳	同上

研究要旨
2020 年 3 月、研究班の総力を結集して、第 1 版の改定版である「サリドマイド胎芽症診療ガイド 2020」を発行し、国内のサリドマイド胎芽症（以下、サ症）の研究班員、医療従事者、関係者らに配布した。本書は各臨床領域における臨床、介護、看護に必要な知識および検討結果が丁寧に記載されているほか、人間工学的な内容やサ症の歴史、サ症の発症メカニズムまで盛り込まれた包括的ガイドブックとなっている。
しかし、サ症の診療を行っているのは、わが国に限らず欧州やブラジル、その他の国でも行われており、ドイツにはわが国よりもはるかに多い 2,000 人以上のサ症者がいる言われている。したがって、サ症診療を行っている世界の多くの国々で本ガイドブックが活用できるよう、「サリドマイド胎芽症診療ガイド 2020」の英語版 “2020 Guide for the Management of Thalidomide Embryopathy” を作成、発行することにした。

A. 研究の背景と目的

2020 年 3 月、研究班の総力を結集して、初版の「サリドマイド胎芽症診療ガイド 2017」の改訂版である「サリドマイド胎芽症診療ガイド 2020」を発行した。本書はサ症診療のあらゆる領域をカバーしている世界で唯一のアップツデートなガイドブックと自負しているが、和書である為、わが国よりもさらにサリドマイド薬禍者が多いドイツや英国、および他の諸外国では利用できない。このことは、サ症の診療や研究のグローバル化を推進してきた本研究班としては看過できない問題である。そこで、初版で “2017 Guide for the Management of Thalidomide Embryopathy” を作成、発行したように、今回も「サリドマイド胎芽症診療ガイド 2020」の英語版を迅速に作成することにした。幸い例年実施している人間ドックの負担が減ったうえ、海外での学会発表、出張などすべて現地開催はキャンセルとなったので、そうした労力を「サリドマイド胎芽症診療ガイド 2020」英語版の作成、編集に振り向けることができた。

B. 研究方法

「サリドマイド胎芽症診療ガイド 2020」は、研究班員および研究班の人間ドック健診従事者、その他のサ症研究者に各専門分野の執筆をお願いしたが（詳細は、別添資料 1 参照)、本書は執筆陣や記載内容をそのままにして、翻訳を専門とするエージェントに英訳を依頼した。英訳された原稿は日ノ下が目を通して監訳し、各執筆者に回して最終的な校正をしてもらった。

執筆者は表題に示した方々であり、編集作業も日ノ下が請け負い、研究助手（松岡）のサポートを受けながら作業を終了した。今回の英語版のタイトルは初版にならって、 “2020 Guide for the Management of Thalidomide Embryopathy” とした。できあがった “2020 Guide for the Management of Thalidomide Embryopathy” は、研究班員やサ症の医療従事者、厚生労働省の担当部局のほか、ドイツ、英国、スウェーデン、スイス、ブラジルなどのサ症専門家、研究者らに郵送した。

C. 研究結果

完成した英語版は別添資料 1 に示した通りである。

D. 考察と今後の展望

サ症研究班が総力を結集して作成した「サリドマイド胎芽症診療ガイド 2020」が英訳され、“2020 Guide for the Management of Thalidomide Embryopathy” として結実したのは意義が大きい。しかも、約 1 年前にでき上った日本語の診療ガイドが、間髪おかず英語に翻訳されたのも特筆すべき点である。つまり、わが国で得られたサ症に関する最新の知見や診療方法、医療対応、看護のあり方などが、遅滞なく欧州やブラジルなどに周知されたことになる。よって、諸外国のサ症の専門家、臨床家、研究者がわが国の最新の知見をリアルタイムで目にするわけで、サ症の診療や研究のグローバル化を目指してきた本研究班の目標に沿った成果であると断言できる。ドイツや英国その他の国のサ症関係者がこの英語ガイドブックを学ぶことにより、同じ土俵の上に立って、今後のサ症の診療や研究を進めていくことが可能となる。特に、サ症のように多くの国々で同じ問題や悩みを抱える領域においては、とても重要な戦略であると言える。

本書の内容について語ると、2020 年 3 月に策定

した「サ症診断の手引き」に触れているほか、サ症の歴史やドイツにおけるサ症診療なども記載されている。さらに、サ症の発症メカニズムに関し世界最先端をいっている東京医科大学のグループにも執筆して頂くなど、本書はある意味であらゆるサ症の問題を取り扱うバイブルのような体裁となっている。これがもし日本語版だけにとどまった場合、世界的なガイドブックであると胸を張って言えないが、どこの国の関係者も理解可能な英語版が発行されたとなると、わが国の研究班がまさに「グローバルスタンダード」を示したと言っても過言ではなかろう。

なお、“2020 Guide for the Management of Thalidomide Embryopathy” は 2020 年度末に完成したので、本書に対する諸外国の実際の評価や反響を検討するのは次年度に待ちたい。

E. 健康危険情報

なし

F. 研究発表

・著書

なし

・総説

なし

・研究会/講演会

なし

G. 知的財産権の出願・登録状況

1.特許取得

2.実用新案登録

3.その他

なし

３．Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo, 2019 の発行

研究代表者　日ノ下　文彦　国立国際医療研究センター病院　腎臓内科

2019 年 7 月 23 日、24 日に開催した 2nd International Symposium on thalidomide embryopathy in Tokyo の内容（英文）を編集し、冊子にまとめた（別添資料 2 参照）

４．小冊子「新型コロナウイルス感染症（COVID-19）の基本的知識と生活上の対応　－サリドマイド被害者の皆様へ－」の発行

研究代表者　日ノ下　文彦　国立国際医療研究センター病院　腎臓内科
研究分担者　長瀬　洋之　帝京大学医学部内科学講座呼吸器・アレルギー学　教授
研究分担者　田上　哲也　国立病院機構京都医療センター健診センター　健診センター長
研究協力者　丸岡　豊　国立国際医療研究センター病院　歯科・口腔外科　診療科長
研究協力者　藤谷　順子　国立国際医療研究センター病院　リハビリテーション科　診療科長

2020 年は、まさに国民生活のすべてが新型コロナウイルス感染症（COVID-19）に振り回されたと言っても過言ではない。特に、普段でも一般人より ADL が低いサ症者にとっては、辛い毎日だったと思われる。そこで、研究分担者の長瀬の提案がきっかけで、サ症者の皆さんが安心して暮らせるよう、COVID-19 対策の小冊子を作成することにした。具体的には、2020 年 11 月に冊子の骨組みを策定したが、主として呼吸器感染症としての COVID-19 に対する対応だけに留まらず、歯科/口腔外科の視点や食事のアドバイス、運動のアドバイスなども含めた幅広い内容の冊子とすることにした。そして、上に示した研究班員が多忙な中、労を厭わず分担執筆してくれたおかげで、2021 年 3 月に無事発行することができた。なお、本冊子は、サ症者各人に配布するため、完成後すぐに必要な部数を公益財団法人「いしずえ」に寄贈した（別添資料 3 参照）。

５．「サリドマイド胎芽症診断の手引き」を世界に発信（48th Annual meeting of the European Teratology Society (Virtual One-Day Meeting）におけるオンライン発表） “A new guide to diagnose thalidomide embryopathy in Japan”

研究代表者　　日ノ下　文彦　　国立国際医療研究センター病院　腎臓内科
研究協力者　　栢森　良二　　帝京平成大学健康メディカル学部理学療法科
サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究班

A. 研究の背景と目的

2020 年 3 月、本研究班によって、現代の考え方に沿った「サリドマイド胎芽症診断の手引き」を策定し発効した。既に英国のグループが、サリドマイド胎芽症（サ症）の診断手順（valiDATE）を発表しているが（Mansour S, Baple E, Hall CM. A clinical review and introduction of the diagnostic algorithm for thalidomide embryopathy (DATE), Journal of Hand Surgery 44(1): 96-108, 2019)、わが国のサ症診断の考え方を世界に発信する必要があると考え、48th Annual Meeting of The European Teratology Society に
発表することにした。

B. 研究方法

2020 年 9 月にマドリード（スペイン）で開催予定だった 48th Annual Meeting of The European Teratology Society (ETS) に演題抄録を提出し受理された。本来なら、日ノ下、栢森が発表に向かう予定であったが、COVID-19 の流行によりこの学会の開催が中止となった。

しかし、発表を少数に絞った 48th Annual meeting of ETS の Virtual One-Day Meeting に招待され、2020 年 9 月 15 日夕（日本時間）にオンライン発表を行った（別添資料 4 参照)。

C. 研究結果

発表内容は別添資料 5 に示した通りである。

D. 考察と今後の展望

Virtual One-Day Meeting は視聴者が限られており、本邦のサリドマイド胎芽症診断手順を世界の多くの関係者に示すには不十分だったかもしれないが、「診断の手引き」を英語で紹介できたのは一定の成果をあげたと考えてよかろう。また、数ある ETS 発表予定抄録の中から本題を僅かしか取り上げられない Virtual One-Day Meeting のトピックに選んでくれたのは、欧州でも本邦の「サ症診断手順」に対する関心が高い証拠だと言えるだろう。

今後は、発表内容をサ症研究会 HP 英語版にわかりやすく掲載するなどして、もっと世界に本邦のサ症診断方法をアピールしてもいいかもしれない。

E. 健康危険情報

なし

F. 研究発表

・著書
　なし
・総説
　なし
・研究会/講演会
　なし

G. 知的財産権の出願・登録状況

1.特許取得

2.実用新案登録

3.その他

なし

６．その他の活動

研究代表者　　日ノ下　文彦　　国立国際医療研究センター病院腎臓内科　診療科長
研究協力者　　栢森　良二　　帝京平成大学健康メディカル学部理学療法科
研究協力者　　松原　正明　　日産厚生会玉川病院整形外科（股関節センター）

1)「サリドマイドー復活した『悪魔の薬』」の出版

研究班の栢森は、現役医師の中でサリドマイド胎

芽症者を最も数多く診療してきたベテランであるが、サリドマイド薬禍とその臨床的・社会的問題を総括する著書を既に何冊か著してきた。この度、栢森はサリドマイド物語の第 2 版に相当する「サリドマイドと医療の軌跡」（西村書店, 2013 年）をさらにアップツデートした「サリドマイド-復活した『悪魔の薬』」（PHP エディターズ・グループ）という著書の執筆と編集に取り組んだ。これは、サリドマイドの悲劇や原因解明の軌跡、臨床上の問題点などを豊富な経験と造詣に基づいて記したものであり、研究班としてもこの貴重な著書の出版を支援することにした。

遅くとも、本書は 2021 年度 5 月下旬には出版予定である。

2）リハビリテーション専門医によるサ症者の個別相談とサ症者の要望に応じた他科の診療

◇リハビリテーション専門医による個別相談
計 4 名《NCGM：2 名、東大：2 名》

◇外来受診（ドック健診受診者による後日受診）
計 2 名
①耳鼻咽喉科 1 名《NCGM 耳鼻咽喉科》
②ペインクリニック科 1 名《NCGM 麻酔科科》

◇手術（ドック健診後 NCGM 腎臓内科より紹介）
1 名《日産厚生会玉川病院 整形外科》

* NCGM = 国立国際医療研究センターの略

3）股関節診療と同部の外科的治療

前年度から日産厚生会多摩川病院股関節センターに正式な協力機関となってもらい、股関節の問題を有するサ症者の診療や外科手術ができる体制を整えた。2019 年度に人間ドック健診を受けた女性のサ症者 1 名が右股関節の疼痛と不自由を訴えたので、同センターを紹介したところ、2020 年 4 月、右股関節の全人工股関節置換術（THA）が同センターで無事に実施され成功をおさめた。

今後、同じ悩みを抱えるサ症者に対し、新たに THA という治療選択枝が増えたと言える。

4）研究代表者（日ノ下）退任のご挨拶

いしずえニュース 3 月号に退任のご挨拶として、これまでの研究班の活動経過やサリドマイド薬禍者の皆様の健康管理に関する内容まとめて寄稿した（別添資料 6）。

また、2021 年 3 月 12 日、都内の目黒区内にある財団法人「いしずえ」サリドマイド福祉センターを訪れ、佐藤嗣道理事長、堀内淳一常務理事、金子美智子専任相談員に班長退任のご挨拶をさせて頂いた。

その際、本研究班の今後の活動や new claimer に対するサ症診断の手続きや対応等についても話し合った。

Ⅲ．分担研究報告　1

厚生労働行政推進調査事業費補助金
医薬品・医療機器等レギュラトリーサイエンス総合研究事業

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究

研究分担者　田上　哲也　（独）国立病院機構京都医療センター健診センター

§サリドマイド胎芽症患者の健康，生活実態の諸問題に関する研究

研究分担者　田上　哲也　（独）国立病院機構京都医療センター健診センター　センター長
研究協力者　島　伸子　同上
研究協力者　難波　綾　同上
研究協力者　前川　高天　同上

研究要旨

当院では，前研究班の時から合わせると，男性 17 名，女性 33 名の計 50 名の検診を行った．前年までに，男性 4 名，女性 10 名の計 14 名は当センターで 2 度の検診を行っていた．本年はコロナ禍の影響で検診を控える方が多く,最終的に当院では 2 名の検診に留まった.両名とも 3 度目の検診であった.トータルの検診件数は，男性 21 件（平均年齢 53.5 歳），女性 45 件（同 53.7 歳）の計 66 件となった.

- これまでに当センターで行った全例の検診結果について総括する.
- 高血圧症で 8 名（男 4，女 4），糖尿病で 4 名（男 2，女 2），脂質異常症で 9 名（男 4，女 5），骨粗鬆症で 2 名（女 2）が治療中であった．2 名（男 2）に痛風の既往があった.
- 肥満（BMI>25kg/m^2）を，男性 1 名（5.9%），女性 10 名（30%）に認めた．女性のうち 1 例は BMI=34.4 の中等度肥満（2 度）であった．また，女性のうち 2 名は前回 BMI27→今回 23kg/m^2（73→63kg），前回 BMI26→今回 23kg/m^2（60→53kg）とそれぞれ減量されていた.逆に，1 例は前回 BMI24→今回 25kg/m^2（59→62kg）と少し増加していた.
- ALT 高値（>30 IU/L）を，男性 4 名（24%，うち 2 例は改善），女性 4 名（12%）に認めた.
- 高 LDL コレステロール（Friedewald 式による）血症（>120 mg/dL）を，男性 8 名（47%），女性 22 名（67%，うち 2 名は改善,2 名は悪化：1 回目正常）に認めた．高中性脂肪（TG）血症（>150mg/dL）を，男性 6 名（35%），女性 8 名（24%，うち 1 名は改善,1 名は悪化：1 回目正常）に認めた．低 HDL コレステロール血症（<40mg/dL）を男性 2 名（12%）に認めた.
- HbA1c(NGSP)高値(>6.2%)は,男性 3 名(18%)，女性 3 名（9.1%）に認めた.
- 高尿酸血症（>7.0 mg/dL）を，男性 8 名（47%，うち 1 例は 8.3 mg/dL）と女性 3 名（9.1%）に認めた.
- CKD(eGFR<60 mL/min/1.73m^2)を,男性 2 名(12%，eGFR=55),女性 2 名(6.1%,うち 1 例は eGFR=17)に認めた.
- 骨密度は，前年までで，腰椎で骨粗鬆症レベル（YAM<70%）が 4 名（男 1，女 3），骨量減少レベル（YAM=70-80%）が 9 名（男 3，女 6），大腿骨頚部で骨粗鬆症レベルが 9 名（男 1，女 8），骨

量減少レベルが 17 名（男 5，女 12）であった．今回測定した 2 名はいずれも女性で,3 度目の検診（足掛け 9 年）の検査となった．

57 歳：腰椎：100%→86%→80%，大腿骨頚部：87%→72%→65%

59 歳：腰椎：101%→94%→86%，大腿骨頚部：90%→77%→78%

以上のように，年々骨密度は低下傾向にあり，特に 1 名は新たに骨粗鬆症と診断され，治療介入が必要と判断された．

- 血中 TSH 値を測定した 3/34 名（9%）に異常を認めた．2 名（5.9%，男 1，女 1）が軽度高値，1 名（2.9%，女）が軽度低値であった．

● 考察

- 生活習慣病：当センターで検診を 2 回受けた 14 名のうち 3 名はこの間に何らかの生活習慣病の治療をあらたに開始されていた（別の 3 名は初回からの治療を継続）．一部の受診者で初回検診の結果が治療開始の端緒になった可能性がある．高血圧症，糖尿病，脂質異常症のうち，二つ以上の治療を同時に受けているものが 5 名（男 2，女 3）いた．リスク因子の蓄積は動脈硬化性疾患の発症につながるため，食事療法・運動療法の徹底（強化）が必要である．
- 過体重：サリドマイド胎芽症（以下，胎芽症）患者では，四肢の発達障害だけでなく，外出が億劫になりがちであることなどから，過体重になりやすいことが想定される．当センターで検診を行った対象者に高度の肥満者（BMI>35）はなかったが，BMI=34 が一人，軽度肥満（BMI>25）に該当する者が 5 人に一人（20%）みられた．今後，高齢化に伴い健常四肢を含めた筋肉量減少（サルコペニア）と，それに伴う基礎代謝低下からくるさらなる体重増加（サルコペニア肥満）が懸念される．各人において，筋肉量を維持する工夫が必要であると考える．
- 脂肪肝：ALT 高値とは別に，腹部超音波検査で脂肪肝の所見（肝腎コントラストの増強）を男性 9 名（53%），女性 13 名（39%）に認めた．食生活の改善が求められる．
- 脂質異常症：半数以上（33 名，男性 10 名[59%]と女性 23 名[70%]）に高 LDL コレステロール血症（>120 mg/dL）を認めた．血中 LDL コレステロール値は，150 mg/dL 台が男性に 3 名，女性に 3 名，170 mg/dL 台が女性に 2 名，200 mg/dL 台が女性に 2 名（1 名は 230 mg/dL 台）あった．血中 TG は，200mg/dL 台が男性に 2 名，女性に 3 名，300mg/dL 台が男性に 1 名，女性に 3 名あった．脂質異常の持続は動脈硬化症の進展につながる．食習慣の是正や適切な薬物治療が望まれる．
- 糖尿病：HbA1c（NGSP）値が，7%台が 1 名（治療中），6%台が 6 名（うち 2 名は治療中，別の 1 名は初回異常なし）あった．2 回の検診を受けたほとんど全員で HbA1c 値が上昇しており，今後も観察が必要である．
- 高尿酸血症：高尿酸血症は痛風（発作）の原因となるだけでなく，現在では動脈硬化性疾患のリスク因子の一つと考えられている．
- CKD:eGFR=17 mL/min/1.73m^2 であった女性では，超音波検査で多発性嚢胞腎の所見を認めた．胎芽症患者では片腎などの形成異常も報告されているが，明らかな形成異常がなくとも，加齢に伴う腎機能低下が健常人より早く進む可能性があり注意（定期検診）が必要である．
- 骨粗鬆症：前年までで，骨密度から骨粗鬆症（腰椎と大腿骨頸部のいずれかが YAM70%未満）と診断されるものは男性 2 名(12%)，女性 9 名(27%)であった．骨量減少（いずれかが YAM70-80%）は男性 6 名（35%），女性 13 名（39%）であった．本年の検査で，新たに 1 名が骨粗鬆症と診断された．骨粗鬆症の危険因子は，内的要因として，①55 歳以上の閉経後女性，②痩せている，③ステロイドを服用している，④糖尿病や甲状腺の疾患を持っている，⑤家族に骨粗鬆症の人がいる，ライフスタイルとして，⑥喫煙者，⑦アルコールの摂取の多い方，⑧運動しない・日光に当たらない，である．胎芽症患者では，特に⑧に注意が必要であると思われる．
- 内分泌・代謝異常：今回は内分泌機能に特に注目した検診は行っていないが，サリドマイド自

体に,①耐糖能異常:インスリン抵抗性の増大,②甲状腺機能低下症:添付文書上の頻度は 0.9%,③甲状腺中毒症：甲状腺炎の惹起，④副腎機能低下症，⑤性腺機能低下症といった副次作用が報告されていることから，胎生期における薬物暴露が内分泌系臓器の発生過程にも何らかの影響を及ぼすことは十分考えられる．引き続き調査を行っていく．

- 以上より，
  - ✧ 運動制限からくる肥満症に留意する
  - ✧ 主に脂肪肝による肝機能障害がみられる
  - ✧ 脂質異常症の頻度が高い
  - ✧ 耐糖能障害や慢性腎臓病（CKD）を呈する症例がある
  - ✧ 女性だけでなく，男性にも骨粗鬆症の症例がある
  - ✧ サリドマイド（誘導体）自体が甲状腺機能異常や内分泌・代謝異常を引き起こす

  と，総括される．

- 本年の 2 名は，今回は消化管内視鏡検査を希望されなかった，腹部超音波検査結果については，「異常なし」と「前回と著変なし」であった．便潜血はいずれも陰性であった

Ⅲ．分担研究報告２

厚生労働行政推進調査事業費補助金
医薬品・医療機器等レギュラトリーサイエンス総合研究事業

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究
サリドマイド胎芽症患者の COVID-19 蔓延期における
生活上の留意に関する検討

研究分担者　長瀬　洋之　帝京大学医学部内科学講座呼吸器・アレルギー学

§サリドマイド胎芽症患の COVID-19 蔓延期における生活上の留意に関する検討

研究分担者　　長瀬　洋之　　帝京大学医学部内科学講座呼吸器・アレルギー学　教授

A. 研究目的

2020 年春から蔓延している COVID-19 の流行期においては、接触感染や飛沫感染を防ぐ生活様式を実行する必要がある。サリドマイド胎芽症患者における、COVID-19 罹患時の重症化リスクは十分明らかになってはいないが、上記の生活上の注意点を実行することは重要である。しかしながら、現在周知されている手指消毒やマスク装着の方法のみでは、サリドマイド胎芽症において、その実行に障壁が存在する状況が想定される。そこで本研究では、サリドマイド胎芽症患者において、実行可能な手指消毒デバイスやマスクについて検討し、わかりやすいマニュアルを作成することを目的とした。

B. 研究方法

「新型コロナウイルス感染症（COVID-19）-流行期における対策のポイント-」と題するマニュアルを作成した。章立ては以下の通りである。

１．新型コロナウイルス感染症とは

2. どのようにして感染するか　-飛沫感染と接触感染-

3. どのような症状が出るか

4. どのように診断するか

5. どのように治療するか

6. どのように予防するか

A. 「３つの密」を避ける

B. マスクを着用する

C. 手洗いと消毒

i）手洗い

ii）手指消毒

D. 新型コロナウイルス接触確認アプリ

E. ワクチン

7. 新型コロナウイルス感染症にかかっていないか調べたいとき

本マニュアルにおいて、特に「6. B. マスクを着用する」の項では、貼るマスク、マスク貼付用テープ、マスクを首にかけるためのストラップ、フェイスシールド・マウスシールドについて写真付きで説明した。また、「6. C. ii）手指消毒」の項では、自動手指消毒器や、その機器を固定するための粘着テープ、マグネット式スタンドや三脚を写真つきで紹介した。

C. 研究結果

次項に、作成したマニュアルを転載する。

新型コロナウイルス感染症 (COVID-19)
流行期における対策のポイント

― サリドマイド胎芽症の皆様へ ―

厚生労働科学研究
サリドマイド胎芽病患者の健康、生活実態の諸問題に関する研究班

長瀬　洋之著
日ノ下　文彦編

１．新型コロナウイルス感染症とは

ヒト由来のコロナウイルスはかぜ (感冒)の原因の 10～15%を占める病原体として知られていました。しかし、より重症な肺炎として、2002 年に中国・広東省に端を発した重症急性呼吸器症候群 (SARS)、2012 年にアラビア半島で中東呼吸器症候群 (MERS)が報告されました。そして、2019 年 12 月から中国・武漢市で発生した肺炎の原因が、新型コロナウイルス (SARS-CoV-2)です。SARS-CoV-2 による感染症を COVID-19 (新型コロナウイルス感染症)と呼びます。

2. どのようにして感染するか　-飛沫感染と接触感染-

感染した人がせきをして飛んだ飛沫に含まれるウイルスを、別の人が口や鼻から吸い込んでしまうのが飛沫感染で、新型コロナウイルス感染の主体と考えられています。

接触感染とは、感染した人がせきを手で押さえた後や、鼻水を手でぬぐった後に、ドアノブなどに触れ、その場所に別の人が手で触れ、鼻、口に再び触れることにより、ウイルスが体内に入り感染することで、これも感染の原因となります。新型コロナウイルスは、プラスチックの表面では最大 72 時間、ボール紙では最大 24 時間生存するとされています。

空気感染とは、小さい病原体が空気中を漂い、広範囲に感染を拡げる状態で、麻しんウイルス (はしか)、結核菌が知られていますが、新型コロナウイルスの主な感染経路とはされていません。

症状が出ている人が感染をうつす主体ですが、発症から間もない時期でも感染性が高いため、感染が拡がる原因となっています。発症 2 日前から発症後 7～10 日間程度の期間に、感染性があると考えられています。

また、COVID-19 を発症した人の家族内感染率は 11.8%とされています。10 歳代の患者さんの家族内感染率は 18.6%と高く，成人患者さんと同等以上でしたが、0～9 歳の患者さんからの家族内感染率は 5.3%と低かったとされています。家庭においても、症状がある家族がいる場合、マスク着用、手指衛生などの予防策をとる必要があります。

コロナウイルス感染症は一般に温帯では冬季に流行しますが、COVID-19 も冬季に流行の拡大がみられています。

3. どのような症状が出るか

初期の症状は、インフルエンザや感冒に似ており、COVID-19 を区別することは困難ですが、インフルエンザにおける突然の高熱、COVID-19 における嗅覚・味覚障害などはそれぞれに特徴的とされています。わが国の解析では、COVID-19 に頻度が高い症状は、発熱、咳嗽、倦怠感、呼吸困難で、下痢は約 1 割で、味覚障害 (17.1%)、嗅覚障害 (15.1%)もみられました。

4. どのように診断するか

PCR 法は、新型コロナウイルスの遺伝子配列を検出する検査法です。感度が高く、検査の主体となっています。「鼻咽腔ぬぐい液」で当初検査されていましたが、発症から 9 日以内

であれば、「唾液」を用いた場合でも、同等の精度が確認されています。

そのほかに抗原検査があり (インフルエンザウイルス検査でよく用いられている方法)、30 分程度で結果が出るなど、メリットがありますが、キットの種類により感度が異なります。

5. どのように治療するか

軽症の場合は、経過観察のみで自然に軽快することが多いですが、発症 2 週目までに急速に病状が進行することがあります。高齢者や、糖尿病、心不全、COPD (タバコ肺)、がん、腎臓病、肝疾患、肥満などの基礎疾患のある方は、重症化する割合が高いとされており、軽症でも入院とする場合があります。

息切れや肺炎のある中等症以上では、入院して治療します。肺炎が進行する場合、ステロイド薬やレムデシビルの使用が考慮され、必要に応じて酸素投与が行われます。重症例では、人工呼吸管理や体外式膜型人工肺 (ECMO)が用いられます。

COVID-19 では、血栓が認められやすく、ヘパリンなどによる抗凝固療法を行うことがあります。そのほかにも、トシリズマブの治験が行われており、ファビピラビル (アビガン®)は、保険承認申請中です。シクレソニドは喘息用の吸入ステロイド薬で、COVID-19 への効果も期待されましたが、最近の研究では、無症状・軽症の患者さんには推奨されない結果が示されました。

6. どのように予防するか

飛沫感染を防ぐために、マスクの着用、「３つの密」の回避を行います。接触感染を避けるために、石けんによる手洗いや、手指消毒用アルコールによる消毒を行います。

A. 「３つの密」を避ける

「３つの密」は、感染を拡大させるリスクとなります。人と人との距離をとること (Social distancing; 社会的距離)が重要です。

i) 密閉空間を避けて、十分に換気する

- 2 方向の窓を数分間開けて、できれば毎時 2 回以上換気しましょう。窓が 1 つしかない場合でも、入口のドアを開ければ、窓とドアの間に空気が流れます。
- 通常の家庭用エアコンは、空気を循環させるだけです。別途、換気が必要です。
- 一般的な空気清浄機は、通過する空気量が少なく、新型コロナウイルス対策への効果は不明です。

ii) 密集場所を避け、隣の人とは互いに手を伸ばして届かない距離を取る

- レジなどで列に並んでいるとき、前の人に近づきすぎないようにしましょう。
- 飲食店では一つ飛ばしに座る、真向かいに座らない、互い違いに座るなどに留意しましょう。
- エレベーターで混みあっているときは、一本遅らせましょう。健康のためにも、階の上下には階段の利用に努めましょう。

iii) 密接場面を避ける

- 5 分間の会話で、1 回の咳と同じくらいの飛沫が飛びます。
- 対面での会議や面談が避けられない場合は、十分な距離を保ち、マスクを着用しましょう。
- エレベーターや電車の中では、会話や携帯電話による通話を慎みましょう。
- 多人数での会食は、マスクを外す時間が長くなり、大声になりがちなため、慎みましょう。
- 多人数かつ室内で呼気が激しくなるスポーツジム、ライブハウス、カラオケは避けましょう。
- 喫煙の際はマスクを外しており、喫煙所では人との「密」が起こります。喫煙者は重症となる可能性が高いことも報告されています。禁煙する選択肢も考慮しましょう。

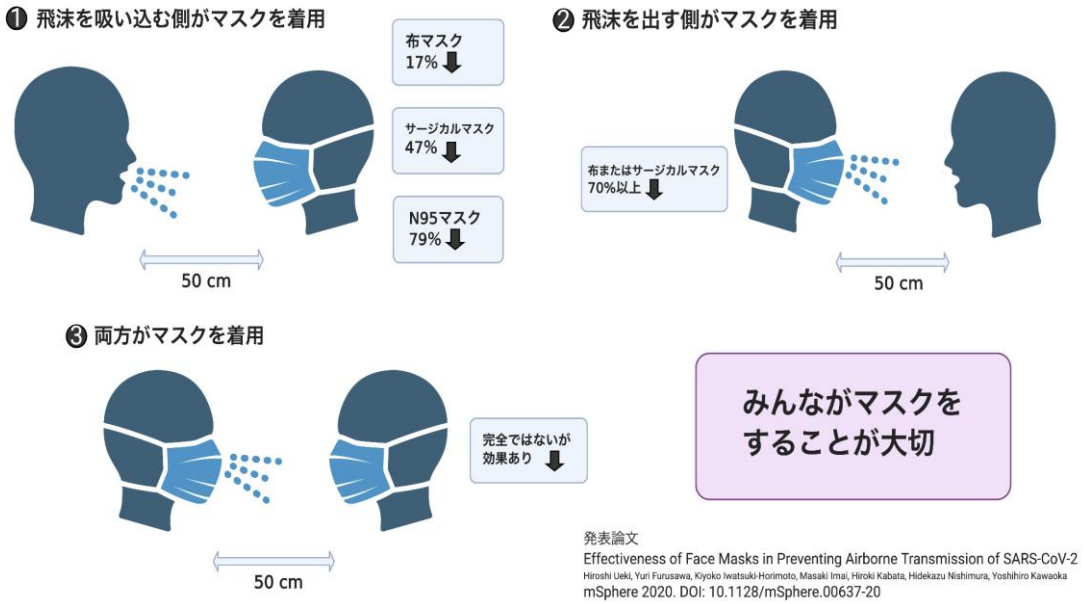
B. マスクを着用する

マスクの素材によって、効果は違います。不織布マスクが最も効果が高く、次に布マスク、その次にウレタンマスクの順です。

マスクは、「飛沫を出す側：自分」「飛沫を吸い込む側：相手」とすると、相手だけがマスクを着用するより、自分だけがマスクを着用する方が効果が高く、7 割以上飛沫を減少させます。自分から相手への感染拡大を防ぐために、話す時はいつでもマスクを着用しましょう。

さらに、自分と相手の双方がマスクを着用することで、吸い込みを 7 割以上抑えます。皆がマスクをすることが大切です。室内で会話する場合は、特にマスクを着用する必要があります。屋外でも、最低 1 メートルの間隔を確保できない場合もありますので、やはりマスクは重要です。

自分の顔にぴったりとフィットしているマスクを選ぶことが重要です。鼻に留め金がある場合は、鼻の形に合わせて固定します。鼻を出した状態では効果が不十分です。



東京大学医科学研究所のデータをもとに内閣官房が作成
https://corona.go.jp/proposal/pdf/mask_kouka_20201215.pdf

・サリドマイド胎芽症の皆様へ

ひものない、貼るタイプのマスク、マスク固定用のテープ、首にかけるマスクがあります。お示しする製品は、アマゾンなどの通信販売サイトで入手可能です。価格は 2021 年 1 月現在の実勢価格です。

● 貼るマスク (5 枚: ¥780)

四隅に粘着テープが貼ってあります。正面から見ると、ひもつきマスクと同じように見えます。



● 貼りマスクテープ (¥980)

市販のマスクのひもを切って改造し、テープを四隅に貼って装着することができます。



● 首にかけるストラップ (¥980)

マスクのゴムにストラップを装着し、首に回します。ウレタン素材で、ソフトに首に固定できます。







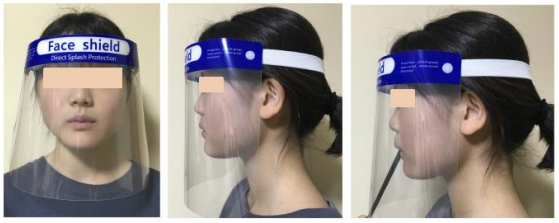


● フェイスシールド・マウスシールド

フェイスシールドはマスクと併用し、眼からの飛沫感染防止のために用いるものですので、マスクと併用しましょう。マウスシールドは、マスクに比べて予防効果が弱く、単独での使用は、できる限り避けましょう。透明のシールドを使用する場合は、ファイスシールドを鼻先から垂直に、あごの下まで隠れるように装着します。

また、マスクを外して飲食せざるをえない場合、フェイスシールドやレイン用サンバイザー、ほほの上部で固定する紙のマスクなどを着用した上で、あごの下からストローを使って飲むように工夫します。

フェイスシールド 10枚 ¥1340



レインバイザー ￥849



ハレマス 貼るマスク
50枚 ¥4235



サンバイザー ¥599



C. 手洗いと消毒

接触感染を予防するために、手洗いや手指消毒を行います。

i) 手洗い

ウイルスは水で洗い流すことで、かなり数を減らすことができます。手指に付着しているウイルス量は、流水による 15 秒の手洗いだけで 1/100 になります。さらに、石けんで 10 秒もみ洗いし、流水で 15 秒すすぐと、1/10,000 に減らすことができます。

石けんやハンドソープを使った
丁寧な手洗いを行ってください。



手洗いを丁寧に行うことで、
十分にウイルスを除去できます。
さらにアルコール消毒液を
使用する必要はありません。

手洗い		残存ウイルス
手洗いなし		約 100万個
石けんや ハンドソープで 10秒もみ洗い後 流水で 15秒すすぐ	1回	約 0.01% (数百個)
	2回 繰り返す	約 0.0001% (数個)

(森功次他：感染症学雑誌、80:496-500,2006 から作成)

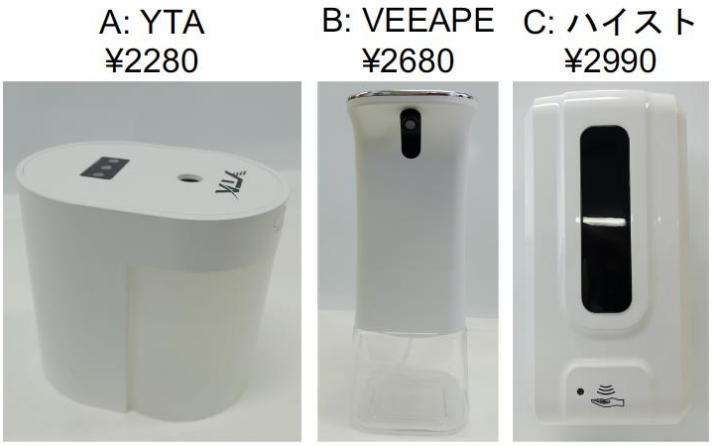
ii) 手指消毒

手洗いがすぐに出来ない状況では、アルコール消毒液 (濃度 70%～95%のエタノール)も有効です。60%台のエタノールによる消毒でも一定の有効性があります。

・サリドマイド胎芽症の皆様へ

ポンプ式の消毒液のほかにも、以下のような自動種手指消毒器があります。手や足をかざすだけで消毒液が噴霧されます。

● 自動手指消毒器



また、さまざまな固定器具があり、高さや角度を変えることができます。

● 粘着テープ

扉の取っ手の横に粘着テープ式のフックを装着すると、開閉時に、すぐ消毒が可能。



● マグネット式スタンド

ドアノブの下にマグネット式スタンドを装着すると、ドア開閉時に自動的にアルコールが噴霧される

アスクル マグネット式スプレースタンド
¥968



● 三脚

高さを調節し、玄関などよく使う場所に、使用しやすいように整える。

三脚 ¥5691



iii) 身の回りのものの消毒・除菌

熱水、次亜塩素酸ナトリウム (いわゆる塩素系漂白剤)、アルコール消毒液による消毒をおすすめします。これ以外では、界面活性剤 (いわゆる住宅用・台所用洗剤)でも、効果が期待できます。新型コロナウイルス感染症や疑われる患者さんがトイレを使用時に、下痢症状などでトイレが汚れた場合には、次亜塩素酸ナトリウムまたはアルコール (70%)による清拭を推奨します。

D. 新型コロナウイルス接触確認アプリ

新型コロナウイルス接触確認アプリ (略称 COCOA)は、陽性者と接触した可能性をいち早く知ることが可能となります。感染者と、「過去 14 日間に」、「概ね１メートル以内で」、「15 分以上の近接した状態」の可能性があった方のスマートフォンに通知が送られます。アプリの通知画面では、接触者外来等の連絡先などが案内されます。通知を受けた方が検査を受ける場合は、行政検査となるため、検査費用の自己負担はありません。新型コロナ対策に非常に有効な手段のひとつですので、スマートフォンへのダウンロードをおすすめ致します。

E. ワクチン

ワクチンの接種は、海外で開始されていますが、わが国では準備段階です (2021 年 1 月現在)。日本政府は、製薬企業 3 社から合計 2 億 9,000 万回分 (1 人に 2 回接種を行うとした場合 1 億 4,500 万人分) の供給を受ける合意をしています。ワクチンが国内で承認され、供給できる準備が整った際は、無料で受けることができます。

7. 新型コロナウイルス感染症にかかっていないか調べたいとき

発熱等の症状のある方は、まずは、かかりつけ医等の身近な医療機関に直接電話相談し、医療機関を受診してください。感染が疑われると判断された場合には検査を受けることができます。

かかりつけ医で検査ができない場合や、かかりつけ医がない場合は、「受診・相談センター」に電話相談してください。

地域により、受付方法が異なりますので、お住いの自治体の情報をご確認ください。

【帰国者・接触者相談センターページ】
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/covid19-kikokusyasessyokusya.html

● おわりに

このパンフレットは、「新型コロナウイルス感染症 (COVID-19)診療の手引き第 4 .1 版」(2020 年 12 月 25 日発行)の内容に準拠して作成しました。

以下の厚生労働省の HP にも、有用な情報が多数掲載されていますので、ご参照ください。

新型コロナウイルスに関する Q&A （一般の方向け）
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/dengue_fever_qa_00001.html

Ⅲ．分担研究報告３

厚生労働行政推進調査事業費補助金
医薬品・医療機器等レギュラトリーサイエンス総合研究事業

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究
サリドマイド胎芽症患者に対するマッサージ等のリハビリテーション診療サポート

研究分担者 芳賀　信彦　東京大学医学部附属病院リハビリテーション科　教授

§サリドマイド胎芽症患者に対するマッサージ等のリハビリテーション診療サポート

研究分担者	芳賀　信彦	東京大学医学部附属病院リハビリテーション科　教授
研究協力者	藤谷　順子	国立国際医療研究センター病院リハビリテーション科　科長
研究協力者	小林　　毅	日本医療科学大学作業療法学専攻　教授
研究協力者	前原　康宏	国立国際医療研究センター病院ペインクリニック内科　科長
研究協力者	藤原　清香	東京大学医学部附属病院リハビリテーション部　講師

研究要旨

サリドマイド胎芽症の二次的運動器障害に対するマッサージを含むリハビリテーション診療について、文献検索と評価法の検討を行った。また日本のサリドマイド胎芽症者を対象に、アンケート調査を行うための検討を始めた。

Ａ．　研究目的

50歳以上に達しているサリドマイド胎芽症者では、四肢や体幹の可動域制限や痛みを生じ、日常生活活動に困難を生じることが多くなってきている。このような二次的な運動器障害に対するアプローチとしてリハビリテーション治療が有効である可能性があるが、学術的な報告は極めて少ない。一方、サリドマイド胎芽症者の中には症状軽減を目的としてマッサージ等の補完代替医療を受けているものがいることが、われわれが2017年度に日本国内５か所で行われた交流会に参加して行った健康ミーティングと個人面談の中でのヒアリングから明らかになっている。

そこで今年度は、サリドマイド胎芽症の二次的運動器障害に対するマッサージ等の効果の検証を目的に、　①サリドマイド胎芽症者とマッサージに関する文献検索、②頸肩腕痛、腰背部痛に対するマッサージの効果判定（評価法）の検討、③日本におけるサリドマイド胎芽症者のマッサージ利用に関する調査、を計画した。

Ｂ．研究方法

【マッサージ等に関する文献検索】

PubMed 及び医中誌 Web を用い、サリドマイド（thalidomide）・マッサージ（massage）、サリドマイド（thalidomide）・リハビリテーション（rehabilitation）のキーワードで、英語と日本語の論文検索を行った。

サリドマイド胎芽症の成人以降の二次的障害に対するアプローチに関して検索する目的で 1990 年以降に発行された論文に限り、更に近年のハンセン病に対する治療薬や悪性腫瘍に対する化学療法等としてのサリドマイドに関する論文やサリドマイドの作用機序に関する論文を除いた。

【マッサージの評価法の検討】

特に頸肩腕痛、腰背部痛に対するマッサージの効果判定に用いられる評価法について、指導的立場にある鍼灸あんまマッサージ師にヒアリングを行った上で、関連する成書や論文を参照し、適切な評価法

を検討した。

【マッサージ利用に関する調査】

日本におけるサリドマイド胎芽症者のマッサージ利用に関するアンケート調査を計画し、関係者で調査の手順及び内容を検討した。

C．研究結果

【マッサージ等に関する文献検索】

サリドマイド（thalidomide）・マッサージ（massage）では、PubMed、医中誌 Web ともに該当する論文はなかった。サリドマイド（thalidomide）・リハビリテーション（rehabilitation）では、PubMed で 13 論文、医中誌 Web で 19 論文が抽出された。

英文論文の中で二次的運動機能障害に対するマッサージを含むリハビリテーション介入について記載のあるものは 2 編であり、1 編は英国からの 50 代男性の症例報告（Morrison D. Poor balance, bilateral upper limb phocomelia, no previous exercise: a challenging combination for fall prevention in a middle-aged thalidomide survivor. BMJ Case Rep 13: e231345, 2020）で、上肢形成不全、腰痛、脚長不等、バランス障害による階段昇降の困難に対し、足底装具の処方、理学療法の介入が行われ、機能が改善した。機能評価には、pain scale、Timed Up and Go Test、Falls Efficacy Test 等が用いられた。もう 1 編は日本からのアンケート調査の報告（Hinoshita F, et al. A nationwide survey regarding the life situations of patients with thalidomide embryopathy in Japan, 2018: First report. Birth Defects Res 111: 1633-1642, 2019）で、症状のある 119 名中 28.6%が、マッサージ、鍼灸治療、カイロプラクティックのいずれかを受けていることが記載されていた。

日本語論文の中で二次的運動機能障害に対するマッサージを含むリハビリテーション介入について記載のあるものはなかった。

【マッサージの評価法の検討】

マッサージ、按摩、指圧の効果判定に関して、鍼灸師、理学療法士、看護師などの職種からの報告があり、プレチスモグラフィーや近赤外線分光法による皮膚や筋の血流変化、血中乳酸濃度やクレアチンキナーゼ値、筋電図を用いた筋疲労、心拍数や皮膚温、発汗などによる自律神経系の変化、が指標としても用いられていることが明らかになった。今後サリドマイド胎芽症者を対象にマッサージ等に介入研究を行う場合、四肢（特に上肢）に形成不全がある、という状況（採血や血圧測定には困難が伴う可能性）も考慮して、適切な評価法を選択する必要があると考えた。

【マッサージ利用に関する調査】

本研究に関わる研究分担者と研究協力者で数回にわたるオンライン会議を開催し、さらにメールで検討を進め、アンケートの内容を確定した。アンケート調査は、公益財団法人いしずえを通じてサリドマイド胎芽症者に依頼し、WEB で回答を得ることになり、依頼を開始した。

アンケートでは、本人の「全身倦怠感」「しびれ」「冷感」のほか、マッサージの対象となりやすい「痛み」「凝り」について、また、「痛み」「凝り」に対してどのようなことをどのくらいの頻度でしているか、その効果はどのくらい持続するのかを質問等した。効果については、主観的な評価として「表情尺度スケール（FRS : face rating scale)」を用い、特にマッサージの前後の効果には日常生活に影響するのかを評価できるように「疼痛生活障害評価尺度（PDAS : Pain Disabilities Assessment Scale)」をもとにした質問項目等とした。

D．考察

本研究より、サリドマイド胎芽症の成人以降の二次的障害に対するアプローチとして、マッサージを含むリハビリテーション診療の介入はほとんど報告されていないことが明らかになった。

われわれはサリドマイド胎芽症における上肢低形成は、その程度が比較的軽い場合には、日常生活活動（Activities of Daily Living: ADL）において上肢を使うことが多いが、加齢に伴い過用や誤用による変化が蓄積し、上肢の関節障害や腱鞘炎、末梢神経障害が生じ、一方、程度が比較的重い場合には、日常生活活動に下肢を用いることが多く、加齢に伴い過用や誤用による変化が蓄積し、脊椎の障害や下肢

の関節障害が生じると考えている。またこれらの障害は過用・誤用だけで生じるとは限らず、四肢・脊椎の先天的な形態異常が症状発現に関係している場合がある。この過用や誤用による変化は、様々な運動器疾患でみられるものであり、その予防、治療としてリハビリテーション診療は頻用されている。サリドマイド胎芽症では成人以降の二次的運動器障害は特に中年期以降に多いことが報告されており、リハビリテーション診療について研究を進めることが重要と考えた。

介入を考える場合、その効果を判定する評価法の選択が重要である。運動器疾患のリハビリテーション介入では多くの評価法が用いられているが、マッサージ等の補完代替医療では報告が限られていることが本研究から明らかになった。四肢（特に上肢）に形成不全がある、というサリドマイド胎芽症の特徴（採血や血圧測定には困難が伴う可能性）を考慮して、適切な評価法を選択する必要がある。

本研究ではリハビリテーション診療の実態と効果を知る手始めとして、マッサージに関するアンケート調査を計画し開始した。研究者間の議論を経て、評価には「表情尺度スケール（FRS：face rating scale)」と「疼痛生活障害評価尺度（PDAS：Pain Disabilities Assessment Scale)」を含めた。今後回答を集計し、介入研究につなげていくことを検討している。

E．結論

サリドマイド胎芽症の二次的運動器障害に対するマッサージを含むリハビリテーション診療について、文献検索と評価法の検討を行った。マッサージを含むリハビリテーション診療の介入はほとんど報告がなく、マッサージ等の補完代替医療では評価法に関する報告が限られていた。日本のサリドマイド胎芽症者を対象に、マッサージ利用に関するアンケート調査を行うための検討を始めた。

F．健康危険情報

該当なし

G．研究発表

1. 論文発表

1) Mano H, Fujiwara S, Haga N: Body knowledge in children with congenital upper limb deficiency. Brain Nerve 72(4): 445-451, 2020

2) Mano H, Fujiwara S, Takamura K, Kitoh H, Takayama S, Ogata T, Haga N*: Treatment approaches for congenital transverse limb deficiency: Data analysis from an epidemiological nation survey in Japan. J Orthop Sci, online ahead of print

3) 遠藤聡、藤原清香、真野浩志、西坂智佳、野口智子、奈良篤史、柴田晃希、越前谷務、芳賀信彦：前腕以遠の先天性横軸形成不全児に対する義手処方と経過. 日本義肢装具学会誌, 36(4): 298-304, 2020

2. 学会発表

1) Haga N: Rehabilitation Management for Survivors of Thalidomide Embryopathy. ACOPRM 2020, 2020.7.17, Korea (Virtual Conference)

2) 真野浩志、藤原清香、芳賀信彦：先天性上肢形成不全児の知的特徴. 第57回日本リハビリテーション医学会学術集会、2020.8.19-22、京都

3) 西坂智佳、藤原清香、遠藤聡、真野浩志、芳賀信彦：先天性片側手部横軸形成不全児における上肢筋群の解剖学的特徴. 第57回日本リハビリテーション医学会学術集会、2020.8.19-22、京都

4) 藤原清香、真野浩志、梅崎成子、西坂智佳、遠藤聡、芳賀信彦：当院におけるスポーツ活動に用いる作業用義手の使用実態. 第57回日本リハビリテーション医学会学術集会、2020.8.19-22、京都

5) 遠藤聡、藤原清香、西坂智佳、真野浩志、唐沢康暉、芳賀信彦：先天性上肢形成不全者が筋電義手を使用する時の脳活動部位の同定 -近赤外線分光法による検討-. 第 57 回日本リハビリテーション医学会学術集会、2020.8.19-22、京都

6) 西本遼輝、藤原清香、西坂智佳、遠藤聡、真野浩志、芳賀信彦：先天性四肢形成不全症児に四肢の補装具によるリハビリテーション治療を行った一例. 第 57 回日本リハビリテーション医学会学術集会、2020.8.19-22、京都

H．知的財産権の出願・登録状況

（予定を含む）該当なし

Ⅲ. 分担研究報告４

厚生労働行政推進調査事業費補助金
医薬品・医療機器等レギュラトリーサイエンス総合研究事業

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究
放射線診断学的見地からの検討

研究分担者　田嶋　強　　国立国際医療研究センター病院放射線診断科

§サリドマイド胎芽症患者の健康、生活実態の諸問題に関する研究
― 放射線診断学的見地からの検討

研究分担者　　田嶋　強　　国立国際医療研究センター病院放射線診断科　診療科長

研究要旨：本研究の目的はサリドマイド胎芽症患者における健康上の問題点を放射線診断学的見地から明らかにすることである. これまで、CT、MRI を用いて全身の画像所見を解析し、身体内部異常の放射線学的所見と頻度について考察を加えて報告してきた。今年度は、健康診断を継続することにより、CT、骨塩定量に関する身体内部異常の評価を継続実施する予定であった。しかしながら、今年度の検診参加者は、コロナ禍の影響が大きく１名のみであった。来年度以降、全国的な感染症の鎮静化が得られた際には、これまで行ってきた解析結果の検証を行う予定である。

A. 研究目的

本研究の目的はサリドマイド胎芽症患者における健康上の問題点を放射線診断学的見地から明らかにすることである. これまで、CT、MRI, 一般撮影を用いて全身の画像所見を解析し、身体内部異常の放射線学的所見と頻度について考察を加えて報告してきた。

今年度は、健康診断を継続することにより、CT に関する身体内部異常の評価を継続実施することを目的とする.

B. 研究方法

・本年度も胎芽症者の健診を実施した.

2021/2/19 に検診を実施した。健診受診者は 1 名（男性 1 名）. 受診者のプロフィールを表 1 に示す.

・実施された健診における放射線関連検査の内容は CT である.

・実施された CT 検査の部位は、頭部、頚部・椎体・四肢・筋、体幹部、脂肪測定（内臓脂肪）であった.

表 1. 受診者のプロフィール

症例番号	性別	年齢（歳）	障害の内訳
1	M	61	聴力障害

C. 研究結果

以下に結果を要約する. 各検査の具体的な結果は以下のごとくである.

1） 側頭骨 CT

複数の異常が見られた（左側耳小骨形成不全、左側外耳道閉鎖、左側慢性中耳炎、両側耳介形成異常）.

2） 頭部 CT

異常なし.

3） 脊椎 CT

塊椎(C6-T1)、変形性頚椎症、変形性胸椎症、腰椎椎弓形成不全、黄色靭帯骨化症、潜在性二分脊椎

4） 体幹部 CT

以下の異常を認めた:心拡大

5） 脂肪測定(内臓脂肪)

内臓脂肪は正常であった。

D. 考察

今回の検診は、コロナ禍の影響で縮小を余儀なくされた。今回の受診者においては、様々な異常が検出されたものの、幸い、前回検査から変化はなく、治療を要するものもなかった。

コロナ禍、とくに緊急事態宣言下の現状においては、サリドマイド胎芽症者にとっては、コロナ感染はとくに注意すべき状況であり、検診を契機とする感染は避けるべきである。胎芽症者にとっては、生活習慣病の罹患や加齢性変化が、今後の生活の質の維持において重要となっていくため、感染症の鎮静化を待って、フォローアップ検査を行っていくことが大変重要と思われる。

E.研究発表

なし

F. 知的財産権の出願・登録状況

1.特許取得

2.実用新案登録

3.その他

いずれも該当なし

Ⅲ．分担研究報告 5

厚生労働行政推進調査事業費補助金
医薬品・医療機器等レギュラトリーサイエンス総合研究事業

サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築に関する研究

研究分担者　曽根　英恵　　国立国際医療研究センター病院精神科

§サリドマイド胎芽症者のこころの健康と QOL（生活の質）に関する研究

研究分担者	曽根　英恵	国立国際医療研究センター病院精神科　心理療法士
研究協力者	加藤　　温	国立国際医療研究センター病院精神科　第一精神科医長
研究協力者	大友　　健	国立国際医療研究センター病院精神科　心理療法士
研究協力者	岡本　　悠	国立国際医療研究センター病院精神科　心理療法士
研究協力者	瀧　　彩栄	国立国際医療研究センター病院精神科　心理療法士
研究協力者	片岡 真紀	国立国際医療研究センター病院精神科　心理療法士

研究要旨

本研究班では各国における QOL に関する研究を踏まえ、本邦におけるサリドマイド胎芽症者の協力を得て痛みや QOL に関するアンケート調査を行った[5]。その結果、身体的および精神的 QOL は一般ノルムの範囲内であったということ、41.2%の参加者が何らかの精神疾患を抱えている、あるいは高いリスクにあること、身体的な痛みと精神的 QOL に直接的な関係は見られず、痛みに対する認知的コーピングの一つである破滅思考が精神的 QOL の低下に関係していることが示唆された。

このような結果を踏まえ、今後予定している研究としては、精神的健康度との関連が予想される要因として新たにレジリエンスとモビリティを測る尺度を加えて調査を行うことを計画している。また、前回調査においては健康診断に訪れた人のみを対象としていたため、結果として身体的な機能やモビリティが良く保たれている方や健康に対して意識を配る方々に限定されるなど、対象の偏りがあったことも考えられる。このような点を解決するために、郵送法による全国調査を計画している。今年度は新型コロナウイルス感染症の拡大により、予定していた調査が行えなかったため、次年度での調査の実施を予定している。

A. 研究計画

サリドマイド胎芽症者の多くが中年期に差し掛かり、自身や家族の健康問題、介護の必要性の増加、退職等による経済的問題などの不安を抱えている[1]。また、加齢に伴って出現する二次的な後遺症（痺れや麻痺）や痛み、それに伴う体の動かしづらさ等の困難を抱えている[2]。本研究班では、英国[3]、ドイツ[2]、スウェーデン[4]で行われた QOL に関する研究を踏まえ、2018 年 10 月までに協力を得られた 67 名のサリドマイド胎芽症者を対象とした痛みや QOL に関するアンケート調査を行い発表した[5]。

その結果、本邦におけるサリドマイド胎芽症者の身体的および精神的 QOL は一般ノルムの範囲内であったということ、精神疾患に関するスクリーニング尺度において 41.2%の参加者が何らかの精神疾患を抱えている、あるいは高いリスクがあることが明らかになった。また、身体的な痛みと QOL の関係について分析を行った結果、痛みは身体的および精神的 QOL に直接的な関係は見られず、痛みに対する認知的コーピングの一つである破滅思考が精神的 QOL の低下に関係していることが示唆された。これらの結果から浮上した疑問として、共通の QOL 尺度を用いたにも関わらず、他国の研究[3][4]と異なり日本においてのみ身体的 QOL が一般ノルムと比較して同程度であるということが挙げられる。これは、各国が調査対象者を訪問したり郵送による質問紙調査を実施していることに対して、本邦では健康診断を受診された対象者のみに限られているため、対象の偏りがあったかもしれないということである。そこで、今後の研究においては、対象者は全国のサリドマイド胎芽症者とし、「公益財団法人いしずえ(サリドマイド福祉センター)」を通じて、調査実施の主旨

に関する研究説明文書、アンケート用紙を全国のサリドマイド胎芽症者に郵送にて送付し、返送にてアンケート用紙を回収することを計画している。また、前回の調査結果を踏まえ、サリドマイド胎芽症者のQOLに関する諸要因の関連や違い、影響についてさらなる調査を進めていく。

サリドマイド被害から50年以上が経過した。加齢と共に、サリドマイド胎芽症者の生活上の困難さやこころの問題は変化していくと考えられるが、そのような側面からの全国調査は齋藤[6]の2005年のアンケート調査を最後に行われていないのが現状である。本研究を通じて、障害と共に生活しているサリドマイド胎芽症者に関する理解が深まると共に、サリドマイド胎芽症者の今後の支援の一助となることを研究意義とする。本邦において、サリドマイド胎芽症者に関する研究し、それらを研究発表等で報告することで、他国のサリドマイド胎芽症者への理解や支援の一助に繋がると考える。

B. 研究方法

調査対象

サリドマイド胎芽症者として「公益財団法人いしずえ（サリドマイド福祉センター)」に登録されている方で、研究参加に関して同意が得られた者を調査対象とした。除外基準は研究責任者が研究への組み入れを不適切と判断した者とした。

調査方法

「公益財団法人いしずえ(サリドマイド福祉センター)」を通じて、調査実施の主旨に関する研究説明文、アンケート用紙を全国のサリドマイド胎芽症者に送付し、返送にて回収する。回収したデータを統計解析にて分析をおこなう。目標回収数は100。

調査協力者がアンケート協力に伴う不利益を被らないよう十分な説明を行った後に同意を得るように配慮する。調査協力者がいつでも同意を撤回できること、同意撤回後も不利益を被らないこと、資料保管について厳重に行うことを書面にて説明し、書面によるインフォームド・コンセントを得る。さらに、記入用紙の上部に今回申請の質問事項については任意であることを表示することにより、本研究に関しての記入についての自由意思・同意における任意性に留意する。

評価項目

①フェイスシート

氏名、年齢、性別、配偶者の有無、同居家族の有無、最終学歴(選択式)、就労状況(選択式)を尋ねた。さらに、「痛みの程度」を測定するために、Numerical Rating Scale (NRS) を用いた。「現在あなたはどのくらいの身体の痛みを感じていますか？当てはまる番号に○をつけてください」という教示を与え、「0.痛みなし」から「10.これ以上ないくらいの痛み」の11段階のあてはまる番号に○をつけてもらった。さらに、「痛みを感じる部位」として、「痛みを感じる部位はどこですか？下の枠内にご記入ください。部位はいくつ書いていただいても構いません」という教示を与え、自由記述式での回答を求める。

②精神的健康度

General Health Questionnaire (GHQ-28) はGoldbergとHillier[7]によって開発された精神的健康の評価尺度であり、中川, 大坊[8]によって日本版に改訂された。GHQは38の異なる言語に翻訳されており、身体疾患を持つ人々を対象とした研究[9]を含むさまざまな集団を対象とした多くの研究[10]で広く使用されている。これらの理由から、我々の研究で使用した。もう一つの理由として、日本では、斎藤[6]やImai[11]によるサリドマイド胎芽症者のメンタルヘルスに焦点を当てた研究が行われており、それらの研究ではGHQ-28を使用している。継続的な観察を行う可能性も考慮し、本研究では同じ尺度を採用した。「身体的症状」「不安と不眠」「社会的活動障害」「うつ傾向」の4要素スケール、全28項目からなる。

③Quality of life

Quality of life（以下QOL）についてはさまざまな評価尺度があり、本研究においてはMOS36-item Short Form Health Survey (SF-36v2スタンダード版)(以下、SF36)の日本語版36項目を、ライセンスの使用登録申請をした上で使用する。SF36は、8つの健康概念(身体機能、日常役割機能【身体】、体の痛み、全体的健康感、活力、社会生活機能、日常生活機能【精神】、心の健康)を測定するための35項目と、健康変化を測定する1個の項目(健康推移)から成り立っている。下位尺度は2つのコンポーネント・サマリースコアである身体的QOL（Physical component summary）と精神的QOL（Mental component summary）に集約する。なお、この質問紙は、日本において、20代から70代の男女を対象として標準化されている(N=2279)[12]。

④痛みに対するコーピング

コーピングとは、人を圧迫するストレスフルな環境や内的要求に対して、それをコントロールするための心理的行動的な努力であると定義される[13]。Coping Strategy Questionnaire (CSQ) はRosenstielとKeefeによって1983年に作成された痛みへの対処方略を測定する尺度である[14]。原版が50項目であるのに対し、日本版は全16項目からな

る短縮版である。この質問紙は、認知的対処方略(12項目)と行動的対処方略(4 項目)の 2 つの概念から構成されている[15]。認知的対処方略は、「願望思考」(2「痛み行動の活性化」(2 項目)、「他の行動の活性化」(2 項目)の 2 つの下位因子からなる。教示文として「現在、感じている痛みに対して、どのように対処していますか」と与え、全 16 項目に対して「0. まったくしない」から「6. いつもする」の 7 件法での回答を求める。コーピングの一つである「破滅思考」は精神的問題を増大させる可能性が指摘されている[16]。

⑤ソーシャル・サポート

ソーシャル・サポートの有無と傾向を明らかにするため、現在の日常生活の各場面でサポートを与えてくれる対象について、「配偶者・パートナー」「配偶者以外の家族」「友人」「その他(自由記述)」「特にいない」の中から該当するものについて回答を求めた(複数回答可)。サポートの内容としては、地域住民用ソーシャル・サポート尺度[17,18]の全 10 項目を参考として設定した。

⑥必要としているサポート：現在、必要としているサポートを把握するため、自由記述にて回答を求める。

⑦モビリティ

これまでサリドマイド胎芽症者の身体的 QOL や身体機能について計量的な調査は行われてきたが[3],[4],[5]、身体的な QOL が低い一方で精神的な QOL は一般的な水準に保たれているという報告が見られる。このことは、身体的な機能等が障害されても精神的な満足感を持って生活することが可能であると解釈される[4]一方で、身体的な機能と精神的な健康との間に介在する変数が存在している可能性も示唆される。QOL に影響を与える要因は多岐に渡るが[19]、とりわけモビリティの制限は感情と心理社会適応に対して悪い影響があることが発見されている[20],[21],[22]。

サリドマイド胎芽症者のモビリティの重要性について言及されているもの[3]、筆者たちの知る限り計量的な調査は現時点では行われていない。本研究では Life-space assessment（LSA）を用いてモビリティを測定し、精神的な指標との関連などを検討する。LSA は居住地点からの最大到達範囲の測定、外出頻度や自立度合いを計算し、生活空間を測定する尺度である[23]。

⑧レジリエンス

項目)、「破滅思考」(2 項目)「自己教示」(2 項目)、「注意の転換」(2 項目)、「思考回避」(2 項目)、「無視」(2 項目)の 6 つの下位因子があり、行動的対処方略は、

サリドマイド胎芽症者の中には、QOL や精神的健康が保たれている方もおり、それらを維持・向上させる要因を検討することも必要であると考え、レジリエンスについての評価項目も加える。レジリエンスとは、「困難で脅威的な状態にさらされることで一時的に心理的不健康の状態に陥っても、それを乗り越え、精神病理を示さずに、よく適応している」[24] 状態を指す概念で、精神的健康度との有意な関連も報告されている[25]。平野[26]の「二次元レジリエンス要因尺度」を用いて、レジリエンスについて調査する。この質問紙では、レジリエンス を「資質的」なものと「獲得的」なものとで要因を分けて捉える尺度となっている。全 21 項目について、5 件法での回答を求める。

今年度は新型コロナウイルス感染症の拡大により、予定していた調査が行えなかったため、次年度での調査の実施を予定している。

引用文献

1) 木村壯介，森吉百合子，吉澤篤人. 全国のサリドマイド胎芽症患者の健康、生活実態に関する研究 吉澤篤人:平成 24 年度厚生労働科学研究費補助金(医薬品・医療機器レギュラーサイエンス総合研究事業)「全国のサリドマイド胎芽病者の健康、生活実態に関する研究(H23－医薬－指定－023)」平成 24 年度総括・分担研究年度終了報告書.2013 年 5 月. 資料 1 p158-175, 2012.

2) Kruse A, Baiker D, Becker G, et al : THALIDOMIDE Inquires to be carried out repeatedly with regard to problems, specific needs and support deficits of thalidomide victims. pp52-59, Institute of Gerontology of the University of Heidelberg, Heidelberg, 2012.

3) Newbronner, L., Chamberlain, R., Borthwick, R., & Baxter, M. Looking to the future: Evaluation of the Health Grant to Thalidomide-Impaired People. Year 2 Final report. Cambridgeshire: The Thalidomide Trust, 2012.

4) Ghassemi Jahani, S.A., Karlsson, J., Brisby, H., & Danielsson A.J. (2016). Health-related quality of life and function in middle-aged individuals with thalidomide embryopathy. Journal of Children's Orthopaedics, 10 (6)：691-703.

5) Imai, K., Sone, H., Otomo, K., Nakano, Y., &

Hinoshita, F. (2020). Quality of life and pain in patients with thalidomide embryopathy in Japan. Molecular Genetics & Genomic MedicineVolume. 8 (11) :e1464.

6) 齋藤高雅. 平成 11 年度 - 平成 13 年度科学研究費補助金(基盤研究(C) (2))研究成果報告書　サリドマイド胎芽病者の精神健康に関する追跡研究, 2002.

7) Goldberg D.P., Hillie V.F. (1979). A scaled version of the General Health Questionnaire. Psychol Med 9 (1)：139-145.

8) 中川泰彬, 大坊郁夫. 精神健康調査票手引：日本語版 GHQ　日本文化科学社, 1985.

9) Sterling, M. (2011). General Health Questionnaire - 28 (GHQ-28). Journal of Physiotherapy. 57, 259. https://doi.org/10.1016/S1836-9553(11)70060-1

10) Jackson, C. (2007). The General Health Questionnaire. Occupational Medicine.57,79. https://doi.org/10.1093/occmed/kql169

11) Imai, K., Iida, T., Yamamoto, M., Komatsu, K., Nukui, Y., & Yoshizawa A. (2014). Psychological and mental health problems in patients with thalidomide embryopathy in Japan. Psychiatry Clin Neurosci. 68 (6)：479-486.

12) 福原俊一･鈴鴨よしみ SF-36v2 日本語版マニュアル：iHope International 株式会社, 2004, 2015. 京都.

13) Lazarus, R. S., & Launier, R. (1978). Stress-related transactions between person and environment.　Pervin & M. Lewis. Perspectives in interactional psychology (pp. 287–327). http://dx.doi.org/10.1007/978-1-4613-3997-7_12

14) Rosentiel, A.K., Keefe, F.J. (1983). The use of coping strategies in chronic low back pain patients：relationship to patient characteristics and current adjustment. Pain. 17 (1)：33-44.

15) 大竹恵子, 島井哲志. (2002). 痛み経験とその対処方略　女性学評論 16, 143-157.

16) Sullivan, M.J.L., Thorn, B., Haythornthwaite, J.A., Keefe, F., Martin, M., Bradley, L.A., & Lefebvre, J.C. (2001). Theoretical Perspectives on the relation between catastrophizing and pain. The Clinical Journal of Pain. 17, 52-64.

17) 堤明純, 堤要, 折口秀樹, 高木陽一, 詫摩衆三, 萱場一則, 五十嵐正紘. (1994). 地域住民を対象とした認知的社会的支援尺度の開発. 日本公衆衛生雑誌 41(10), 965-974.

18) 堤明純, 萱場一則. (2000). Jichi Medical school ソーシャルサポートスケール (JMS-SSS)：改訂と妥当性・信頼性の検討.

19) La Grow, S., Yeung, P.,Towers, A., Alpass, F., & Stephens, C. (2013) The impact of mobility on quality of life among older persons. Journal of Aging Health. 25 (5) : 723-736. doi: 10.1177/0898264313490198. Epub 2013.

20) Drewnowski, A., & Evans, W. J.(2001). Nutrion, Physical activity, and qulaity of life in older adults. The Journals of Gerontology: Series A, 56(2): 89-94. https://doi.org/10.1093/gerona/56.suppl_2.89

21) La Grow, Alpass, F., Stephens, C., Towers, A.(2011). Factors affecting perceived quality of life of older persons with self-reported visual disability. Qual Life Res. 20(3) : 407-413. doi: 10.1007/s11136-010-9758-6. Epub 2010 Oct 15.

22) Salkeld, G., Cameron, I.D., Cumming, R.G., Easter, S. Seymour, J. Kurrle, S.E., & Quine, S. (2000) Quality of life related to fear of falling and hip fracture in older women: a time trade off study. British Medical Journal. 320 : 341-346. doi: 10.1136/bmj.320.7231.341.

23) Peel, C., Baker P.S., Roth, D.L., Brown, C.J., Brodner, E.V., & Allman, R.M. (2005). Assessing mobility in older adults: the UAB Study of aging life-space assessment. Phys Ther. 85(10)：1008–1019.

24) 小塩真司, 中谷素之, 金子一史, 長峰伸治. (2002). ネガティブな出来事からの立ち直りを導く心理的特性-精神的回復力尺度の作成　カウンセリング研究 35(1), 57-65.

25) Haddadi, P., Besharat, M.A. (2010). Resilience, vulnerability and mental health. Procedia Social and Behavioral Science 5 639-642.

26) 平野真里 (2010).　レジリエンスの資質的要因･獲得的要因の分類の試み:――二次元レジリエンス要因尺度（BRS）の作成　A Study of the Classification of Resilience Factors: Development of the Bidimensional Resilience Scale (BRS)　パーソナリティ研究 19(2), 94-106.

F. 健康危険情報

特になし

G. 研究発表

1.　論文発表

該当なし

Ⅳ．研究成果の刊行に関する一覧表

・書籍

発表者氏名	論文タイトル名	発表書籍	巻号	ページ	出版年
Tetsuya Tagami	・Endocrine and Metabolic Disorders	Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo (edited by Fumihiko Hinoshita)		8-12	2020
Nirou Tayama	・Medical Check-up of Oto-rhinolaryngology (ORL) for the Patients of Thalidomide Embryopathy (TE)			13-21	
Ryoji Kayamori	・Two New Claimers in Japan			22-28	
Emma Baple	・A Diagnostic Aid to Thalidomide Embryopathy			29-41	
Hiroshi Handa	・Mechanisms of Thalidomide Teratogenicity			42-54	
Fumihiko Hinoshita	・Activities of the Japanese Research Group on TE and Nation-wide Survey of Actual Life Situation in Subjects with TE in Japan, 2018			55-64	
Hiroyuki Nagase	・Preserved Pulmonary Function in Thalidomide Embryopathy in Japan			65-74	
Jan Schulte-Hillen	・Mortality in Thalidomiders in Germany Is Underdiagnosed Hypertension the Cause?			75-81	
Nobuhiko Haga	・Lessons from Thalidomide Embryopathy and Sharing Information with the Next Generation ~From Physiatrists' Points of View~			82-89	
Shadi-Afarin Ghassemi	・Thalidomide Embryopathy – Orthopaedic Aspects, Degenerative Changes and Quality of Life at Age 45			90-97	
Klaus M. Peters	・Outpatient Center for Thalidomiders in Gemany: Treatment Strategies and First Results			98-103	
Dee Morrison & Elizabeth Newbronner	・Growing Older with Thalidomide Embryopathy – Research and Support in the UK			104-112	
Christina Ding-Greiner	・Ageing with Thalidomide Damage: Evaluation 2019 – Special Needs			113-118	
John Skinner	・Total Hip Replacement in Thalidomide Enbryopathy? What Are We Worried About?			119-136	
Lavínia Schuler-Faccini	・Thalidomide in Brazil: Recent Experience			137-147	
Many panelists mainly mentioned above	* **Panel Discussion**			148-159	
日ノ下 文彦		老い楽のすゝめ（文芸社）		1-190	2021
栢森　良二		サリマイド ー復活した「悪魔の薬」（PHP エディターズ・グループ）		*in press*	2021

Ryoji Kayamori	・History and Overview of Thalidomide Embryopathy(TE)	2020 Guide for the Management of Thalidomide Embryopathy		8-14	2021
Takumi Ito Yuki Yamaguchi Hiroshi Handa	・Mechanism of Thalidomide Embryopathy(TE)			16-20	
Ryoji Kayamori	・Diagnostic Procedures for Thalidomide Embryopathy(TE)			22-29	
Tomoko Shiga	・Internal Medical Care Managing Lifestyle Diseases			30-32	
Tetsuya tagami	・Internal Medical Care Endocrine and Metabolic Disorders			34-36	
Fumihiko Hinoshia	・Internal Medical Care Kidney Disease, Hypertension, and Cardiovascular Disease			38-42	
Hiroyuki Nagase	・Internal Medical Care Preventing Respiratory Diseases and Infections			44-47	
Nobuko Shiga Takama maekawa	・Internal Medical Care Esophagogastroendoscopy（EGD）and Gastrointestinal			48-50	
Nobuhika Haga	・Orthopedic Surgery and Rehabilitation Diagnosis and Assessment/Testing			52-55	
Nobuhiko Haga Ryoji Kayamori Yasuhiro Maehara	・Orthopedic Surgery and Rehabilitation Treatment and Support[1]Drug Therapy			56	
Nobuhiko Haga Ryoji Kayamori	・Orthopedic Surgery and Rehabilitation Treatment and Support[2]Surgery and Indication			57	
Takeshi Kobayashi Junko Fujitani	・Orthopedic Surgery and Rehabilitation Treatment and Support[3]Properly Interacting with People with Thalidomide Embroyopathy (TE):Aphysical and Occupational Therapy Perspective			58-61	
Hiroji Tsujimura Shin-idhi Shirahoshi	・Orthopedic Surgery and Rehabilitation Treatment and Support[4] Addressing Musculoskeletal Pin and Inconveniences in Daily Living Through an Erogonomic Approach			62-64	
Tsuyoshi Tajima Azusa Minagawa Masafumi Shinozaki	・Radiological Examination and Evaluation			66-77	
Jun Harada Niro Tayama	・Otorhinolaryngology			78-79	
Yutaka Maruoka	・Dentistry and Oral Surgery Examination			80-81	
Miyuki Nagahara Ken Otomo Hanae Sone	・Ophthalmologic Care ・Psychiatric Care			82-84 86-87	

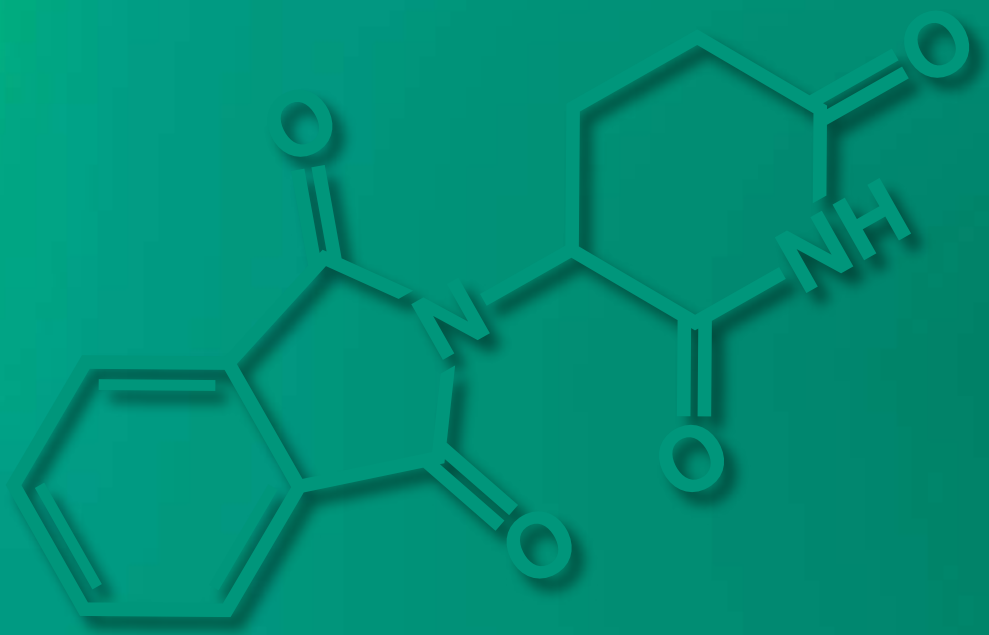
Yuki Nakano On Kato Fumihiko Hinoshita	・Problems Encountered in Clinical Settings Blood Sampling			88-89	
Fumihiko Hinoshita	・Problems Encountered in Clinical Settings Measuring Blood Pressure			90-91	
Yasuhiro Maehara	・Problems Encountered in Clinical Settings Surgery for Patients with Thalidomide Embryopathy (TE): Considerations for Perioperative Management			92-93	
Keiko Tanaka Chika Kuge	・Problems Encountered in Clinical Settings Nursing			94-95	
Ryoji Kayamori Fumihhiko Hinoshita	・Care for Thalidomide Embryopathy (TE) in Germany			98-101	

・論文発表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Haga N Fujiwara S	Body knowledge in children with congenital upper limb deficiency.	Brain Nerve	72(4)	445-451	2020
Haga N Mano H, Fujiwara S Takamura K Kitoh H Takayama S Ogata T	. Treatment approaches for congenital transverse limb deficiency: Data analysis from an epidemiological nation survey in Japan.	J Orthop Sci	online ahead of print		2020
芳賀信彦 遠藤聡 藤原清香 真野浩志 西坂智佳 野口智子 奈良篤史 柴田晃希 越前谷務	前腕以遠の先天性横軸形成不全児に対する義手処方と経過	日本義肢装具学会誌	36(4)	298-304	2020
Imai K Sone H Otomo K Nakano Y Hinoshita F	Quality of life and pain in patients with thalidomide embryopathy in Japan.	Molecular Genetics & Genomic Medicine	Vol8,11	2020 Nov; 8(11):e1464. doi: 10. 1002/mgg3. 1464.	2020

・小冊子

発表者氏名	冊子タイトル名	発表誌名	巻号	ページ	出版年
日ノ下 文彦 長瀬　洋之 田上　哲也 丸岡　豊 藤谷　順子	新型コロナウイルス感染症(COVID-19)の基本的知識と生活上の対応 ーサリドマイド被害者の皆様へー			1-16	2021



Guide for the Management of Thalidomide Embryopathy 2020

Edited by
Fumihiko Hinoshita
Center Hospital of the National Center for Global Health and Medicine

2020 Guide for the Management of Thalidomide Embryopathy

Edited by
Fumihiko Hinoshita
Center Hospital of the National Center for Global Health and Medicine

A message to healthcare professionals involved in the support of thalidomide victims

Keiko Ebi

Director, Office of Drug Induced Damages, General Affairs Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Thalidomide drug products initially marketed as sleeping medications in Japan in 1958 tragically led to the birth of many children with arm and auditory defects by women who took these drugs while pregnant. Accepting responsibility for these injuries in the 309 certified victims, the national government endeavors to support them.

Now in their late 50s, many of the victims suffer lifestyle diseases, psychiatric conditions, and a host of other health issues on top of their congenital deficits. Their growing health burden will require care from healthcare professionals in a range of fields. However, there are not necessarily many health professionals who have encountered patients with thalidomide embryopathy (TE).

To address these trends, The Research Group on Grasping the Health and Living Situation as well as Creating the Support Infrastructure for Thalidomide-Impaired People in Japan revised this "Guide for the Management of Thalidomide Embryopathy" for the first time in 3 years. The Research Group supplemented the matter in the previous version with findings from the latest research to provide information that will assist caregivers in all relevant fields. I sincerely hope that healthcare professionals and all others involved in supporting thalidomide victims around the world make use of this guide to support the lives of these special patients.

TABLE OF CONTENTS

I Introduction 7

II History and Overview of Thalidomide Embryopathy (TE) 8
1. The Advent and Efficacy Profile of Thalidomide 8
2. Side Effects Begin to Appear 9
3. The Thalidomide Saga 10
4. Lenz's Warning Emerges from an Onerous Investigation 10
5. Avoidable Cases of TE 11
6. New Cases Occur in Brazil 11
7. The Use of Thalidomide Drug Products in Japan 12
8. One Hundred Years After the Birth of Dr. Lenz 12

III Mechanism of Thalidomide Embryopathy (TE) 16
1. About Drug Targets 16
2. Identifying Thalidomide's Target Molecule 16
   (1) Isolating and identifying thalidomide-binding proteins using affinity bead technology 16
   (2) Proving that CRBN is a TE target 17
3. Proving that CRBN is also a Target for the Anticancer Effects of Thalidomide 17
   (1) Second-generation thalidomide derivatives 17
   (2) The contribution of CRBN to the anticancer effects of thalidomide and other IMiDs 18
   (3) Optical isomers of thalidomide 18
   (4) Mechanism of the anticancer effects of thalidomide and other IMiDs 18
4. Research Leads to New CRBN Modulators 18
5. Mechanism of TE 19
   (1) Lessons learned from thalidomide's mechanism of the primary pharmacologic effect 19
   (2) Identification of p63, a new TE-related substrate 19
6. Conclusions 19

IV Diagnostic Procedures for Thalidomide Embryopathy (TE) 22
1. Introduction 22
2. New Claimers Around the World 22
3. Requirements for a Diagnosis of TE 23
4. Physical Manifestations of TE 24
   (1) Preaxial longitudinal hypoplasia 24
   (2) Symmetry and upper limb domination 25
   (3) Severity classifications for upper-limb hypoplasia 25
   (4) Lower-limb hypoplasia 25
   (5) Auditory hypoplasia 26
5. Diagnosing TE 26
6. New Claimers in Japan 27
7. Differentiating TE from SALL4-related Disorders 28
8. Is Embryopathy Genetically Heritable? 29

V Internal Medical Care

V-1 Managing Lifestyle Diseases 30
1. Lifestyle Diseases 30
   (1) Definition and concept of lifestyle diseases 30
   (2) Frequency of lifestyle diseases in patients with TE 30
2. Gallbladder Agenesis 32

V-2 Endocrine and Metabolic Disorders 34
1. Introduction 34
2. Lifestyle Diseases 34
3. Overweight 35
4. Hepatic Steatosis 35
5. Dyslipidemia 35
6. Abnormal Glucose Metabolism 35
7. Hyperuricemia 35
8. Chronic Kidney Disease 35
9. Osteoporosis 35
10. Endocrine and Metabolic Abnormalities 35

V-3 Kidney Disease, Hypertension, and Cardiovascular Disease 38
1. Chronic Kidney Disease (CKD) 38
   (1) Definition and concept of CKD 38
   (2) Diagnosing and scrutinizing CKD 38
   (3) Significance and progression of CKD 39
   (4) CKD-related findings from comprehensive medical examinations 39
2. Hypertension 39
   (1) Diagnosing hypertension 40
   (2) Measuring and evaluating blood pressure 40
   (3) More information about lower-limb blood pressure 40
   (4) Hypertension-related findings from comprehensive medical examinations 41
   (5) Treatment of hypertension 41
3. Cardiac Diseases 41
   (1) Congenital heart disorders 41
   (2) Ischemic heart disease and cardiac failure 41

V-4 Preventing Respiratory Diseases and Infections 44
1. Findings of Pulmonary Function Tests in 55-year-old Patients with TE 44
2. Preventing Respiratory Infections 45
3. Preventing Infectious Gastroenteritis 45
4. Commentary on Disinfection 46
5. The Importance of Smoking Cessation 46

V-5 Esophagogastroduodenoscopy (EGD) and Gastrointestinal Diseases 48
1. Status 48
2. Determining Patient Information 48
3. Observable Areas in EGD 48
4. Advantages and Disadvantages of Transoral and Transnasal Endoscopy and Route Selection 48
5. Sedation 49
6. Local Anesthesia 49
7. Informing the Patient before the Procedure 49
8. Endoscopic Pretreatment 49
9. Transnasal Insertion 49
10. Guidance 50
11. Diagnosis of helicobacter pylori (HP) Infections 50
12. Handling Epistaxis and Nose Pain from Transnasal Endoscopy 50
13. Findings 50

VI Orthopedic Surgery and Rehabilitation

VI-1 Diagnosis and Assessment/Testing 52
1. Congenital Musculoskeletal Malformations 52
2. Age-related Musculoskeletal Disorders 54

VI-2 Treatment and Support [1] Drug Therapy 56

VI-2 Treatment and Support [2] Surgery and Indications 57

VI-2 Treatment and Support [3] Properly Interacting with People with Thalidomide Embryopathy (TE): A Physical and Occupational Therapy Perspective 58
1. Introduction 58
2. Characteristics of Upper-limb Defects and Approaches to Guidance 58
3. Characteristics of Finger Defects and Approaches to Guidance 59
4. Characteristics of Auditory Defects and Approaches to Guidance 60
5. Conclusions 60

VI-2 Treatment and Support [4] Addressing Musculoskeletal Pain and Inconveniences in Daily Living Through an Ergonomic Approach 62
1. Introduction 62
2. Disabilities in Daily Activities due to Musculoskeletal Impairment by Upper-limb Hypoplasia 62
(1) Effects of shortened limbs 62
(2) Shoulder hypoplasia 62
(3) Hypoplasia of the upper-limb musculature 62
(4) Spinal column symptoms 63
(5) Wrist pain 63
3. Identifying Issues in Interviews 63
4. Ergonomic Remedies 63
5. Recommendations for Health Management 64
6. Conclusions 64

VII Radiological Examination and Evaluation 66
1. Preparing for Radiological Procedures 66
(1) Interviewing and informing the patient before the procedure 66
(2) Changing into gown and preparation 67
2-1 General Imaging: Chest X-rays 67
(1) Chest X-rays for TE patients with upper-limb hypoplasia 67
(2) Chest X-rays for TE patients with auditory hypoplasia 68
2-2 General Imaging: Bone Mineral Density (BMD) Analysis 68
(1) Definition of osteoporosis 68
(2) BMD analysis 68
(3) Characteristics of BMD in patients with TE 68
(4) Considerations for BMD analysis for patients with TE 69
2-3 General Imaging: Mammography 69
(1) Mammography 69
(2) Mammography imaging techniques for patients with TE 69
(3) Considerations for mammography for patients with TE 70
3. Computed Tomography (CT) 70
(1) Significance of CT 70
(2) Positioning 70
(3) Imaging protocol 70
4. Magnetic Resonance Imaging (MRI) 72
(1) Interviewing the patient before the procedure 72
(2) Informing the patient before the procedure 72
(3) Changing clothes and preparation 72
(4) During the procedure 73
5. Diagnostic Imaging: Tips and Warnings for Radiographic Evaluation 73
(1) MRI of head and sinuses 73
(2) Temporal bone CT: Evaluate the following on axial and coronal images 73
(3) Cervical vertebral CT: Evaluate the following with a focus on reconstructed sagittal images 73
(4) Trunk CT: Evaluate the following with a focus on axial images 73
(5) Presentation of scans 73

VIII Otolaryngology 78
1. Auditory Defects 78
(1) Outer ear malformations 78
(2) Middle ear malformations 78
(3) Inner ear malformations 78
2. Facial Nerve Palsy 79
3. Abducens Nerve Palsy 79
4. Vestibular Dysfunction 79
5. Orofacial Abnormalities 79
6. Other Comment 79
7. Relationship Between Otolaryngological Deformation and Limb Malformation 79
8. Other Considerations for Patient Care 79

IX Dentistry and Oral Surgery Examination 80
1. Oral Examination 80
(1) Teeth 80
(2) Tooth alignment 80
(3) Fillings, artificial teeth, and dental implants 80
(4) Periodontal tissues 81
(5) The tongue, lips, and oral mucosa 81
2. Jaw and Other Bone Disorders 81
(1) Jaw 81
(2) Temporomandibular joint 81

X Ophthalmologic Care 82
1. Introduction 82
2. Malformations of the Eyes and Their Symptoms 82
(1) Microphthalmos 82
(2) Uveal coloboma 83
(3) Congenital aniridia 83

XI Psychiatric Care 86
1. Psychiatric Issues in Patients with TE 86
2. Quality of Life (QOL) of Patients with TE 87
3. Tips for Caring for Patients with TE 87

XII Problems Encountered in Clinical Settings
XII-1 Blood Sampling 88
1. Blood Collection: Being Prepared 88
2. Technical Challenges of and Techniques for Collecting Blood 88
3. Blood Sampling Kits 89
XII-2 Measuring Blood Pressure 90
Measurement by Healthcare Professionals 90
1. Before Measuring Blood Pressure 90
2. Selecting a Site to Measure Blood Pressure 90
3. Cuff Placement on the Upper and Lower Limbs 90
4. Selecting the Appropriate Cuff Size (particularly relevant to patients with upper-limb hypoplasia) 90
5. Evaluating Lower-limb Systolic Blood Pressure 91
6. Evaluation When peripheral arterial disease (PAD) Is Suspected
7. Recommendations of a Overseas Expert on Blood Pressure Measurement 91
8. Other Information 91
Home-based Blood Pressure Measurement Procedures 91
XII-3 Surgery for Patients with Thalidomide Embryopathy (TE): Considerations for Perioperative Management 92
1. General Preoperative Issues 92
2. What Range of Preoperative Tests Is Possible? 92
3. Issues Facing Anesthesia and Intraoperative Management 92
(1) Measuring blood pressure and ensuring venous access 92
(2) Airway management and intubation 93
(3) Options other than general anesthesia 93
(4) Maintaining body positioning during surgery 93
4. Postoperative Management 93
XII-4 Nursing 94
1. Urinalysis 94
2. Abdominal Ultrasonography 94
3. Electrocardiography 94
4. Computed Tomography (CT) 94
5. Hearing Tests and Otolaryngology Examinations 94
6. Gynecological Examinations 95
7. Breast Surgery Examinations 95
8. Upper Gastrointestinal Endoscopy 95
9. Examinations and Nutritional Guidance 95
10. Others 95
XII-5 Information on Supporting Patients with Auditory Defects 96
Information on Hearing Aids 96
Smartphone Apps 96

XIII Care for Thalidomide Embryopathy (TE) in Germany 98
1. Dr. Becker Rhein-Sieg-Klinik 98
2. Thalidomide Clinic Hamburg 100

XIV Releted Information 102
1. Network of Healthcare Providers Serving Thalidomide Survivors 102
2. Website of the Thalidomide Embryopathy Research Group 102
3. Information on the Ishizue Foundation 102
4.Notable Sites for Information on Thalidomide Embryopathy Outside Japan 102

XV Index 104

List of Authors

Ryoji Kayamori	Department of Physicotherapeutics, Teikyo Heisei University, Tokyo, Japan
Takumi Ito	Department of Chemical Biology, Tokyo Medical University, Tokyo, Japan
Hiroshi Handa	Department of Chemical Biology, Tokyo Medical University, Tokyo, Japan
Yuki Yamaguchi	School of Life Science and Technology, Tokyo Institute of Technology, Kanagawa, Japan
Tomoko Shiga	Department of Complete Medical Checkup, Department of General Medicine, Tokyo Women's Medical University, Tokyo, Japan
Tetsuya Tagami	Center for Health Examination, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
Fumihiko Hinoshita	Department of Nephrology, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan
Hiroyuki Nagase	Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan
Nobuko Shima	Center for Health Examination, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
Takama Maekawa	Center for Health Examination, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
Nobuhiko Haga	Department of Rehabilitation Medicine, The University of Tokyo, Tokyo, Japan
Yasuhiro Maehara	Department of Anesthesiology and Pain Clinic, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan
Takeshi Kobayashi	Department of Rehabilitation : Occupational Therapy Course, Nihon Institute of Medical Science, Saitama, Japan
Junko Fujitani	Department of Rehabilitation, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan
Hiroji Tsujimura	Division of Occupational and Environmental Health, Department of Social Medicine, Shiga University of Medical Science, Shiga, Japan
Shin-ichi Shirahoshi	Department of Physical Therapy, Bukkyo University, Kyoto, Japan
Azusa Minagawa	Radiological Physics and Technology Department, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan
Masafumi Shinozaki	Radiological Physics and Technology Department, National Cancer Center Hospital East, Chiba, Japan

Jun Harada	Radiological Physics and Technology Department, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan
Tsuyoshi Tajima	Department of Radiology, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan
Niro Tayama	Department of Otorhinolaryngology, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Yutaka Maruoka	Department of Oral and Maxillofacial Surgery, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Miyuki Nagahara	Department of Ophthalmology, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
On Kato	Department of Psychiatry, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Ken Otomo	Department of Psychiatry, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Hanae Sone	Department of Psychiatry, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Yuki Nakano	Department of Psychiatry, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Keiko Tanaka	Nursing Department, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan
Chika Kuge	Nursing Department, Center Hospital of the National Center for Global Health and Medicine Hospital, Tokyo, Japan

Editor

Fumihiko Hinoshita	Head, The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan

* Note: This Guide was created under the FY2020 Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Health Labour Sciences Research Grants (under the title of "The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan"). We express our gratitude to Ms. Chiharu Matsuoka for providing editing services for this Guide and to Ms. Chikako Toyota for doing office work of the research group.

I Introduction

The marketing of the over-the-counter thalidomide drug Contergan® by a German pharmaceutical company, Grünenthal, in 1957 was soon followed in 1958 and beyond by countless children with congenital limb defects being born to mothers who had taken Contergan while pregnant. Products containing thalidomide, the same active ingredient found in Contergan, were marketed in Japan and many other countries worldwide. Again, countless children with thalidomide-induced disorders (e.g., congenital limb defects, auditory defects, facial abnormalities) were born until several years thereafter. The German pediatrician, Dr. Widukind Lenz, eventually identified the cause of these unexplained disorders as drug-induced events caused by thalidomide taken by pregnant women, sending a shockwave across the world. Thalidomide embryopathy (TE) raised the issue of responsibility in many countries, substantially affecting drug development and regulation thereafter.

The recall of thalidomide in Japan began in 1962, and almost all over-the-counter thalidomide products had been recalled by 1963, but not before several hundred children with TE had been born. The Ministry of Health and Welfare of Japan officially recognized 309 cases at the time. The victims born bearing these disorders are now around 60 years of age. In addition to the orthopedic and auditory defects they've had to face since childhood, they must now deal with secondary consequences such as overuse syndrome, lifestyle diseases (e.g., hypertension, obesity, hepatic steatosis, dyslipidemia, chronic kidney disease), and psychiatric issues. Thalidomide victims are developing a wide range of clinical manifestations added to the direct impact of their congenital conditions.

To address the wide range of clinical manifestations of thalidomide victims, the Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-impaired People in Japan published the "Guide for the Management of Thalidomide Embryopathy 2017" in the year 2017, preparing an English translation the following year. In April 2017, the Research Group was renewed and became The Research Group on Grasping the Health and Living Situation as well as Creating the Support Infrastructure for Thalidomide-Impaired People in Japan. Now with more investigators, the Research Group is committed to continuing to perform its activities. The Research Group revised the "Guide for the Management of Thalidomide Embryopathy 2017" on the basis of its achievements over the past 3 years, publishing the "Guide for the Management of Thalidomide Embryopathy 2020" in Japanese. Although the initial 2017 version provided comprehensive information on almost all relevant fields, this revision offers updated information and includes the exploration of new areas such as ergonomics and the mechanisms responsible for TE. Please consult this guide to learn about the latest findings on TE so that you can confidently provide medical and nursing care, rehabilitation services, and other care for victims. The English version of this guide was translated into English almost half a year after the original publication in Japanese.

I believe this new guide could be considered an up-to-date standard English TE textbook for Japan and other countries around the world. I am convinced that it will benefit doctors, nurses, and other healthcare professionals, as well as researchers, bureaucrats, and others involved with TE.

March 1, 2021

Fumihiko Hinoshita,
Head,
The Research Group on Grasping the Health and Living Situation as well as
Creating the Support Infrastructure for Thalidomide-Impaired People in Japan
Department of Nephrology, Center Hospital of the National Center for
Global Health and Medicine

II History and Overview of Thalidomide Embryopathy (TE)



- TE was the first drug-induced tragedy with a global reach.
- This chapter briefly discusses the onset and course of thalidomide-induced injuries in West Germany and Japan.
- Thalidomide is a shortened form of α-phthal-imido-glutarimide, the true name of the compound.
- Brand names include Contergan® (West Germany), Distaval® (UK), and Isomin® and Proban M® (Japan).
- West Germany and other Western countries revoked marketing authorization and issued recalls through the end of 1961. Japan followed suit in September 1962. Avoidable cases of TE occurred during this 10-month lag.
- The withdrawal of thalidomide from the market stopped more cases of TE, demonstrating the importance of epidemiological investigations and academic scrutiny.
- New cases have been reported in Brazil since 1965.
- Thalidomide is currently used in Japan to treat other diseases.
- Dr. Lenz would have celebrated his 100th birthday in 2019.

1 The Advent and Efficacy Profile of Thalidomide

Thalidomide was first synthesized as a derivative of glutamic acid by the Swiss pharmaceutical company CIBA in 1953 (Figure 1). Identifying no pharmacological effects, CIBA abandoned further research. Dr. Heinrich Mückter, the chief scientist at Grünenthal (a pharmaceutical company in Stolberg, West Germany), synthesized thalidomide in 1954 and then resumed development. Thalidomide was originally marketed as an antiepileptic drug, but was not very effective for this indication. Thalidomide did, however, have a powerful sedative and hypnotic effect, and was marketed as a hypnotic and antianxiety drug beginning in October 1957 under the brand name Contergan®. The drug's effect as a hypnotic was fast-acting and produced no hangover. Since thalidomide could not be used to commit suicide because it was not fatal, even in large doses, it became a drug of West Germany, available without prescription. It became the most popular hypnotic, gaining widespread acceptance in hospitals and psychiatric institutions. With its excellent safety and efficacy profiles, thalidomide became used as a sleep medication in electroencephalography in children as well as a "drug cradle" for nighttime crying. Thalidomide was even known as "cinema juice" because some parents gave it in liquid form to their children before going out at night to see a movie. Through affiliates around the world, thalidomide was immediately marketed in 11 countries in Europe, 7 in Africa, 17 in Asia, and 11 in the Western Hemisphere, but notably not in the United States.

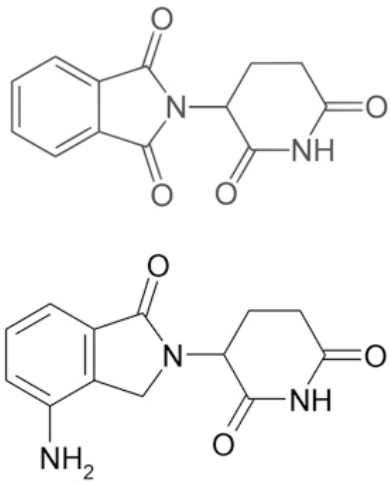


Figure 1 Chemical formula of thalidomide
The upper formula shows thalidomide, a shortened form of α-phthal-imido-glutarimide.
The lower formula shows lenalidomide, a compound now used in the treatment of multiple myeloma



Thalidomide, embryopathy, Grünental, Contergan, Distaval, Isomin, Carl Schulte-Hillen, Widukind Lenz, new cases in Brazil

In Japan, a researcher at Dainippon Pharmaceutical Co., Ltd., inspired after reading an article written by Grünenthal's Dr. Mückter in a pharmacology journal, independently developed a different process for synthesizing thalidomide. Under Japanese law then, patents were granted for drug manufacturing processes but not for drugs and other substances. This led to a legal dispute between Dainippon Pharmaceutical and Grünenthal that continued until the thalidomide tragedy emerged.

Dainippon Pharmaceutical filed for a patent in November 1956 and began clinical study around March 1957. The company submitted an application for manufacturing approval to the then Ministry of Health and Welfare in August 1957 and released the drug under the brand name Isomin® in January 1958. Dainippon Pharmaceutical offered Isomin® as 25-mg tablets and a powder containing 10 mg per gram. In newspapers and on television, the company widely touted the effectiveness of thalidomide in insomnia and sedation before operations or for anxiety, claiming that it was safe and harmless even in pregnant women and children. In 1960, Dainippon Pharmaceutical began marketing Proban M®, a combination drug containing 6 mg of thalidomide and 7.5 mg of propantheline bromide for the treatment of excess stomach acid, gastritis, and peptic ulcers.

Thalidomide was sold under different brand names in different countries. Adding to this complexity were various branded combination drug products that paired thalidomide with other active ingredients. Examples include Softenon® sold in West Germany and other locations in Western Europe, Distaval® sold in the UK, Neurosedyn® marketed in Sweden, and Kevadon® and Talimol® sold in Canada. Combination drug products included Grippex® (gripp means cold), Algosediv® (algo means pain, sediv means sedation), Enterosediv® (entero means intestines), Noctosediv® (nocto means night), Valgraine® (for migraine headaches), Asmaval® (for asthma), Tensival® (tens means tension), Valgis®, and Peracon®. Several other combination products in addition to Isomin® and Proban M® were available in Japan. These included the combination products Glutanon®, Porbren®, Sanodolmin®, New Nifrol®, Sleeban®, New Night S®, and Nelufanan®. This wide availability of thalidomide drugs meant that despite warnings of thalidomide teratology issued in West Germany in November 1961 and worldwide coverage of this by news outlets, including United Press International, many doctors throughout the world were convinced that this news was unrelated to the drugs they were prescribing. The general population, too, continued taking thalidomide-containing drugs, unaware they were using thalidomide.

2 Side Effects Begin to Appear

A large-scale campaign focusing on pediatricians and gerontologists was launched under a massive advertising push waged from 1957 to 1958. Advertisers repeatedly advised doctors to use thalidomide for their patients with diabetes and liver disease. Under Grünenthal's advertising blitz, thalidomide use increased in all areas of medicine and across all age groups. Acting on Dr. Mückter's guidance, medical representatives repeatedly insisted to doctors that thalidomide was flawless, claiming that the ongoing use of thalidomide by patients did not need to be managed by doctors in hospitals. These actions magnified the risks from using this new drug, as side effects became increasingly overlooked by doctors who were not examining their patients enough.

With the surge in Contergan sales in 1959 came increasing criticism. Constipation, dizziness, hypotension, amnesia, and other events were reported. Grünenthal, however, tried to ignore the side effects as much as possible, attributing them to overuse or long-term use. The company remained steadfast in its denials, telling reporters that it had never heard of the side effects they were mentioning.

In December 1960, a letter titled "Is Thalidomide to Blame?" appeared in the correspondence section of the *British Medical Journal*[3]. The letter reported four patients who had taken thalidomide for 18–24 months. The author stated that the patients complained of (1) marked paraesthesia of the hands and feet, (2) coldness of the extremities and marked pallor of the toes and fingers on exposure to cold, (3) slight ataxia, and (4) nocturnal cramps in the legs. These side effects improved but still remained with discontinuation, the author continued. Strangely enough, the author ends the letter by stating, "I might add that I have found it otherwise to be a most effective hypnotic with no 'morning hangover' effect. It has been especially useful in patients with skin pruritus and discomfort."

But much worse news was yet to come. These reports of axonal degeneration-type polyneuropathy were just the who took thalidomide during early pregnancy.

In 1960, Drs. Kosenow and Pfeiffer in the Department of Pediatrics at the Univeristy of Münster, presented on two babies with short limbs, facial hemangioma, and duodenal stenosis, which had rarely been reported, at a local meeting of the German Society of Pediatrics. (The university, officially called "Westfälische Wilhelms-Universität," is the largest university in Germany and is commonly referred to as the University of Munster.) In 1961, Dr. Wiedemann, a professor at the Children's Hospital, University of Kiel, reported that over the last 10 months, nine children had been born with phocomelia or amelia at his hospital, in addition to 80 similar cases in 12 other cities[4]. A paper published in 1962 was truly exceptional and shocking with its presentation of the photographs of 33 thalidomide babies, which strongly conveyed the unfolding tragedy. This carried enough weight to establish

this condition as Wiedemann Syndrome until thalidomide could later be identified as the cause of embryopathy. From 1960 to 1961, the cause of all these previously unseen deformities remained a mystery.

3 The Thalidomide Saga

The first chapter of the thalidomide saga begins on June 23, 1961, when the lawyer Carl Schulte-Hillen approached the pediatrician Widukind Lenz of the University of Hamburg about the lawyer's son. Schulte-Hillen practiced in Hamburg but lived in a small town called Minden near Munster. On March 15, 1961, he visited his sister, who had recently given birth. He visited alone because his wife, who was herself in the last month of pregnancy, did not want to travel. Shocking news awaited him. His newborn niece had arms that extended only to the elbows, and her hands had only three fingers. His son, born 6 weeks thereafter, on April 25, 1961, had the same deformities: short arms, deficient radius, and hands with only three fingers. He wondered if his family may have had some sort of genetic disease but was unconvinced about that hypothesis after finding nothing in his son's family tree. Possibly some shared external factor could be responsible. Mrs. Schulte-Hillen was of fine health, and the pregnancy had gone normally, requiring no medical care. Her husband desired to know why this had happened, but received no satisfactory answers from nearby doctors. This is why he decided to approach Dr. Lenz at the University of Hamburg. Lenz, listening carefully and showing sympathy with Schulte-Hillen, promised to seek the cause.

Was it true that Mrs. Schulte-Hillen had taken no drugs during her pregnancy as reported? Revisiting her pregnancy, she remembered an event she had previously dismissed as unrelated. Following the sudden death of her father in August 1960, she visited a neighborhood pharmacy, seeking a sedative to calm her nerves. She was given Contergan and took two tablets. That dose, albeit small, was enough to disfigure her child.

In August 2016, some of the Guide authors on the Thalidomide Research Group saw Jan, the son, again for the first time in a year (Figure 2). Jan lives in the suburbs of München, Germany but works as an emergency physician in a hospital in Lucerne, Switzerland. He told us that his father had mild dementia but was otherwise healthy. Jan later contacted us on January 14, 2017 to tell us that his father Carl had died (Figure 3).

4 Lenz's Warning Emerges from an Onerous Investigation

Few people can remember the drugs they took several years ago. That is what made Lenz's investigation so onerous. He reported his suspicions to Professors Kosenow and Wiedemann on November 13, 1961. On November 15, Lenz called Dr. Mückter at Grünenthal to report he believed that thalidomide was related to the recent increase in births with deformities. This became known later as Lenz's warning. He said that a drug used by the masses appears to be the cause of deformities, but that there was not yet sufficient proof. Lenz added that prescription records in hospitals and drugs used in homes would have to be investigated. He proceeded to state his personal opinion that the drug should be immediately withdrawn until its harmlessness could be demonstrated. "Every month's delay in clarification," he added in conclusion, "means that 50 to 100 children with horrible deformities will be born."



Figure 2 Dr. Jan Schulte-Hillen and his wife


In ihm sei's begonnen, der Monde und Sonnen
an blauen Gezelten des Himmels bewegt.
Du, Vater, du rate! Lenke du und wende!
Herr, dir in die Hände sei Anfang und Ende
sei alles gelegt!

Lieber Carl, lieber Vater und Großvater, Schwiegervater,
Bruder, Schwager, Onkel und Freund,
ein langer Weg ist nun zu Ende.
Deinen letzten Kampf, den gegen Alzheimer, hast Du verloren,
deine anderen Kämpfe, in denen Du Tausenden zu Gerechtigkeit verholfen hast,
bleiben unvergessen.

Carl-Hermann Schulte-Hillen

* 28.3.1929 † 14.1.2017

Wir denken mit Liebe und Hochachtung an Dich:
Linde Schulte-Hillen
Jan und Iris mit Hagen und Ruben
Sven und Vicky mit Daniel und Lina
Catrin und Jean-Clément mit Gaspard und Jeannot
Lea-Anne mit Alexandre, Gabriel und William
Polly und Nanni

57072 Siegen, Gustav von Mevissen Straße 71, den 17. Januar 2017

Die Trauerfeier findet Donnerstag, den 19. Januar 2017 um 11.00 Uhr in der Martinskirche in Siegen, Grabenstraße 27, 57072 Siegen statt.

Die Beisetzung erfolgt später im Familiengrab in Hamburg im engsten Familienkreis.

Figure 3 A notice of the death of Mr. Carl Hermann Schulte-Hillen

On November 24, representatives of Grünenthal met with Lenz in the Ministry of the Interior of the State of North Rhine-Westphalia. On November 25, the international press erroneously reported that the decision had been made to withdraw thalidomide from the market. This was soon retracted, but not before it was reported by newspapers worldwide. Headlines in November 26 German newspapers read, "Drug-induced deformities: Suspicions fall on a drug marketed worldwide." Similar headlines appeared in newspapers throughout Europe.

5 Avoidable Cases of TE

Marketing authorization for thalidomide was withdrawn and a recall took place in West Germany on November 27, 1961. Northern European countries followed suit on November 30, the UK on December 2, and Sweden, somewhat later, on December 18.

UPI reported news about TE in Japan on November 27. The drug, however, was referred to mostly as thalidomide, the name of the active ingredient, rather than the brand names Isomin® or Proban M®, which were more familiar to the public. Many doctors failed to notice the relationship. Tokujiro Miyatake was then the President of Dainippon Pharmaceutical. He wrote a letter to tell distributors that although the company would stop shipments, sales should continue. (Tokujiro Miyatake would go on to become a very active director in the Ishizue Foundation, a welfare foundation supporting thalidomide victims.)

Tadashi Kajii, an instructor in the Department of Pediatrics at Hokkaido University, wrote a short report on seven cases that appeared in the *Japanese Pediatric Journal* in 1962 and the British medical journal the Lancet in March 1963[5]. This information was presented at a Sapporo regional meeting of the Japan Pediatric Society on August 26, 1962. An article on this presentation ran in the *Yomiuri* the following day and was then picked up by other media outlets. Dainippon Pharmaceutical decided to withdraw the drug on September 13, a whole 295 days after the West German recall and 274 days (9 months) after recalls in other European countries. The recall, moreover, did not end until mid- to late 1963, almost 2 years later than the West German recall. After Lenz reported on thalidomide's teratogenic effects, more than 100 children were born in Japan to women who had taken the drug.

No new cases of TE occurred after market withdrawal and the recall (Figure 4). This proved the thalidomide theory, demonstrating the importance of epidemiological investigations and academic scrutiny.

6 New Cases Occur in Brazil

In a report from the Estudo Colaborativo Latino-Americano de Malformações Congênitas (Latin American Collaborative Study of Congenital Malformations) in Brazil[6], Castilla and others reported in 1996 that 34 patients with TE had been registered since 1965. All cases occurred in areas where leprosy was prevalent. It so happens that 1965 was the year when the Israeli Jacob Sheskin informed the world that leprosy patients with insomnia from nighttime itchiness achieved a miraculous resolution of lesions 48 hours after taking thalidomide[7]. (Leprosy is now called Hansen's disease in Japan, but is still sometimes referred to as leprosy in English-speaking countries. Many do not realize that leprosy and Hansen's disease are synonymous.) Thalidomide was subsequently placed back on the market in Brazil. The United States Food and Drug Administration (FDA) allowed the use of thalidomide for patients with leprosy in 1998 and those with multiple myeloma (MM) in 1999.

In 2007, a decade after Castilla's paper, Schüler-Faccini reported that three cases of TE had occurred in Brazil since 2005[8]. Noting that these cases had not been registered through a systematic surveillance system, Schüler-Faccini speculates that the occurrence of TE is as common as it was 10 years ago in the northern Amazonian region of Brazil, where surveillance systems do not reach and poverty and illiteracy run high[9].

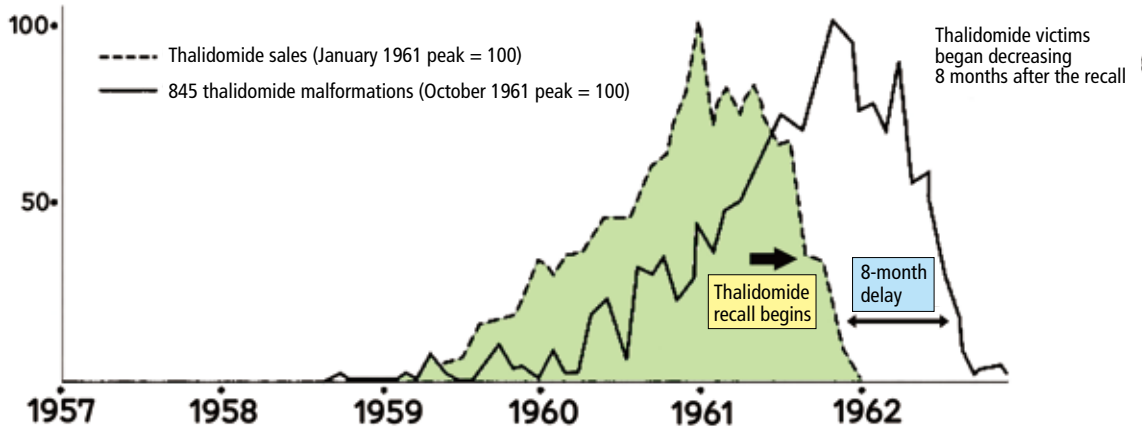


Figure 4 Thalidomide sales and the incidence of thalidomide malformations
Nilsson R, Sjöström H: Thalidomide and the Power of the Drug Companies, Penguin Books, UK Ltd., 1972.

7 The Use of Thalidomide Drug Products in Japan

Japan's Ministry of Health, Labour and Welfare approved the use of thalidomide as an insurance-covered drug for erythema nodosum leprosum (ENL) and MM in 2008. From 1993 to 2009, there were 215 patients with leprosy in Japan, among whom, 19 had ENL eligible for insurance coverage, and only five used thalidomide. A survey of 13 medical institutions from 2005 to 2009 found that 13 of the 15 patients with ENL treated with thalidomide (87%) responded to treatment and that the other two remained on treatment[10].

Multiple myeloma, the other disease treated with thalidomide, begins increasing in the fifth decade of life. The number of people with MM in 2014[URL1] amounted to 3,488 men and 3,075 women. The number in those in their 70s or 80s was 2,240 (64%) for men and 2,076 (68%) for women. Thalidomide as an immunomodulator is available as three drug products: lenalidomide (Revlimid®: taken as a once-daily 25-mg oral dose for 21 days followed by 7 off-treatment days; 46,697.5 yen/day, 11.76 million yen/year), pomalidomide (Pomalyst®: taken as a once-daily 4-mg oral dose for 21 days followed by 7 off-treatment days; 60,548 yen/day, 15.26 million yen/year), and thalidomide (Thaled®: 100 mg/day; 6,758.1 yen/day, 2.44 million yen/year, not to exceed 400 mg/day). Celgene markets the first two drug products, and Fujimoto Pharmaceutical markets Thaled®. RevMate® (procedures for the proper control of Revlimid®/Pomalyst®) and the Thalidomide Education and Risk Management System (TERMS®) were established to prevent TE. Those using these drugs, however, find the control procedures strict and difficult to follow. The procedures, moreover, are gradually becoming more lax. When the cost of drugs, specialist visits, and tests are included, the treatment of MM costs around 20 million yen a year, since drugs other than these thalidomide products must also be used, the disease is rarely cured and the drugs are taken for an extended time. Health budgets are becoming strained as the number of patients grows. Since MM often occurs in those aged 70 years or older, some die alone or in a care facility. TERMS® and RevMate® are revised to specify how remaining medication should be handled.

8 One Hundred Years After the Birth of Dr. Lenz

Widukind Lenz, a central character in the thalidomide saga who was dubbed the "Father of Thalidomide Victims," would have turned 100 in 2019. His life is described in this section. Lenz was born in Eichenau in the state of Bayern on February 4, 1919, just 3 months after the defeat of Germany in World War I. His father, Fritz Lenz, was a eugenicist and Germany's leading proponent of *rassenhygiene*, or racial hygiene. During the Nazi era, Fritz's teachings were used to claim the superiority of the "master race" on genetic grounds. When naming his son, Fritz surely had in mind Widukind von Sachsen, the chief enemy of the Frankish king Charlemagne (Charles the Great, 742–814). Beginning in 772, Charlemagne launched more than 10 campaigns in an attempt to conquer the Sachsens, a Germanic tribe in northern Germany, finally forcing their leader Widukind to surrender in 785. Had Fritz named his son after this hero with the hope that he could save Germany following its defeat?

Widukind Lenz graduated from Universität Greifswald (founded in 1456) in 1942. In 1943, he completed his doctoral thesis, titled "Changes in human growth of today," passed the summer doctor's examination, and was assigned to an air-force hospital in Germany. In 1944, he was transferred to a Luftwaffe hospital in France as a commissioned medical officer in an airborne artillery unit. Lenz was captured by the Allied Forces in October 1944 and lived in a prisoner-of-war camp in the UK until his release in May 1948. After working in the fields of biochemistry in Göttingen and medicine at Kiel University, he served as a pediatrician at the University of Hamburg (Universitätsklinikum Hamburg-Eppendorf, UKE) from 1952 to 1961. Hamburg was in a sense the starting point of the thalidomide saga. It was there that the lawyer Carl Schulte-Hillen approached Lenz on June 22, 1961 to investigate the cause of the short-arm deformities in his son Jan, who was born on April 25, 1961. (At the time, Lenz was an instructor of pediatrics at the University of Hamburg.) Responding to Lenz's warning in November 1961, thalidomide manufacturer Grünenthal and the UK and Australian marketer Distillers recalled the drug, helping to wrap up the TE epidemic. This paved the way for epidemiology to be established as an academic discipline. Lenz's warning, however, prompted the pharmaceutical company to use his father's involvement in racial hygiene during the Nazi era to libel and slander him and the head professor at his university to warn him that he would find himself on the receiving end if he pushed too hard. That year, Lenz was promoted to Professor of Human Genetics of the newly established UKE and subsequently became the director of the Institute of Human Genetics at the University of Münster in 1965.

While Hamburg may have been the starting point of the thalidomide saga, Münster was where it concluded, for it was there that Lenz raised the profile of the epidemic through teratological and genetic investigations and thalidomide lawsuits around the world were most active. At the university there, the pediatrician Dr. Kosenow and the human geneticist Dr. Degenhard reported the first case of what was called Wiedemann Syndrome in 1960, when the cause of TE was still unknown. (Hans-Rudolf Wiedemann was a professor of pediatrics at Christian-Albrechts-University in Kiel). The university is a leading university in the state of Nordrhein-Westfalen, which is also home to the city of Aachen. (Aachen is known for its spas left over from the days of the Roman Empire.) The king Charlemagne frequently visited, spending his final days there. He is buried in Aachen Cathedral. For a time, Roman emperors were coronated in Aachen Cathedral.) Aachen is home to the headquarters of thalidomide manufacturer Grünenthal. (The company was

founded in 1946 and is a global leader in the field of sedatives such as tramadol hydrochloride.) More babies with TE were born in Nordrhein-Westfalen than anywhere else. In 1988, Jan graduated from the university and was awarded his PhD in 1991. The 2016 documentary "No Limits: The Thalidomide Saga" by Oscar-winning filmmaker John Zaritsky presents the lives of TE victims in Germany, the UK, Canada, Belgium, and Australia. In the movie, the free-spirited lifestyle of Jan, who was raised by amazing parents, truly stands out. The movie also tells of the murder of the TE victim Corinne, who was born into the Belgian aristocratic Vandeput family only to be given an overdose of phenobarbital in her milk at the age of 7 days. The movie "Mercy Gets the Verdict" tells of the acquittal of the doctor who prescribed the phenobarbital, the beautiful young mother, and the family. Dr. Mückter, who synthesized thalidomide, is portrayed as a doctor of the Nazis and a villain.

Witness statements in the first trial began in 1965 in Sweden. In Germany, the investigation concluded in September 1965, and the final inquiries began in August 1966. The trial was scheduled to take place in Aachen municipal court on April 12, 1967, but, because the classical building was too small, was moved to the brass-mine entertainment complex in Alsdorf, where it began on August 12, 1968. In the trial, Lenz remained unperturbed by and steadfast in the face of 12 days of counterarguments and snide remarks about his incompetence and untrustworthiness by 18 opposing lawyers. He patiently and calmly repeated the facts he had observed. His cool and calm demeanor deeply impressed all present. The August 31 issue of the *Westfälische Nachrichten* newspaper (Figure 5) reported, "There was only person in Alsdorf who didn't lose their self-control, only one person who kept their ascetic calm in the face of numerous provocative questions and caustic remarks about their knowledge and insults about the futility of their approach, and that person was Professor Lenz. He courteously answered each and every question（Figure5）.

In his first trip to Japan, Lenz visited to attend a by-invitation lecture of the International Pediatric Association in November 1965. He was already a central figure in the debate surrounding TE at the time. He remarked, "When I arrived in Japan, I first visited Sengakuji Temple in Takanawa to see the Graves of the 47 Ronin because I wanted to know about the Japanese way of thinking." In the Japanese reconciliation trials from 1963 to 1974, he visited Japan six times to participate in the TE certification project of the Ministry of Health and Welfare and gave statements in court, including 11 times as a thalidomide trial witness in the Tokyo District Court in 1971. Lenz visited Japan for the eighth time in May 1992 at the invitation of Ishizue, a group that had been agreed to be established under a memorandum from the 1974 reconciliation (Figure 6). (The group was originally a gathering of affected parents but is now a public interest incorporated foundation run by thalidomide victims.) He toured the Okura Shukokan, an art museum on the



Figure 5 Dr. Lenz in Alsdorf

premises of the Hotel Okura, and the Archaeology Gallery of Tokyo National Museum in Ueno, Tokyo. Lenz died of liver cancer on February 25, 1995. He replied to all of the letters he received from Japanese children with TE (Figure 7). In a New Year's card he sent to a TE victim in January 1995, he wrote, "It was with great shock that I watched on my television the terrible earthquake that struck Kobe and Osaka. Having turned 75, I was ailing from kidney stones and other conditions, but I am gradually recovering." His March 4, 1995 funeral announcement encouraged attendees to refrain from giving flowers and instead send them to the new TE victims in Brazil (Figure 8).



Figure 6 Dr. Lenz and his wife
during their visit to Japan in May 1992

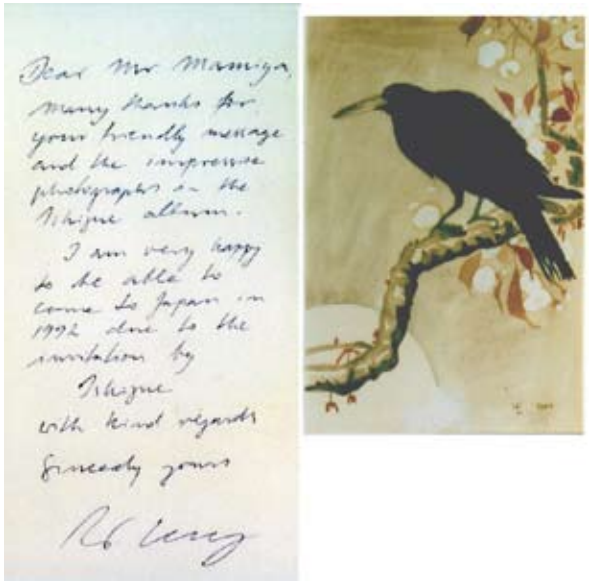
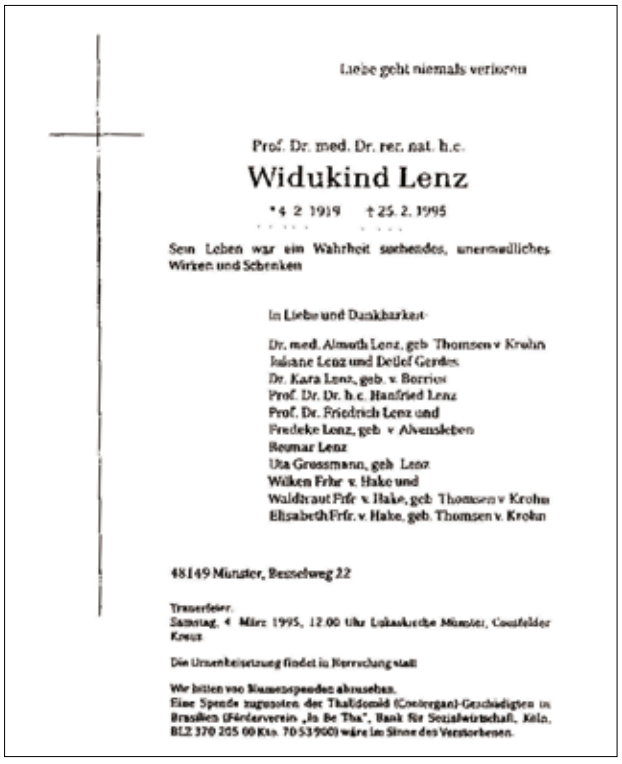


Figure 7 A postcard handwritten by Dr. Lenz


Liebe geht niemals verloren

Prof. Dr. med. Dr. rer. nat. h.c.

Widukind Lenz

* 4. 2. 1919 † 25. 2. 1995

Sein Leben war ein Wahrheit suchendes, unermüdliches Wirken und Schenken

In Liebe und Dankbarkeit

Dr. med. Almuth Lenz, geb. Thomsen v. Krohn
Juliane Lenz und Detlef Gerdes
Dr. Kara Lenz, geb. v. Borries
Prof. Dr. Dr. h.c. Hanfried Lenz
Prof. Dr. Friedrich Lenz und
Fredeke Lenz, geb. v. Alvensleben
Reimar Lenz
Uta Grossmann, geb. Lenz
Wilken Frhr. v. Hake und
Waldtraut Frfr. v. Hake, geb. Thomsen v. Krohn
Elisabeth Frfr. v. Hake, geb. Thomsen v. Krohn

48149 Münster, Besselweg 22

Trauerfeier:
Samstag, 4. März 1995, 12.00 Uhr Lukaskirche Münster, Coerdelder Kreuz

Die Urnenbeisetzung findet in Norderney statt

Wir bitten von Blumenspenden abzusehen.
Eine Spende zugunsten der Thalidomid (Contergan)-Geschädigten in Brasilien (Förderverein „Ju Be Tha", Bank für Sozialwirtschaft, Köln, BLZ 370 205 00 Kto. 70 53 900) wäre im Sinne des Verstorbenen.

Figure 8 The funeral announcement of Dr. Lenz
The text at the bottom urges attendees to send a donation to a bank account in Cologne for a group of thalidomide victims in Brazil in lieu of flowers.

Reference

1) Kayamori R: Medical trajectories of Thalidomide. Nishimura-shoten,Tokyo,Japan.2013 (in Japanese).
2) Kayamori R: The thalidomide saga. Ishiyaku Publishers, Tokyo,Japan,1997 (in Japanese)
3) Florence AL: Is thalidomide to blame?. Br. Med. J 1960 Dec 31; 2(5217): 1954
4) Wiedemann, HR and Aeissen, K: Zur Frage der derzeitigen Häufung von Gliedmaßen Fehbildungen. Med Mschr 12;816-818,1961
5) Kajii T, Shinohara M; Thalidomide in Japan. Lancet 1963 Mar 2; 1(7279): 501-2.
6) Castilla EE, et al. Thalidomide, a current teratogen in South America. Teratology 54:273-7, 1996
7) Sheskin J. Thalidomide in the treatment of lepra reaction. Clin Pharmacol Therapeutics 6:303-306, 1965
8) Schüler-Faccini L, et al. New cases of thalidomide embryopathy in Brazil. Birth Defects Res A Clin Mol Teratol 79:671-2, 2007
9) Schüler-Faccini L. Thalidomide in Brazil-Recent experience, The 2nd International Symposium on Thalidomide Embryopathy, Sola City Conference Center, Tokyo, Japan, on July 14-15,2019.
10) Ishii N: For adaptation of thalidomide to leprosy erythema nodosum. Jpn J Lepr 78: 275-279, 2010 (in Japanese)

URL

Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan
https://ganjoho.jp/reg_stat/statistics/stat/summary.html

[Ryoji Kayamori]

III Mechanism of Thalidomide Embryopathy (TE)



- Cereblon (CRBN) is an intracellular target associated with the teratogenic and anticancer effects of thalidomide.
- The S and R forms of thalidomide have different binding affinities for CRBN. The difference in efficacy between the S and R forms appears to be attributable to the difference in affinity.
- CRBN combines with DDB1 and other proteins to form E3 ubiquitin (Ub)-ligase complex, which functions as a substrate receptor.
- Thalidomide and thalidomide derivatives, including lenalidomide and pomalidomide, produce their effects by binding to CRBN to alter its substrate specificity and thereby induce the ubiquitination and degradation of new substrates.
- The CRBN substrate p63, a member of the p53 transcription factor family, contributes to TE.
- The degradation of p63 isoform ΔNp63α appears to contribute to limb malformations in TE, with the degradation of the isoform TAp63α contributing to ear malformations.

1 About Drug Targets

Most drugs derive their effects by binding to a specific target protein in the body to alter its function. Characterizing drug targets helps lead to an understanding of the biological reactions in which the target is involved, and how to regulate those reactions, informing the life sciences. This process also opens new avenues in drug discovery. The presence of several hundred thousand different proteins in the human body, however, made isolating and identifying actual targets extremely difficult. Through more than two decades of research, we successfully developed nano-sized ferrite-glycidyl methacrylate (FG) beads to simplify this process[1–4]. Using FG beads with drug molecules secured to their surface, we established a technology for the one-step affinity purification of drug-bound proteins that include the target from a protein library and a technology to isolate the target. FG beads were well received both inside and outside of Japan, and commercial production was started to meet the demand.

2 Identifying Thalidomide's Target Molecule

(1) Isolating and identifying thalidomide-binding proteins using affinity bead technology

We previously identified the targets of over 20 drugs and other small-molecule compounds, characterizing the regulatory mechanisms and networks of the biological reactions in which these targets are involved. Our work includes the discovery of CRBN, the target in TE (Figure 1), which had remained elusive for over half a century[5]. Our findings, which are documented in a research article in a 2010 issue of *Science*, were widely covered by the media both in Japan and abroad.

Marketed as a hypnotic in 1957, thalidomide was soon found to cause phocomelia and other forms of embryopathy in the offspring of women who took the drug during pregnancy. It was almost completely withdrawn from the market around 1962. Three decades later, however, it was reintroduced after investigators discovered it was effective in treating the refractory condition leprosy and the hematologic cancer, multiple myeloma (MM). The diverse pharmacological actions of thalidomide, which include early developmental inhibition (embryopathy) and anticancer effects, caught our attention. Thalidomide's mechanism of action was not known when we began researching the drug. After deciding that isolating and iden-



Thalidomide, FG beads, ubiquitin, substrate, cereblon, zebrafish, p63, CRBN modulator, chemical biology

tifying the direct target of thalidomide's actions would be the best way to unlock its mechanisms, we embarked on attempts to purify and identify proteins that thalidomide specifically binds using thalidomide-immobilized FG beads.

First, thalidomide-immobilized FG beads were combined with cell lysate (the protein library). The mixture was allowed to react for 2 hours and thoroughly washed. This resulted in the isolation of two proteins that bound specifically to the thalidomide on the beads. Mass spectrometry showed these proteins to be CRBN and DNA damage-binding protein 1 (DDB1). We used recombinant proteins in the next step of our research, finding that CRBN binds directly to thalidomide, but that DDB1 binds only indirectly to thalidomide via CRBN[5]. We also determined that CRBN combines with DDB1 and other proteins to form E3 Ub-ligase complex, which is involved in protein degradation pathways. CRBN functions as a substrate receptor, binding selectively to substrate proteins to undergo ubiquitination[5].

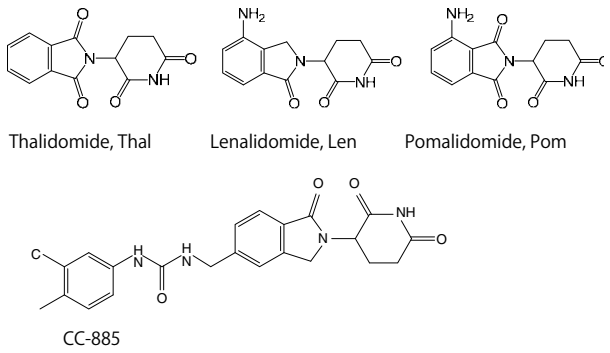


Figure 1 Molecular structures of thalidomide and thalidomide derivatives

Thalidomide derivatives lenalidomide, pomalidomide, and CC-885 all share a glutarimide moiety. Lenalidomide and pomalidomide were previously placed in the broad category of immunomodulators (IMiDs) for their potent immunomodulatory effects, but these derivatives are now known as CRBN modulators, a category created because the ability of CC-885 to inhibit the proliferation of acute leukemia cells by degrading translation termination factors showed that the effects of thalidomide derivatives are not limited to immunomodulation.

(2) Proving that CRBN is a TE target

As rodents are resistant to thalidomide, we used zebrafish as a TE model. Zebrafish have pectoral fins corresponding to the limbs that are visible beginning 3 days after fertilization. As with TE in humans, fertilized zebrafish eggs that were incubated in a tank containing thalidomide showed signs of developmental impairment of the pectoral fins (which correspond to upper limbs) and otocysts (which correspond to ears). To prove that CRBN is a genuine target, we made a CRBN mutant (YW/AA) that does not bind thalidomide but retains all other functions normally. The mRNA of wild-type CRBN and the YW/AA mutant was introduced into fertilized eggs to cause the expression of these proteins. The eggs were incubated in the presence of thalidomide. As in the control embryos, signs of TE appeared in the embryos overexpressing wild-type CRBN, but TE was suppressed in the embryos overexpressing the YW/AA mutant. This rescue experiment demonstrated that CRBN is the main target for TE. We made similar findings in a study in fertilized chicken eggs, proving that CRBN is a genuine target of thalidomide teratogenicity. Through further research, we showed that thalidomide itself rather than a metabolite is responsible for TE and that the anti-neovascularization effects of thalidomide are not the primary cause of TE. Thalidomide causes TE by targeting the function of CRBN[5].

3 Proving that CRBN is also a Target for the Anticancer Effects of Thalidomide

(1) Second-generation thalidomide derivatives

Our article in *Science* helped launch an international industry–academia research project with the American pharmaceutical company Celgene (now part of Bristol Myers Squibb). Celgene reintroduced thalidomide to the market as an anticancer drug and developed and marketed the second-generation thalidomide derivatives lenalidomide and pomalidomide (Figure 2), which have

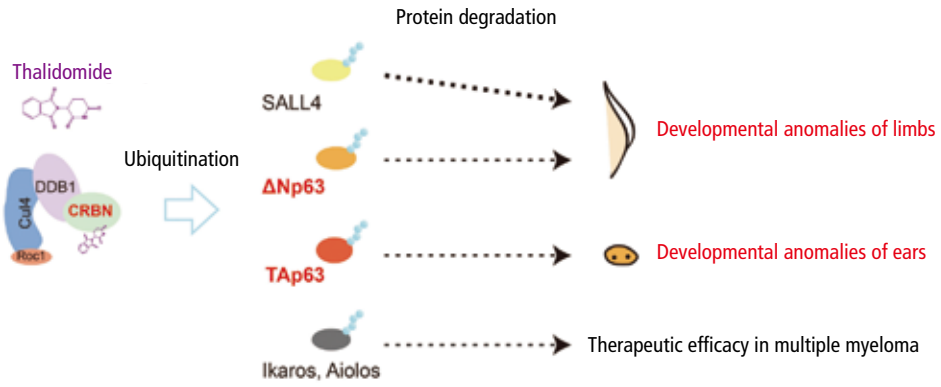


Figure 2 Molecular mechanism of thalidomide

When thalidomide binds to the target factor CRBN, the complex recognizes and degrades new substrate proteins. This can result in a therapeutic effect when Ikaros and Aiolos are degraded in multiple myeloma cells or cause developmental anomalies when DNp63 (including Sall4) and TAp63 are degraded in the limbs and ears of a developing embryo.

anticancer activity superior to thalidomide. These three drugs are known as immunomodulatory imide drugs (IMiDs) because they modulate the immune system by activating T cells. IMiDs inhibit cancer cell proliferation in MM and derive a wide array of anticancer effects by activating cytotoxic T cells by inducing the expression of interleukin-2 (IL-2) in immunocompetent T cells. We worked with Celgene to determine whether CRBN contributes to the effects of IMiDs.

(2) The contribution of CRBN to the anticancer effects of thalidomide and other IMiDs

It turned out that CRBN was a target for not only the thalidomide side effects of TE, but also the primary anticancer effects of IMiDs[6].

Our first finding was that normal MM cell lines are sensitive to IMiDs, showing inhibited growth when treated with IMiDs, whereas CRBN-knockdown MM cells are resistant to IMiDs, not showing inhibited growth. We also found that MM cells cultured for an extended time in the presence of IMiDs develop IMiD resistance, expressing much less CRBN. These findings suggested that CRBN is involved in the anticancer effects of IMiDs. It was already known that IMiD treatment suppressed the expression of c-myc and interferon regulatory factor 4 (IRF-4), which MM cells need to proliferate and survive. The fact that the treatment of CRBN-knockdown MM cells with IMiDs failed to suppress c-myc and IRF-4 expression and inhibit cell proliferation demonstrated that CRBN is a target for the inhibitory effects of IMiDs on MM cell proliferation and that IMiDs suppress c-myc and IRF-4 expression via some mechanism[6].

We used X-ray crystallographic structural analysis to determine the conformation of human CRBN-IMiD complexes. The results showed that thalidomide, lenalidomide, and pomalidomide bind to CRBN via their glutarimide moiety (Figure 2), which enters a thalidomide pocket composed of three tryptophans (W) called the tri-W pocket at the C terminus of CRBN[7].

(3) Optical isomers of thalidomide

Thalidomide and the other IMiDs occur as optical isomers with *S* and *R* forms due to their chiral carbons. In 1979, Dr. Blaske hypothesized that the *S* form causes teratogenicity while the *R* form has hypnotic effects. Having identified CRBN as the primary target of thalidomide, we decided to revisit this hypothesis on a molecular level.

Analyses with multiple approaches, including biochemical studies and X-ray crystallography, showed that the *S* form binds CRBN much more strongly and stably than does the *R* form and that the *S* form is the major contributor to both TE and anticancer effects[8].

Under physiological conditions, the optical isomers of the IMiDs readily change from the *S* form to the *R* form and back, forming a racemic mixture. In the human body, therefore, IMiDs preferentially bind to CRBN as the *S* form, with the unbound *R* form isomerizing to replenish the *S* form, which means that optical purity is not very relevant to IMiD efficacy[8].

Our findings allowed us to reject the common belief that low optical purity was responsible for the thalidomide tragedy.

(4) Mechanism of the anticancer effects of thalidomide and other IMiDs

Knowing that CRBN is the target for both the primary pharmacological effects and side effects of thalidomide and the other IMiDs begs the question of what happens once these drugs bind to CRBN. Proteins whose CRBN-mediated ubiquitination is elevated in MM cells treated with IMiDs were recently discovered, and the blood-cell transcription factors Ikaros and Aiolos were identified as substrate proteins that undergo ubiquitination at the highest level[9]. It turned out that the ubiquitination and degradation of these two transcription factors is also elevated in healthy T cells treated with an IMiD.

Ikaros and Aiolos are known to be IL-2 transcription repressors and IRF-4 and c-myc transcription activators. Their levels are reduced when they are ubiquitinated and degraded following IMiD treatment, which disinhibits the expression of the IL-2 gene under their suppression in T cells. IL-2 expression consequently increases, which induces the activation of cytotoxic T lymphocytes. This is the mechanism of immunomodulation involved. When Ikaros and Aiolos are degraded in MM cells, the expression of IRF-4 and c-myc, which are activated by Ikaros and Aiolos and needed for cancer cell proliferation and survival, is reduced, which inhibits cancer cell proliferation (Figure 2). This explains the mechanism of the anticancer effects of IMiDs[9–11]. It also demonstrates the excellence of their wide-ranging anticancer effects that involve inhibiting cancer cell proliferation and activating cytotoxic T lymphocytes via the ubiquitination and degradation of Ikaros and Aiolos after IMiDs bind to CRBN[9–11].

Of the IMiDs, only lenalidomide is effective in myelodysplastic syndrome (5q syndrome), but its effects in that condition involve a substrate, other than Ikaros and Aiolos, called casein kinase 1α. The mechanism is not discussed further here. Differences in the molecular structures of thalidomide and pomalidomide are critical for selective substrate recognition[12,13].

4 Research Leads to New CRBN Modulators

Celgene recently developed third-generation thalidomide derivatives that include CC-885 (Figure 1). On binding to CRBN, CC-885 recruits the translation stop control factor GSPT1 onto CRBN as a new substrate, leading to its ubiquitination and degradation. This inhibits the proliferation of acute myeloid leukemia cells. We identified GSPT1 as a new CC-885-dependent substrate and determined the conformation of the DDB1/CRBN/CC-

885/GSPT1 complex with X-ray crystallographic structural analysis and cryogenic electron microscopy, showing that CC-885 serves as a molecular glue to bridge CRBN and GSPT1[14].

These third-generation thalidomide derivatives do not fit in the range of immunomodulation associated with the second-generation derivatives. We therefore decided to assign the general designation "CRBN modulators" to thalidomide and all thalidomide derivatives that (1) bind to CRBN, (2) recruit a unique substrate onto CRBN, (3) bridge the substrate to CRBN, and (4) are ubiquitinated and degraded by E3 Ub-ligase activity to (5) produce their therapeutic efficacy[14]. Several promising CRBN modulators are currently under development.

5 Mechanism of TE

(1) Lessons learned from thalidomide's mechanism of the primary pharmacologic effect

As stated above, CRBN modulators derive their pharmacologic action by recruiting a unique substrate onto CRBN to induce its ubiquitination and degradation. It naturally follows that there must be some substrate responsible for TE.

On this topic, two American research groups very recently identified Sall4, a regulatory factor involved in differentiation, as a new substrate responsible for TE[15,16]. The groups discovered that treating human embryonic stem cells with thalidomide markedly reduced Sall4 expression in a CRBN-dependent manner. The fact that Sall4 has been implicated as the causative gene of genetic diseases that feature limb and other malformations led the groups to claim that Sall4 is the substrate responsible for TE. But while TE occurs in humans, rabbits, chickens, and zebrafish, Sall4 is degraded only in humans and rabbits. Moreover, as no definitive experiments have been performed to create animals resistant to TE by modifying Sall4, no conclusive proof that Sall4 is indeed the primary substrate behind the teratogenic activity of thalidomide has been given.

(2) Identification of p63, a new TE-related substrate

Through our work with Associate Professor Luisa Guerrini of the University of Milan in Italy over the past several years, we found that p63, a member of the p53 transcription factor family known as tumor suppression factors, may be the new substrate responsible for TE. The *TP63* gene codes mainly for two proteins: TAp63α, and ΔNp63α, which lacks a trans-activation domain at the N terminus. *TP63* mutations in humans have been associated with limb malformations. Knocking out a gene homologous to *TP63* in mice and zebrafish results in limb and pectoral fin malformations.

Treating the HaCat human epithelial keratinocyte line with thalidomide induces the CRBN-dependent ubiquitination and degradation of ΔNp63α. In the presence of thalidomide, human and zebrafish ΔNp63α binds to the CRBN of the respective species. We created the zΔNp63α mutant G506A, which does not undergo thalidomide-induced degradation. Embryonic zebrafish made to express this mutant protein were highly resistant to TE. Our findings led us to conclude that thalidomide-induced pectoral fin (limb) anomalies are attributable to ΔNp63α degradation.

The other gene product TAp63α is also a substrate of CRBN, but does not contribute to limb formation. Inspired by a study finding that mTAp63α is involved in early ear development in mice, we knocked down zTAp63α in zebrafish, finding that otocyst size was reduced as a result. Based on this finding, we followed our research on zΔNp63α by creating the G599A mutant of zTAp63α, which does not undergo thalidomide-induced degradation. Embryonic zebrafish made to express this mutant protein were highly resistant to otocyst anomalies caused by thalidomide. This demonstrates that TAp63α is the substrate responsible for ear hypoplasia in TE. More specifically, thalidomide binds to CRBN, which induces the degradation of ΔNp63α and TAp63α, which in turn causes TE by triggering limb and ear anomalies[17] (Figure 2).

6 Conclusions

The affinity bead technology we developed has helped us isolate and identify many targets of small-molecule compounds. We were the first to identify CRBN as the target of thalidomide, finding that the drug binds to CRBN to alter its substrate selectivity to produce both beneficial anticancer effects and harmful thalidomide teratogenicity[18]. We are convinced that our technologies have made a modest contribution to basic research in the life sciences and the field of chemical biology, which uses small-molecule compounds as tools. We are honored to see that our discovery of CRBN and unlocking of its mechanism led to the development of two new types of drugs: CRBN modulators, and CRBN-based degraders, which (although not discussed here) selectively degrade targeted proteins[18]. We consider these accomplishments the result of our original, innovative, and unwavering research, carried out under the creed of "Excellent basic research always leads to application, and excellent applied research always begets new basic research."

References

1) Inomata, Y., Handa, H. et al : Direct purification of multiple ATF/E4TF3 polypeptides from HeLa cell crude nuclear extracts using DNA affinity latex particles. Anal. Biochem. 206 : 109-114, 1992
2) Shimizu, N., Handa, H. et al : High-performance affinity beads for identifying drug receptors. Nat. Biotechnol. 18 : 877-881, 2000
3) Nishio, K., Handa, H. et al : Development of novel magnetic nano-carriers for high-performance affinity purification. Col-

loids Surf. B 64 : 162-169, 2008
4) IOP ebooks, Series in physics and engineering in medicine and biology, Magnetic nanoparticles for medical diagnostics (Sandhu, A. and Handa, H. eds) IPEM, 2018
5) Ito, T., Yamaguchi, Y., Handa, H. et al : Identification of a primary target of thalidomide teratogenicity. Science 327 : 1345-1350, 2010
6) Lopez-Girona, A., Ito, T., Handa, H. et al : Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia 26 : 2326-2335, 2012
7) Chamberlain, P. P., Ito, T., Handa, H. et al : Structure of the human cereblon-DDB1-lenalidomide complex reveals basis for responsiveness to thalidomide analogs. Nat. Struct. Mol. Biol. 21 : 803-809, 2014
8) Mori, T., Ito, T., Handa, H. et al : Structural basis of thalidomide enantiomer binding to cereblon. Sci. Rep. 8 : 1294, 2018
9) Gandhi, A. K., Ito, T., Handa, H. et al : Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN). Br. J. Haematol. 164 : 811-821, 2014
10) Lu, G. et al : The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science 343 : 305-309, 2014
11) Krönke, J. et al : Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science 343 : 301-305, 2014
12) Krönke, J. et al : Lenalidomide induces ubiquitination and degradation of CK1 α in del(5q) MDS. Nature 523 : 183-188, 2015
13) Ito, T. and Handa, H. : Another action of a thalidomide derivative. Nature 523 : 167-168, 2015
14) Matyskiela, M. E., Ito, T., Handa, H. et al : A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. Nature 535 : 252-257, 2016
15) Donovan, K. A. et al : Thalidomide promotes degradation of SALL4, a transcription factor implicated in Duane Radial Ray syndrome. eLife 7 : e38430, 2018
16) Matyskiela, M. E. et al : SALL4 mediates teratogenicity as a thalidomide-dependent cereblon substrate. Nat. Chem. Biol. 14 : 981-987, 2018
17) Asatsuma-Okumura, T., Ito, T., Handa, H. et al : p63 is a cereblon substrate involved in thalidomide teratogenicity. Nat. Chem. Biol. 15 : 1077-1084, 2019
18) Asatsuma-Okumura, T., Ito, T. and Handa, H. : Molecular mechanisms of cereblon-based drugs. Pharmacol. Ther. 202 : 132-139, 2019

[Takumi Ito, Yuki Yamaguchi, Hiroshi Handa]

IV Diagnostic Procedures for Thalidomide Embryopathy (TE)



- A Even 60 years after the thalidomide tragedy, new claimers are appearing around the world, insisting that they have TE. However, debate continues as to whether these cases are TE that should have been certified or are a malformation unrelated to TE.
- Under the leadership of the World Health Organization (WHO), St. George's University of London developed the diagnostic algorithm for thalidomide embryopathy (DATE). DATE has excellent reliability. Diagnosis under DATE begins with the two epidemiologically focused requirements that the mother of the person lived in a location where thalidomide was available and the person had been born when the drug was available, plus a third condition that the person has no family history of similar malformations.
- Thalidomide embryopathy has several characteristic external and visceral malformations. Victims are classified into upper limb hypoplasia and auditory hypoplasia types. The upper limb hypoplasia type features upper limb domination and preaxial longitudinal hypoplasia. The auditory hypoplasia type features deafness, auricular malformation, Duane syndrome, and facial nerve palsy.
- Embryopathy occurs during the embryonic phase of gestation and particularly 35–50 days after the last menstrual period of the mother. External factors such as radiation, drugs (especially antiepileptics), and viruses (e.g., rubella) cause morphological and functional anomalies of the limbs, eyes, ears, and heart.
- Genetic SALL4-related disorders are morphologically very similar to TE. The two are often very difficult to differentiate.
- Diagnoses should be made in overall consideration of epidemiological factors, external and visceral malformations, and genetic factors.

1 Introduction

Thalidomide, branded the "Drug of the Devil," was hastily pulled from the market in 1961–1962. It returned, however, in 1965 as an immunomodulatory "Blessed Drug." Thalidomide is currently approved for use in the treatment of erythema nodosum of leprosy and for multiple myeloma by the United States Food and Drug Administration and in other countries around the world. It is even covered under Japan's national health insurance. Newborns with TE are born even today in Brazil, where thalidomide drug products are actively marketed. Even 60 years after the thalidomide tragedy, new claimers are appearing in many countries throughout the world, convinced that their malformations are the result of TE. This chapter explores the basics involved in diagnosing TE.

2 New Claimers Around the World

A total of 2,397 people have been officially certified as having TE in Germany, with 105 new claimers applying from 2009 to 2017. Of these, 10 were certified, 43 were rejected, and 49 had an undecided status (Figure 1)[1)]. The UK previously had 467 people with certified TE, with 276 new claimers applying from 2013 to 2018. Four were given a diagnosis of TE, and litigation is underway to decide the fate of another six. The others were diagnosed as not having TE (Figure 2)[2)].

In Spain, 24 people were certified as having TE through 2010 and received lump-sum compensation of 100,000 euros. In a September 23, 2015 Supreme Court decision involving 186 new claimers, however, the justices found their malformations to be unrelated to thalidomide drug products, handing a victory to the marketer Grünenthal[URL1)].



New claimer, thalidomide embryopathy diagnosis, diagnostic criteria and severities, upper-limb hypoplasia, auditory hypoplasia, Duane syndrome, facial nerve palsy, Holt–Oram syndrome, Okihiro syndrome, diagnostic algorithm for thalidomide embryopathy

A settlement was reached on December 2, 2013 in lawsuits brought by over 100 new claimers in Australia and New Zealand. Diageo, the company that acquired Distillers (the thalidomide marketer at the time), agreed to pay 81 million dollars[URL2].

Recognizing these developments, the WHO convened a meeting of experts on TE in Geneva, Switzerland in 2014. At the meeting, it was announced that St. George's University of London in the UK was developing a DATE[URL3].

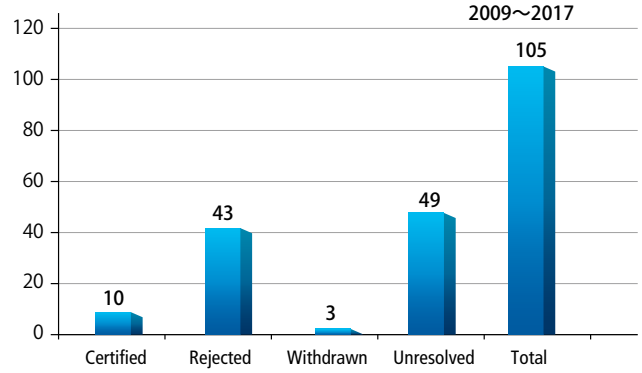


Figure 1 New claimers in Germany

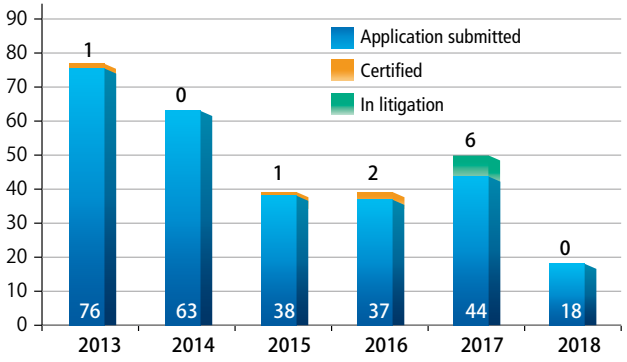


Figure 2 New claimers in the UK

3 Requirements for a Diagnosis of TE

TE is defined as a malformation in the offspring of a mother who took thalidomide 34–50 days after her last menstrual period. Genetic diseases are not included. Thalidomide was marketed in Japan from 1959 to 1962 for morning sickness and insomnia associated with pregnancy (Figure 3). Obtaining evidence of maternal thalidomide use, the most important element for diagnosing embryopathy, is difficult or impossible because by now, after six decades have passed, medical records will have been destroyed, and the prescribing physicians will have died. As shown in Figure 4 in Chapter II, TE does not occur in places where thalidomide is unavailable. On the basis of this epidemiological point, the requirements for a diagnosis of TE require (1) that the mother of the person lived in a location where thalidomide was available, (2) that the person had been born when the drug was marketed, and (3) that the person has no family history of similar malformations. Finally published in 2019, the DATE paper lists these three points (Figure 4)[3].

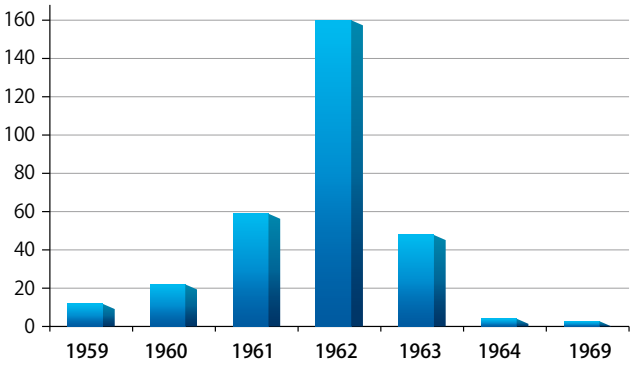


Figure 3 Numbers of babies born with thalidomide embryopathy in Japan

In West Germany, the recall of thalidomide drug products began in November 1961. Product recalls did not begin in Japan until September 1962. Many avoidable cases of embryopathy occurred because of this 10-month delay.

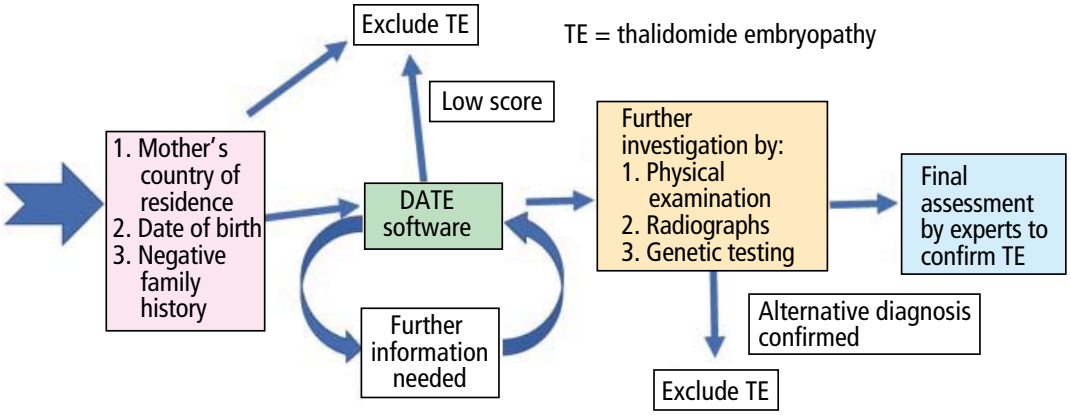


Figure 4 Overview of the Diagnostic Algorithm for Thalidomide Embryopathy (DATE) (adapted from Reference 3)
DATE Diagnostic algorithm for thalidomide embryopathy

4 Physical Manifestations of TE

A TE checklist by the Japanese Ministry of Health, Labour and Welfare (formerly the Ministry of Health and Welfare) is shown in Figure 5. At the time, TE victims were classified into three groups according to the particular physical manifestations present. The first, called the "short-arm group," contains 230 of the 309 Japanese thalidomide victims (75%). The other, called the "hearing-loss group," contains 59 of the 309 victims (19%). There is also a mixed group containing 20 of the 309 victims (6%) (Figure 6).

(1) Preaxial longitudinal hypoplasia

Preaxial longitudinal hypoplasia is a feature of upper- or lower-limb reduction malformations. Hypoplasia occurs in the order of the thumb, trapezium, scaphoid, radius, and humerus. The ulna and ulnar digits (i.e., middle, ring, and small fingers) are minimally affected or, if affected, only in the end. Skeletal muscle hypoplasia accompanies skeletal hypoplasia (Figure 7). Some victims have hypoplasia of the arm muscles despite having a normally formed humerus, scapula, and clavicle.

	Right (R)	Left (L)		Right (R)	Left (L)
Upper arm muscles hypoplasia			Facial paralysis		
Dislocation of shoulder joint			Abduces paralysis		
Humerus defect			Crocodile tears		
Humerus rudiment			Others paralyses		
Humerus shortening			Obstruction of auditory canal		
Elbow joint hypoplasia			Auricle anotia		
Forearm short or defect			Auricle microtia		
Radius defect or rudiment			Auricle dysplasia		
Ulna short or defect			Helix defect		
Dislocation of wrist			Helix hypoplasia		
Club hand			Helix dysplasia		
Thenar muscle hypoplasia			Sensorineural deafness		
Thumb defect			Conductive deafness		
Thumb rudiment			Mixed deafness		
Thumb hypoplasia			Congenital heart defect		
Thumb triphalangia			Others malformations		
Digit II defect or rudiment				R	L
Digit II contracture			Auditory acuity	dB	dB
Digit III defect or rudiment					
Digit III contracture			Others		
Digit IV contracture			Rank		
Lower extremity dysplasia					
Dislocation of hip joint					

Figure 5 Diagnostic criteria for thalidomide embryopathy by the Ministry of Health, Labour and Welfare
The rank is assigned a number of 1 to 5 or a letter of A to E based primarily on the diagnostic criteria for upper-limb hypoplasia or deafness and in further consideration of lower-limb hypoplasia, heart defects, and other internal disorders. A rank of 5 or A indicates "most severe" disease, 4 or B, "severe" disease, 3 or C, "moderate" disease, 2 or B, "mild" disease, and 1 or E, "normal" health.

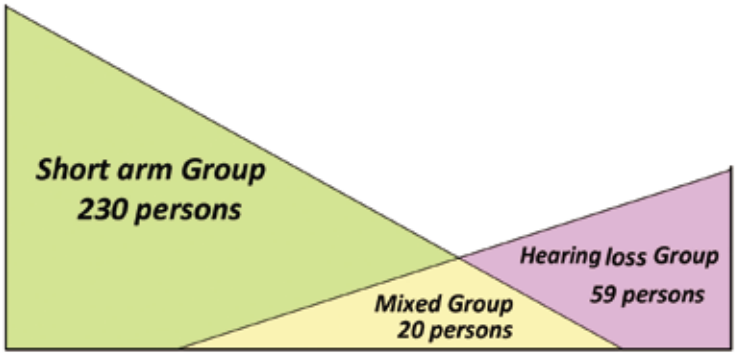


Figure 6 Physical manifestations of thalidomide embryopathy
Patients are classified into a short-arm or hearing-loss group.

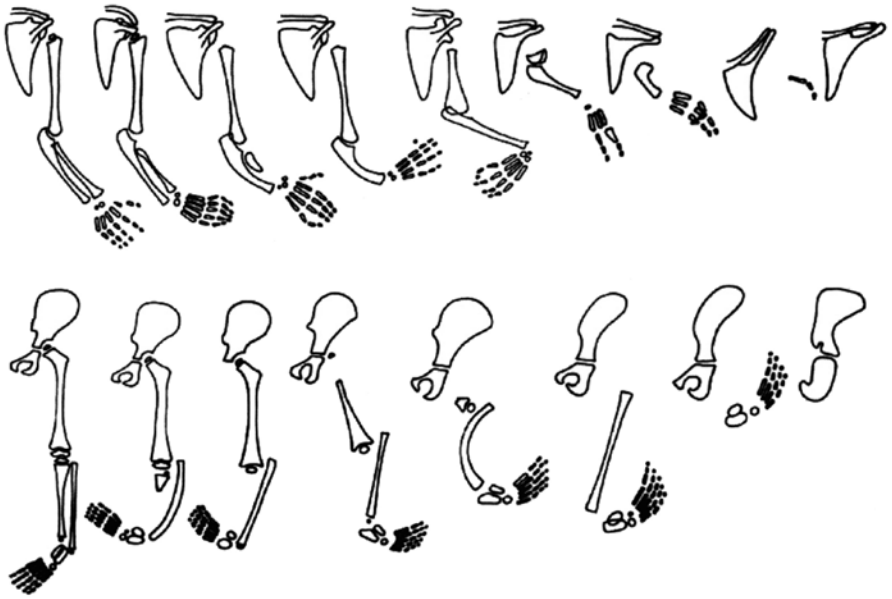


Figure 7 Pattern and severity classification of preaxial longitudinal hypoplasia in thalidomide embryopathy

(Henkel HL, Willert HG: Dysmelia: A classification and a pattern of malformation in a group of congenital deformities of the limbs. J Bone & Surg 1969;51:399-414.)

(2) Symmetry and upper limb domination

The manifestations of TE generally appear bilaterally. There are often certain left–right differences. Some of those with upper-limb hypoplasia appear to be normal on one side but, on closer observation, have slight thenar hypoplasia. This might be attributed to thalidomide's entry into the fetal circulation via umbilical blood after being taken by the mother. Minimally affected victims have thenar hypoplasia with mild hypoplasia of the trapezium and scaphoid evident only on X-rays. None of the Japanese TE victims has unilateral manifestations. Some of the German new claimers claim to be bilaterally affected on the basis of their dominant and nondominant upper limbs having different lengths or circumferences[4].

In the Japanese victims, the lower limbs are often unaffected, with manifestations limited to the upper limbs.

(3) Severity classifications for upper-limb hypoplasia

Criteria developed by the Japanese Ministry of Health, Labour and Welfare classify upper-limb hypoplasia into four grades: most severe, severe, moderate, and mild (Table 1, Figures 8 and 9). Victims most typically fall into the severe category, followed in decreasing order by moderate, mild, and most severe.

(4) Lower-limb hypoplasia

Sixty-five of the 467 patients certified in the UK and 150 of the 2,397 patients certified in Germany have lower-limb hypoplasia. By contrast, only two of the 309 patients certified in Japan have lower-limb hypoplasia. As shown in Figure 7, this takes the form of preaxial hypoplasia of the tibia and femur. The Japanese patients are further characterized by a lack of toe defects. In no patient does lower-limb hypoplasia occur alone. Upper-limb hypoplasia is always present[1,2].

Table 1 Severity classification criteria for upper-limb hypoplasia

Most severe	a) bilateral amelia or phocomelia b) amelia or phocomelia+severe ectromelia
Severe	a) phocomelia+ectromelia b) bilateral severe ectromelia c) severe ectromelia+ectromelia
Moderate	a) severe ectromelia+hand anomaly b) bilateral ectromelia=forearm involvement c) ectromelia+hand anomaly =thumb involvement
Mild	a) bilateral hand anomaly b) unilateral hand anomaly

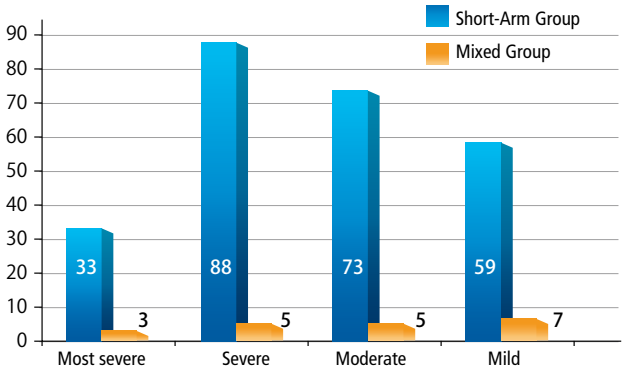


Figure 8 Severity classifications of upper-limb hypoplasia



Figure 9 Upper-limb hypoplasia shown in decreasing order of severity

(5) Auditory hypoplasia

Classification involves the three elements of the auricles, ear canals, and deafness. Manifestations include outer ear malformation accompanying outer or inner ear hypoplasia, conductive deafness accompanying middle ear canal stenosis and related conditions, and sensorineural deafness caused by hypoplasia of the inner ear in the 8th cranial nerve (Figure 10, Table 2)[5]. Other frequent manifestations include Duane syndrome, which has innervation by aberrant branches of the 3rd cranial nerve accompanying defects of the 6th cranial nerve nuclei, facial nerve palsy with hypoplasia of the 7th cranial nerve nuclei, and crocodile tears, which involves aberrant regeneration. Upper-limb hypoplasia occurred in just 20 (6%) of the 309 victims in the hearing-loss group. Auditory hypoplasia severity is typically classified according to the severity of hearing loss. Auditory hypoplasia severity is therefore based on the severity of hearing loss at the ages of 12–14 years, when the legal evidence is created. Recently, patients with previous moderate deafness have progressed to most severe deafness in the fourth to fifth decade of life. The worsening of deafness with aging is pronounced. A recent problem for patients with facial nerve palsy is age-related eyelid ptosis indicated for plastic surgery.

Severity	Hearing loss
Most severe	Bilateral > 60 dB
Severe	Bilateral > 30–60 dB
Moderate	Unilateral > 60 dB
Mild	Unilateral > 30–60 dB

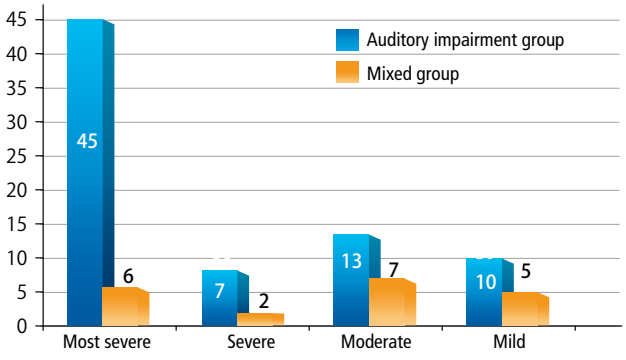


Figure 10 Classifications of deafness in auditory hypoplasia

5 Diagnosing TE

In the 1970s, TE was officially certified on the basis of external malformations and plain X-ray imaging. The severity of cardiac malformations and anal atresia, relatively easy conditions to evaluate, was also factored into diagnoses. With recent advances in computed tomography (CT), magnetic resonance imaging (MRI), and other imaging modalities, it is becoming apparent that a substantial proportion of patients with mild external malformations also have malformations of the internal organs. (For more information, see Chapter VII "Radiological Examination and Evaluation".) The Japanese version of DATE will be prepared with non-X-ray imaging findings factored into new-claimer diagnoses. Such imaging is not included in the English version of DATE.

One problem facing those diagnosing TE is the array of genetic diseases with malformations very similar to those in TE. These must be included in the differential diagnosis. They are (1) Holt–Oram syndrome (HOS), which has a TBX5 gene abnormality (there is also HOS with SALL4 involvement); (2) Duane-radial ray syndrome (DRRS; Okihiro syndrome), which involves a *SALL4* mutation; (3) Townes–Brocks syndrome, an autosomal dominant genetic disorder featuring anal atresia, auricular malforma-

Table 2 Types and classifications of auditory defects

N=75 (43 men and 32 women), 150 ears		
Auricular deformities		77 ears
	Anotia	10
	Microtia	47
	Dysplasia	20
Ear canal deformities		64 ears
	Atresia	28
	Stenosis	36
Deafness		147 ears
	Conductive deafness	18
	Sensorineural deafness	97
	Mixed deafness	32

(Adapted from Reference 6)

tion, thumb malformation, and kidney malformation that is caused by a heterozygous mutation in the *SALL1* gene (chromosome 16q12.1); (4) thrombocytopenia-absent radius syndrome, which is associated with the *RBM8A* gene on chromosome 1q21.1; (5) VATER or VACTERL syndrome; these initials stand for vertebral anomalies (V), anal atresia/malformation (A), tracheo-esophageal fistula (TEF), and renal/radial malformation (R); cardiac malformation (C) and limb malformation (L) are also present in VACTERL syndrome; and finally, (6) Fanconi anemia, which involves cardiac, limb, and vertebral abnormalities, and must be factored into differential diagnoses.

Generally, genetic diseases can be ruled out if there is no supporting family history.

6 New Claimers in Japan

Four patients were evaluated at the request of the Ishizue Foundation over the 4-year period from 2015 to 2019. Two patients with findings suggestive of TE are presented here.

Patient 1: Man born in 1962 with triphalangeal thumbs of both hands (Figures 11 and 12). Abdominal CT and MRI suggested gallbladder agenesis, severe atrophy of the right kidney, and multiple cysts and vascular malformation of the right posterior peritoneum (Figures 13 and 14).



Figure 11 Triphalangeal thumbs of both hands
The thumbs are triphalangeal instead of having the normal two joints. Thenar hypoplasia is also present.
The affected digits are not actually thumbs. This constitutes polydactyly. Functionally, these digits lack the ability of thumbs to grip and pinch. The patient pinches items at the area between the pisiform bone and the finger in the location of the index finger. The finger between the index finger and middle finger is used to pinch.



Figure 12 An X-ray of both hands
The thumbs are triphalangeal. Hypoplasia is seen in the trapezium, scaphoid, and styloid process of the radius.

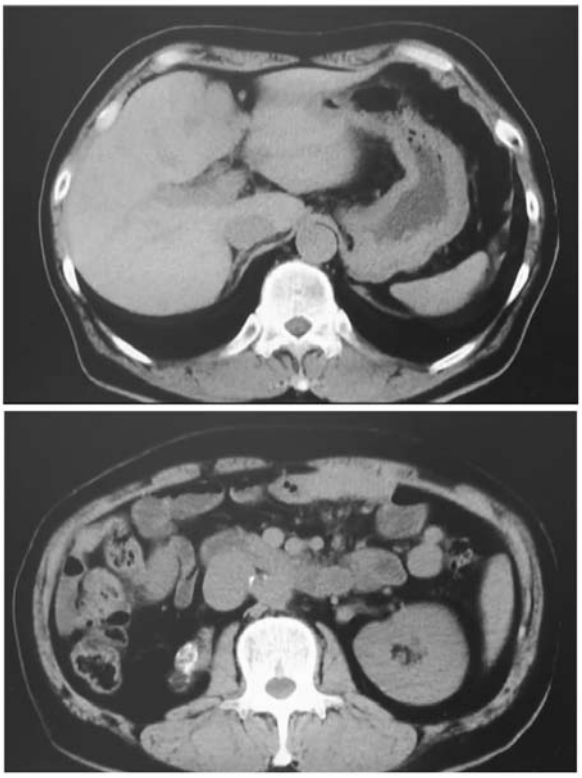


Figure 13 Axial abdominal cavity CT scans
The upper scan, a cross-section at the hepatobiliary level, shows gallbladder agenesis. The lower scan, at the renal level, shows severe atrophy of the right kidney. (Unless otherwise indicated, the right side from the perspective of the viewer is the left side of the viscera, and the left side from the perspective of the viewer is the right side of the viscera.)



Figure 14 Coronal abdominal cavity MRI scan
The scan shows findings indicative of severe atrophy of the right kidney and multiple cysts and vascular malformation of the right posterior peritoneum.

Patient 2: Woman born in 1971 with hypoplasia of the left forearm and right thenar hypoplasia (Figure 15). X-ray imaging of the upper limbs showed hypoplasia of the left radius and thumb and indistinct separation of the left carpal bones. X-ray imaging of the right forearm and hand was indistinct because of technical issues, but the patient was found to have hypoplasia of at least the thumb (Figure 16).

Three-dimensional CT imaging of the hips showed subluxation of the femur head due to hypoplasia of the left hip cup (Figure 17). Sagittal CT imaging of the abdominal cavity showed severe atrophy of the right kidney, hypoplasia of the left hip cup, and scoliosis (Figure 18).

Patients 1 and 2 had external malformations of the preaxial hypoplastic kind and severe atrophy or aplasia of the right kidney, which are consistent with TE. They had no relevant family history. The only remarkable difference between the two was their dates of birth. One was born in 1962, when thalidomide drugs were on the market. The other was born in 1971, well after thalidomide drugs had been recalled. According to the DATE criteria, Patient 1 very likely has TE. Patient 2, on the other hand, probably does not.



Figure 15 Photographs of the forearms and hands



Figure 16 X-rays of the forearms and hands
The X-rays to the right show the patient's left forearm and hand. The X-rays to the left show the patient's right forearm and hand. There is agenesis of the left radius, hypoplasia of the ulna, and unseparated carpal bones as well as hypoplasia of the right thumb.

7 Differentiating TE from SALL4-related Disorders

In humans, SALL4-related disorders are caused by anomalies of the transcription factor SALL4 found on chromosome 20q13. (The transcription factor SALL [sal-like] 4, which is pronounced "Sal four," is a human gene related to the developmental regulatory factor sal of common fruit flies. There are also SALL1, 2, and 3.) SALL4-related disorders include DRRS (Okihiro syndrome[5]: Michael Masaru Okihiro[6] is a Hawaiian neurologist), acro-renal-ocular syndrome, and HOS, all of

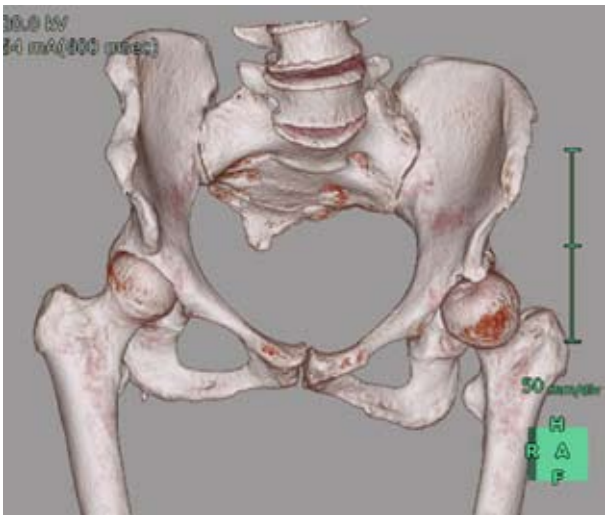


Figure 17 Hypoplasia of the left hip acetabulum in 3D CT



Figure 18 Severe atrophy of the right kidney seen in abdominal cavity CT
Marked scoliosis is also present.

which morphologically closely resemble TE. The Australian McBride, who was the first to report TE in the English-speaking world[7], stated in 1994, "Thalidomide may be a mutagen"[8]. Misinterpreting "mutagen" to equate to genetic transmission, many thalidomide victims became extremely anxious. His words triggered a lasting wave of debate in the *British Medical Journal*. Jürgen Kohlhase, the leading authority on SALL4-related disorders, claims that the second TE case reported by McBride actually had a SALL4-related disorder[9]. Most of the features of TE fall within the range of the clinical symptoms of SALL4-related disorders (Table 3)[URL4].

8 Is Embryopathy Genetically Heritable?

Congenital rubella syndrome is one of the most well-known forms of embryopathy. Embryopathy that originates from 35 to 50 days after the mother's last menstrual period, when the growing embryo is most susceptible, have three hallmarks: heart disease, visual impairment, and auditory defects. Embryopathy originating after this time features only auditory defects[URL5]. Thalidomide, rubella, and other factors are mutagenic, but are not genetically heritable. *SALL4* anomalies cause conditions that are difficult to differentiate from TE. Conversely, the differential diagnosis of SALL4-related disorders includes TE. No genetic analyses of patients with TE have been performed.

References

1) Personal Communication, 21 Sep.2018, Dr. Christina Ding-Greiner, Institute of Gerontology, University of Heidelberg, Germany.
2) Personal Communication, 21 Sep.2018, Dr.Dee Morrison, The Thalidomide Trust, St Neots, UK.
3) Mansour S, Baple E, Hall CM: A clinical review and introduction of the diagnostic algorithm for thalidomide embryopathy (DATE), Journal of Hand Surgery, 2019,44(1):96-108.
4) Personal Communication, 14 Jul.2019, Dr. Christina Ding-Greiner, Institute of Gerontology, University of Heidelberg, Germany.
5) Tanaka Y.: T Thalidomide-induced Otolaryngological Defects. Otolaryngology 58:35-44, 1986
6) Okihiro MM, et al: Duane syndrome and congenital upper-limb anomalies. A familial occurrence. Arch Neurol.1977 Mar;34(3):174-9.
7) McBride WG:Thalidomide and congenital abnormalities. Letter to the Editor, The Lancet 2,Dec.16,1961:1358.
8) McBride WG: Thalidomide may be a mutagen. BMJ. 1994 Jun 18; 308(6944):1635–1636
9) Kohlhase J, et al: Mutations at the SAL locus on chromosome 20 result in a range of clinically overlapping phenotypes, including Okihiro syndrome, Holt-Oram syndrome, acro-renal-ocular syndrome, and patients previously reported to represent thalidomide embryopathy. J Med Genet 2003;40:473-478.

URL

1) BBC News: Badcock J : Spain's forgotten Thalidomide victims see glimmer of hope. 23 Dec.2016. https://www.bbc.com/news/world-38386021
2) BBC News:Willmore J: Australia thalidomide victims win $81m payout. https://www.aljazeera.com/news/asia-pacific/2013/12/australian-thalidomide-victims-81m-payout-201312311650206211.html
3) WHO: Thalidomide Embryopathy - Report of a meeting of expert. www.who-umc.org/graphics/28280.pdf
4) Kohlhase J: SALL4-Related Disorders. GeneReviews® -NCBI Bookshelf [Internet]. Initial Posting: August 16, 2004; Last Update: January 15, 2015. https://www.ncbi.nlm.nih.gov/books/NBK1373/#__NBK1373_ai__
5) Katow S: Surveillance of congenital rubella syndrome in Japan, 1978–2002: effect of revision of the immunization law. https://doi.org/10.1016/j.vaccine.2004.03. 055Get rights and content

[Ryoji Kayamori]

Table 3 Clinical findings in SALL4-related diseases

Eyes	Microphthalmia (rare); iris, retinal, and choroidal coloboma; cataract; optic disc hypoplasia
Upper extremities	Concomitant shortening of ulna, syndactyly, radial clubhand, shortened humeri, hypoplasia of deltoid muscles
Kidneys	Renal agenesis, crossed renal ectopia, position anomalies of kidneys
Ears/hearing	Sensorineural and/or conductive deafness, abnormal pinnae, slit-like opening of auditory canals, small ears
Heart	Atrial septal defect, ventricular septal defect, tetralogy of Fallot
Gastrointestinal	Anal stenosis, imperforate anus
Face	Epicanthal folds, widely spaced eyes, depressed nasal bridge, hemifacial microsomia
Lower extremities	Talipes, clubfoot, tibial hemimelia, syndactyly of toes
Spine	Fused vertebrae
Pituitary	Growth hormone deficiency, postnatal growth retardation, pituitary hypoplasia
Central nervous system	Neural tube defects (rare); meningomyelocele has been observed in two affected individuals [J Kohlhase, unpublished results].
Blood	Mild thrombocytopenia and leukocytosis; present in some individuals.

Adopted from reference URL 4.

V Internal Medical Care

1 Managing Lifestyle Diseases



- Thalidomide victims with lifestyle diseases have been predominantly men, but a larger proportion of women with thalidomide embryopathy (TE) will likely develop lifestyle diseases as they enter menopause.
- About 40% of those with hepatic steatosis have dyslipidemia. Patients found to have hepatic steatosis in abdominal ultrasonography, a procedure that does not involve pain, should be encouraged to give a blood sample to use to test for lifestyle diseases such as abnormal lipid metabolism and/or metabolic syndrome.
- In addition to upper-limb hypoplasia and auditory hypoplasia, a substantial proportion of thalidomide victims have cardiac malformations, gallbladder agenesis, and other internal disorders. About 40% of those without a gallbladder have block vertebrae. Those with neck stiffness or pain who are found to have gallbladder agenesis in abdominal ultrasonography should be encouraged to undergo cervical vertebra X-ray or magnetic resonance imaging (MRI) to check for block vertebrae.

1 Lifestyle Diseases

Like the general Japanese population, patients with TE may develop lifestyle diseases.

(1) Definition and concept of lifestyle diseases

A lifestyle disease is a disease caused or worsened by a lifestyle habit, such as poor eating (e.g., overconsumption of calories, salt, or fat), inactivity, smoking, or drinking. Examples include diabetes mellitus (DM), dyslipidemia, hypertension, and hyperuricemia.

Prevalent diseases have changed in Japan as the population rapidly ages. Lifestyle diseases such as DM, hypertension, dyslipidemia, cancer, ischemic heart disease, and cerebrovascular disease make up a growing proportion of all diseases afflicting society.

(2) Frequency of lifestyle diseases in patients with TE

The frequency of lifestyle diseases in patients with TE is shown in Table 1. Hepatic steatosis and hypertension were common, affecting about half of both sexes. In decreasing order of prevalence, other common

Table 1 Frequency of lifestyle diseases in patients with thalidomide embryopathy

Factor	Overall (%)	Men (%)	Women (%)
Central obesity	20/82 (24.4)	14/33 (42.4)	6/49 (12.2)
Dyslipidemia	26/73 (26.3)	18/44 (40.9)	8/55 (14.5)
Hypertension	42/85 (49.4)	26/39 (66.7)	16/46 (34.8)
Impaired glucose tolerance	16/98 (16.3)	12/43 (27.9)	4/55 (7.3)
Hyperuricemia	22/99 (22.2)	19/44 (43.2)	3/55 (5.5)
Central obesity + dyslipidemia	3/94 (3.2)	3/40 (7.5)	0/54 (0.0)
Central obesity + hypertension	5/85 (5.9)	2/34 (5.9)	3/51 (5.9)
Central obesity + glucose metabolism disorder	1/91 (1.1)	0/37 (0.0)	1/54 (1.9)
Metabolic syndrome	7/87 (8.0)	7/34 (20.6)	0/53 (0.0)
Hepatic steatosis	43/84 (51.2)	25/37 (67.6)	18/47 (38.3)
Nonalcoholic fatty liver disease	16/48 (33.3)	13/24 (54.2)	3/24 (12.5)
Osteoporosis	8/64 (12.5)	3/27 (11.1)	5/37 (13.5)



Lifestyle diseases, hepatic steatosis, dyslipidemia, hyperuricemia, metabolic syndrome, gallbladder agenesis, block vertebrae, menopause

lifestyle diseases were nonalcoholic fatty liver disease, dyslipidemia, central obesity, hyperuricemia, and impaired glucose tolerance. Metabolic syndrome was common only in men, with a prevalence of about 20%. Lifestyle diseases were noted more often in men in the latest round of health examinations. Female hormones may have protected women from developing metabolic syndrome. No consensus has been reached on the relationship of male and female hormones to insulin sensitivity and metabolic syndrome. One study found a significantly lower incidence of metabolic syndrome in supposedly premenopausal women 50 years of age or younger with a homeostasis model assessment-insulin resistance (HOMA-R) score of ≥3.0. (HOMA-R was determined as the product of the fasting plasma insulin level [μU/mL] and fasting plasma glucose level [mg/dL] divided by 405) Scores were assessed as an indicator of insulin resistance. A HOMA-R score of ≤1.6 was considered normal, and a score of ≥2.5 indicated insulin resistance. Female hormones are believed to be interrelated with metabolic syndrome pathogenesis because women with polycystic ovary syndrome, who have amenorrhea and hyperandrogenemia, show metabolic syndrome-like insulin resistance, and these patients, when undergoing treatment with metformin or a thiazolidine drug to lower insulin resistance, show a response in terms of not only their metabolic syndrome-like condition, but also amenorrhea[1]. A larger proportion of women with TE will likely develop lifestyle diseases as they enter menopause.

Similar to metabolic syndrome, hepatic steatosis was common in the men of this population. About four times as many men as women had nonalcoholic fatty liver disease. A study found that the prevalence of hepatic steatosis remains constant in men beginning at age 30 but increases with age in women to a level comparable to men by the time women are in their 60s[2]. This study suggests that female hormones may be related to the frequency of onset of hepatic steatosis, as was the case with metabolic syndrome in men. Since estrogen protects against visceral obesity, reductions in female hormones following menopause likely contribute to the progression of hepatic steatosis. Hepatic steatosis is therefore expected to occur more often in women with TE as they enter menopause. This group must eat better to prevent hepatic steatosis. About 40% of those with hepatic steatosis had dyslipidemia. Hepatic steatosis is generally considered a hepatic manifestation of metabolic syndrome. Our findings indicate that patients found to have hepatic steatosis in abdominal ultrasonography, a procedure that does not involve pain, should be encouraged to give a blood sample to use to test for lifestyle diseases such as abnormal lipid metabolism and/or metabolic syndrome.

Hyperuricemia and dyslipidemia are risk factors for arteriosclerosis and poor renal function. These lifestyle diseases must be identified early through health examinations and treated with a therapeutic regimen that includes guidance on diet and nutrition to prevent complications. An investigation of the eating habits of patients with TE showed that a high proportion ate non-fish meat three to seven times a week (Figure 1). Although no statistically significant correlations were found between eating habits and lifestyle diseases, the high prevalence of dyslipidemia indicates the need for diet therapy in which patients are advised to reduce meat consumption. Overconsumption of fructose is another relevant dietary habit that can cause hyperuricemia[3]. The

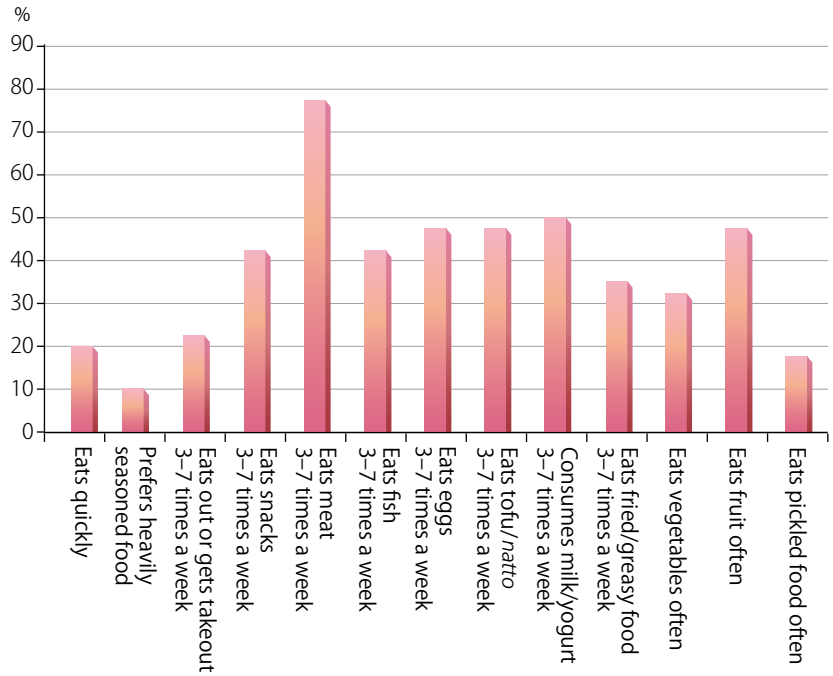


Figure 1 Eating habits

general eating habits of those with TE (Figure 1) indicate that a relatively high proportion eat fruit daily. Future dietary guidance for patients with TE should include a warning not to overconsume fructose.

Hyperuricemia is known to contribute to chronic kidney disease (CKD) via the rennin-angiotensin system. Renal function must be protected in thalidomide victims because administering dialysis in people with upper-limb defects is difficult. One goal of physicians examining patients with TE must be to protect renal function by keeping uric acid levels in check.

Although we did not find hypertension to be a risk factor for left ventricular hypertrophy in this latest round of health examinations of patients with TE, the presence of left ventricular hypertrophy in electrocardiography should be grounds to use echocardiography and other tools to further examine the heart because left ventricular hypertrophy may be the result of a failure to diagnose latent hypertension. Patients with left ventricular hypertrophy identified through electrocardiography must have their blood pressure properly controlled under the guidance of their physician as they monitor blood pressure at home. Just as collecting blood from patients with TE with upper-limb hypoplasia is difficult, catheter-based treatment for ischemic heart disease and shunting for dialysis are often unfeasible. Preventing cerebrovascular disease and other such vascular diseases is therefore very important. Controlling blood pressure helps prevent vascular disease in the brain and other locations. An arm cuff is typically used to measure blood pressure in patients with mild upper-limb defects. It must be remembered, however, that a small upper-limb circumference may result in an underestimation of blood pressure (Section XII-2).

2 Gallbladder Agenesis

A substantial proportion of patients with TE have cardiac malformations, gallbladder agenesis, and other internal defects, in addition to upper-limb hypoplasia and auditory hypoplasia. Internal abnormalities apparently congenital in nature were identified in the latest round of health examinations. These included conditions involving cranial nerves and diseases of the cervical vertebrae, blood vessels, gallbladder, and liver[4]. An investigation of the interrelation of these internal defects with a focus on gallbladder agenesis revealed block vertebrae in about 40% of the patients with TE with no gallbladder. Those with neck stiffness or pain who are found to have gallbladder agenesis in abdominal ultrasonography should be encouraged to undergo cervical vertebra X-ray or MRI to check for block vertebrae. Gallbladder agenesis was seen only in the upper-limb hypoplasia and mixed patients; it was absent in the patients with auditory hypoplasia alone. A total of 87.5% of the patients with block vertebrae fell into the upper-limb hypoplasia or mixed category. Although no statistically significant relationships were found between upper-limb hypoplasia and these internal organ defects (gallbladder agenesis and block vertebrae), teratogenically, vertebral formation begins in the sixth week of gestation. Block vertebrae are sometimes attributed to localized blood-flow disorders in the third to eighth weeks of gestation, which coincide well with the embryonic period when upper limb defects occur (third to seventh weeks of gestation). Since the mechanism of TE may involve impaired neovascularization, it follows that block vertebrae sometimes appear in TE upper-limb defects[5].

References

1) Noguchi Y, Tatsuno I, Saito Y: Gender difference of metabolic syndrome. Obstetrical and Gynecological Therapy 94 Suppl:518-522, 2007. (*in Japanese*)
2) Kojima S, Watanabe N, Numata M, et al: Increase in the prevalence of fatty liver in Japan over the past 12 years:analysis of clinical background. J Gastroenterol 38:954-961, 2003.
3) Masuzaki H, Yabiku K, Yamakawa K: Endocrine disease: progress in diagnosis and treatment. Topics: III. Recent topics; 2. Dyshomeostasis of uric acid metabolism in humans: recent research progress and clinical perspective. Nihon Naika Gakkai Zasshi 101:1027-1033, 2012. (*in Japanese*)
4) Hasuo K, Wada T: Study of internal disorders in thalidomide embryopathy. In: Yoshizawa A, principal investigator. The second report of the study funded in FY2011 by a Grant-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare of Japan under the title 'National Study on the Health and Living Situation of Thalidomide-Impaired People'. Tokyo: Hakuaisha. 14-16, 2013. (*in Japanese*)
5) Yoshizawa A, Kimura S, Moriyoshi Y, et al: National Study on the Health and Living Situation of Thalidomide-Impaired People. In: Yoshizawa A, principal investigator. The first report of the study funded in FY2011 by a Grant-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare of Japan under the title 'National Study on the Health and Living Situation of Thalidomide-Impaired People'. Tokyo: Hakuaisha. 1-5, 2012. (*in Japanese*)

[Tomoko Shiga]

V Internal Medical Care

2 Endocrine and Metabolic Disorders



- Obesity may be the result of limited physical activity.
- Hepatic dysfunction is often caused by hepatic steatosis.
- Patients often have dyslipidemia.
- Some patients have impaired glucose tolerance or chronic kidney disease (CKD).
- Osteoporosis may affect men as well as women.
- halidomide and its derivatives cause thyroid dysfunction and, endocrine and metabolic disorders.

1 Introduction

We have examined 16 men and 31 women with TE (47 patients; mean age: 52 years) at National Hospital Organization Kyoto Medical Center. Four of the men and eight of the women (12 patients) have undergone two examinations, which brings the total number of examinations to 20 for men and 39 for women, or a total of 59 examinations (mean age: 53 years). A summary of our findings as follows.

- We have treated seven patients (three men and four women) for hypertension, four (two men and two women) for diabetes mellitus (DM), nine for dyslipidemia (four men and five women), and two (two women) for osteoporosis. Two patients (two men) had a history of gout.
- A man (6.3%) and nine women (29%) had obesity (i.e., body mass index [BMI] >25 kg/m^2). One of the women had a BMI of 34.4, which constitutes moderate (Class II) obesity. Two of the patients had lost weight since the previous examination, experiencing a decrease in BMI from 26 to 23 kg/m^2 (60 to 53 kg) and 27 to 23 kg/m^2 (73 to 63 kg).
- Four men (25%) and four women (13%) had high alanine aminotransferase (ALT) levels (>30 IU/L). (Two of the men experienced improvement.)
- Eight men (53%) and 19 women (61%) had hyper low-density-lipoprotein (LDL) cholesterolemia (Friedewald equation) (>120 mg/dL). (Two of the women experienced improvement.) Six men (38%) and seven women (23%) had hyper triglyceridemia (TG) (>150 mg/dL). A man (6.3%) had hypo-high density lipoprotein (HDL) cholesterolemia (<40 mg/dL).
- Three men (19%) and three women (10%) had a high hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program) level (>6.2%).
- Seven men (44%) and three women (9.7%) had hyperuricemia (>7.0 mg/dL). (One of the men had a level of 8.3 mg/dL.)
- CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) was seen in a man (eGFR = 55) and two women (eGFR = 17, 59).
- Bone mineral density (BMD) analysis revealed a lumbar spine density constituting osteoporosis (<70% of the young adult mean [YAM]) in three patients (a man and two women) and reduced bone mass (70–80% of YAM) in nine patients (three men and six women). Femoral neck density constituted osteoporosis in eight patients (a man and seven women) and reduced bone mass in 17 (five men and 12 women).
- Blood thyroid stimulating hormone (TSH) levels were abnormal in three of the 29 patients (10%) tested. The level was slightly high in two patients (6.9%, a man and a woman) and slightly low in a patient (3.4%, woman). 2. Overweight

2 Lifestyle Diseases

Three of the 12 patients examined twice at this medical center had started a new treatment for a lifestyle disease between the examinations. (Another three remained on the treatment they were on at the first examination.) The findings of the first examination may have prompted some of the patients to start treatment. Five of the patients (two men and three women) were being concurrently treated for at least two of the following diseases: hypertension, DM, and dyslipidemia. Accumulating risk factors, which ultimately lead to atherosclerotic diseases, must be addressed through consistent (stepped up) diet and exercise therapy.



Lifestyle diseases, obesity, hepatic steatosis, dyslipidemia, impaired glucose tolerance, chronic kidney disease, osteoporosis, thyroid dysfunction, endocrine and metabolic disorders

3 Overweight

Patients with TE are prone to becoming overweight because of developmental limb disorders or being a stay-at-home person. Although no patient we examined at this medical center had severe obesity (BMI >35), one had a BMI of 34, and one in five patients (21%) had mild obesity (BMI >25). As these patients age, they will be at increased risk of reduced muscle mass in their healthy limbs (sarcopenia) and weight gain as this reduction lowers their basal metabolism (sarcopenic obesity). Ways must be found to maintain muscle mass in these patients.

4 Hepatic Steatosis

Hepatic steatosis: Unrelated to high ALT, abdominal ultrasound showed findings of fatty liver (high hepato-renal echo contrast) in nine men (56%) and 12 women (39%). At-risk patients would benefit from an improved diet (2014 Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis, ed. by Japanese Society of Gastroenterology).

5 Dyslipidemia

More than a half of the patients (27 of 47, eight men [53%] and 19 women [61%]) had hyper LDL cholesterolemia (>120 mg/dL). Blood LDL cholesterol levels were 150–159 mg/dL in three men and two women, 170–179 mg/dL in two women, and 200–299 mg/dL in two women. Blood triglyceride levels were 200–299 mg/dL in two men and three women and 300–399 mg/dL in a man and two women. Persisting lipid disorders exacerbate arteriosclerosis. At-risk patients would benefit from proper eating habits and appropriate pharmacotherapy (2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases: ed. by Japan Atherosclerosis Society).

6 Abnormal Glucose Metabolism

HbA1c (NGSP) was in the 7% range in a patient (on treatment) and the 6% range in five (two on treatment, another with no abnormal level in the first examination). Most of the patients examined twice had elevated HbA1c levels and therefore require follow-up (Japanese Clinical Practice Guideline for Diabetes 2019: ed. by Japan Diabetes Society).

7 Hyperuricemia

Hyperuricemia not only causes gout flare-ups, but also is now considered a risk factor for arteriosclerotic diseases. One male patient had a blood uric acid level on the order of 8 mg/dL. Pharmacotherapy would be recommended in such a patient if urinary calculus, renal disorders, hypertension, ischemic heart disease, DM, metabolic syndrome, or another such comorbidity were present (Third Edition of the Guideline for the Management of Hyperuricemia and Gout 2019, ed. by Japanese Society of Gout and Nucleic Acid Metabolism).

8 CKD

CKD is described further in another section. A female patient with an eGFR of 17 mL/min/1.73 m^2 showed findings of polycystic kidneys on an ultrasound examination. Solitary kidney and other deformations are reported in patients with TE. Caution in the form of regular health examinations is needed, even when no clear evidence of deformation is present, because these patients may experience age-related decreases in renal function more quickly than healthy people (2018 Evidence-based Clinical Practice Guideline for CKD, ed. by Japanese Society of Nephrology).

9 Osteoporosis

Two men (13%) and eight women (26%) had osteoporosis diagnosed based on BMD findings. Five men (31%) and 14 women (45%) had osteopenia. Endogenous risk factors for osteoporosis include (1) being a postmenopausal woman at least 55 years of age, (2) being underweight, (3) being on corticosteroids, (4) having DM or a thyroid disease, and (5) having a family member with osteoporosis, and lifestyle factors include (6) being a smoker, (7) being a heavy drinker, and (8) not exercising or getting adequate sunlight (2015 Guideline for Prevention and Treatment of Osteoporosis, ed. by Japanese Society for Bone and Mineral Research). Risk factor #8 is a particular concern in patients with TE.

10 Endocrine and Metabolic Abnormalities

Although we did not perform any health examinations focusing on endocrine function, the secondary effects to thalidomide listed below suggest that embryonic exposure could possibly affect the development of endocrine tissues.

The secondary effects of thalidomide and the thalidomide derivative lenalidomide on endocrine and metabolic function are as follows:

(1) Abnormal insulin resistance: Increased insulin resistance[1)]
(2) Hypothyroidism[2–5)]: Incidence of 0.9% (per package insert)
(3) Thyroid toxicity: Cause of thyroiditis[6,7)]
(4) Hypoadrenalism[8)]
(5) Hypogonadism[9)]

References

1) Iqbal N, Zayed M, Boden G. Thalidomide impairs insulin action on glucose uptake and glycogen synthesis in patients with type 2 diabetes. Diabetes Care 23:1172-6, 2000
2) Alexander, IRW. Acute Myxedema. Br Med J 2:1434, 1961
3) de Savary N, Lee R, Vaidya B. Severe hypothyroidism after thalidomide treatment. JR Soc Med 97:443, 2004
4) Figaro MK, Clayton W Jr, Usoh C, et al. Thyroid abnormalities in patients treated with lenalidomide for hematological malignancies: results of a retrospective case review. Am J Hematol 86:467-70, 2011
5) Iams WT, Hames ML, Tsai JP, et al. Increased serum tumor necrosis factor α levels in patients with lenalidomide-induced hypothyroidism. Exp Hematol 43:74-8, 2015
6) Stein EM, Rivera C. Transient thyroiditis after treatment with lenalidomide in a patient with metastatic renal cell carcinoma. Thyroid 17:681-3, 2007
7) Hamnvik OP, Larsen PR, Marqusee E. Thyroid dysfunction from antineoplastic agents. J Natl Cancer Inst 103:1572-87, 2011
8) Yorke RA, Sutton WS, Kilshaw D, et al. Neuropathy, hypoglycaemia, and adrenal dysfunction during treatment with thalidomide. Br Med J 8:306, 1962
9) Ordi J, Cortes F, Martinez N, et al. Thalidomide induces amenorrhea in patients with lupus disease. Arthritis Rheum 41:2273-5, 1998

[Tetsuya Tagami]

V Internal Medical Care

3 Kidney Disease, Hypertension, and Cardiovascular Disease



- To keep patients off dialysis, chronic kidney disease (CKD) should be identified early and, when found, immediately brought to the attention of a nephrologist.
- Malformations of the kidneys, urinary tract, and urinary system must be kept in mind.
- Although blood pressure should always be measured accurately, when a patient is unsuited to arm blood pressure measurement, blood pressure should be measured near the medial malleolus and arm systolic blood pressure should be estimated using an estimating equation.
- Do not overlook congenital heart disease.
- Refer patients with a clinically significant electrocardiographic abnormality or echocardiographic finding to a cardiologist at a hospital familiar with thalidomide embryopathy (TE).

1 Chronic Kidney Disease (CKD)

Patients with TE are prone to developing CKD because of associated lifestyle diseases, including lack of exercise, obesity, impaired glucose tolerance, dyslipidemia, and hypertension. (Hypertension tends to be diagnosed late because many patients do not undergo routine measurement of blood pressure.) Healthcare professionals must realize that lifestyle diseases can progress rapidly in those people with TE who tend to avoid medical care at medical institutions and dislike using drugs out of concern for side effects.

(1) Definition and concept of CKD

CKD, which has become a well-known concept, is defined here.

i. A urinary abnormality, diagnostic imaging, blood work, or pathology distinctly indicate the presence of a renal disorder. The presence of proteinuria of ≥0.15 g/g serum creatinine (Cr) is particularly telltale.
ii. Glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2.

The persistence of i and/or ii for at least 3 months demonstrates CKD.

CKD is often the result of chronic glomerulonephritis, nephrotic syndrome, diabetic nephropathy, and hypertensive renal disease (e.g., nephrosclerosis), which cause urine test abnormalities. Solitary kidney, polycystic kidney, and other anatomical abnormalities, as well as tubule-related hypokalemia and other electrolyte abnormalities, may also contribute.

(2) Diagnosing and scrutinizing CKD

CKD is clinically diagnosed by proteinuria of at least 0.15 g per gram Cr and GFR less than 60 mL/min/1.73 m^2.

GFR is determined according to serum Cr, age, and sex. In adults, the estimated GFR (eGFR) is determined using a formula for estimating GFR in Japanese people[1)]. CKD can therefore be readily diagnosed based on routine diagnostic tests.

The severity of renal impairment is classified according to eGFR. A grade of G3a is assigned for eGFR levels of 45 to <60, G3b for levels of 30 to <45, G4 for levels of 15 to <30, and G5 for levels of <15. Patients with TE require no special attention when renal function is G1 or G2 (i.e., eGFR ≥60); however, when renal function is G3a or above, they should be referred to a nephrologist to maintain renal function.

Patients with TE often have congenital organ abnormalities in addition to congenital limb malformations. Ultrasonography, CT, or MRI should be performed in



Chronic kidney disease, lifestyle diseases, glomerular filtration rate, kidney/urinary tract malformation, undescended testicle, renal biopsy, hemodialysis, shunt, hypertension, upper-limb defect, elbow, blood pressure measurement technique, blood pressure cuff, lower-limb blood pressure, upper-limb systolic blood pressure estimate, peripheral artery disease, Doppler blood flow meter, Guidelines for the Management of Hypertension, compliance, congenital heart disease, ischemic heart disease, cardiac failure, electrocardiography, echocardiography, cardiac catheter, coronary arteries, auditory defect

a medical examination to check for not uncommon renal and urinary tract malformations. (Patients with TE enrolled in the detailed health examination program of the Ministry of Health, Labour and Welfare's TE Research Group never fail to undergo organ screening.) Patients should be checked for solitary kidney, morphological anomalies of the renal pelvis, ureters, and bladder, and undescended testicles. Having a solitary kidney could mean poor renal function in older age. Undescended testicles left alone are more likely to undergo malignant transformation. TE experts in Japan, Germany, and the UK list these conditions as requiring special consideration.

(3) Significance and progression of CKD

CKD is a risk factor for cardiovascular disease (CVD). The lower the GFR, the greater the risk of CVD. In this respect, CKD should be checked to prevent CVD.

Patients with CKD caused by diabetes mellitus (DM) or hypertension are at greater risk of developing CVD than patients with CKD caused by nephritis. Patients with TE will be prone to these diseases as they age. Management and treatment are therefore very important. As they enter their advanced years, patients with TE should all have a doctor to routinely monitor for and control these lifestyle diseases.

Doctors identifying a patient with TE with a CKD stage of G3a or greater should work with a nephrologist to maintain GFR as best as possible. Care should focus on treating the underlying disease: DM should first be controlled in patients with diabetic nephropathy, and nephritis treatment should be given priority in patients with primary glomerulonephritis. Once the underlying disease is treated, blood pressure should be properly controlled and diet therapy (e.g., reduced sodium, protein, and potassium diets, sufficient water intake in the pre-dialysis stage) should be considered. Factors that worsen renal function (e.g., contrast agent use, nonsteroidal anti-inflammatory drugs [NSAIDs], dehydration) must also be explained.

Caution is required when performing a renal biopsy on identifying proteinuria or nephrotic syndrome. Renal biopsy is generally not impossible but is more difficult in patients with TE and should therefore be done at an experienced medical institution. Specifically, patients with upper- or lower-limb defects may find maintaining certain postures on a bed difficult during renal biopsy and may have organs that are anatomically displaced. Organ placement must therefore be carefully determined before the biopsy. Patients with an auditory defect must be communicated with via sign language or signs. Greater effort is required to ensure that the procedure proceeds properly and safely.

Patients whose CKD has progressed to end-stage renal failure must begin hemodialysis (HD) or peritoneal dialysis, which present their own challenges for those with TE. In Eastern and Western countries, most patients with TE and with end-stage renal failure are placed on HD. Although exact figures are unavailable, at least two to three or more patients with TE in Japan, Germany, and the UK are on HD. Patients who begin maintenance HD must be shunted (blood access) to allow needle insertion for each session. Shunting in patients with TE is challenging because their blood vessels are narrow and underdeveloped and are often not arranged as in anatomical textbooks. Moreover, deformities and shortening of forearm bones and joints can complicate vascular anastomosis. Even experienced vascular surgeons and nephrologists will find creating a normal arteriovenous fistula (AVF) of the forearm difficult. Whenever possible, careful up-front evaluation with angiography, ultrasonography, or a vein imaging device should be performed. As AVF creation can be extremely challenging, artificial graft insertion is sometimes necessary. Patients with end-stage renal failure who require a shunt should therefore be referred to an experienced shunt specialist so that sufficient blood flow can be achieved with just one operation. These words of caution apply not only to dialysis shunts. All vascular procedures are more difficult to perform in patients with TE than in general patients.

(4) CKD-related findings from comprehensive medical examinations

Examination data from the previous research group (FY2014–2016) are available and presented here for reference.

The mean eGFR of the 57 examined patients was 85.5±20.4 mL/min/1.73 m^2. Only four of these patients had CKD as defined by an eGFR of <60 mL/min/1.73 m^2 (≥ stage G3), and no patient was on HD or had end-stage renal disease. The three patients who were positive for both urinary protein and occult blood in urinalysis had an eGFR of ≥60 mL/min/1.73 m^2. Although these patients will have to be closely monitored for CKD if they continue to have abnormal urinalysis results, CKD does not appear to be more common in the patients examined than in the general population. Mean uric acid was 5.7±1.4 mg/dL, and 11 (19.3%) of the 57 patients had hyperuricemia (≥7.0 mg/dL) requiring treatment. Since CKD and hyperuricemia remain largely asymptomatic in the early stages, patients should undergo regular serum Cr (or eGFR) and uric acid tests, and start conservative therapy if the levels are persistently abnormal.

2 Hypertension

Hypertension affects an estimated 43 million people in Japan. Hypertension is estimated to cause about 100,000 deaths annually, second only to cigarettes. About half of all cerebro- and cardiovascular deaths are attributable to blood pressure exceeding the optimal range (120/80 mmHg)[2]. In the Japanese population aged 40–74 years, the prevalence of hypertension amounts to 60% in men

Table Blood pressure categories for adults (mm Hg)

Class	Examination room blood pressure (mm Hg)			Home blood pressure (mm Hg)		
	Systolic blood pressure		Diastolic blood pressure	Systolic blood pressure		Diastolic blood pressure
Normal blood pressure	<120	and	<80	<115	and	<75
High normal blood pressure	120–129	and	<80	115–124	and	<75
Hypertension	130–139	and/or	80–89	125–134	and/or	75–84
Hypertension I	140–159	and/or	90–99	135–144	and/or	85–89
Hypertension II	160–179	and/or	100–109	145–159	and/or	90–99
Hypertension III	≥180	and/or	≥110	≥160	and/or	≥100
(Isolated) systolic hypertension	≥140	and	<90	≥135	and	<85

2019 Guidelines for the Management of Hypertension, Japanese Society of Hypertension[2)]

and 41% in women. Hypertension is therefore a concern in people with TE now that they are around 60 years old.

(1) Diagnosing hypertension

Consecutive hospital-measured blood pressure readings of ≥140/90 mmHg constitute hypertension (Table)[2)]. The blood pressure of patients with TE, if they have upper limb defects, must be carefully measured by, for example, comparing the left and right arm blood pressure readings or taking multiple measurements on different days.

(2) Measuring and evaluating blood pressure

When a patient has a mild malformation of the upper arm or forearm, the caregiver should measure blood pressure as normal after checking for the pulse of the brachial artery at the elbow. In patients with substantial left–right differences in upper arm and forearm morphology, blood pressure should be measured on the side that has less elbow deformation and greater development of the bones to the wrist. In these patients in particular, the measurement site must be selected in careful consideration of the pulse determined through palpation on the left and right sides. When hypoplasia will not allow blood pressure to be measured at either elbow, a lower-limb blood pressure measurement performed as described below can be corrected with a formula to arrive at an estimated upper-limb blood pressure measurement.

A proper cuff size must be selected when measuring upper-arm blood pressure. Usually, medium blood pressure cuffs can accommodate upper-arm circumferences of 21–30 cm. Medium cuffs are therefore well-suited to the average arm size, but a small cuff may give a more accurate measurement in small-armed patients with TE whose upper-arm circumference is obviously <20 cm.

When lower-limb blood pressure measurement is necessary, the posterior tibial artery should be identified by palpation near the medial malleolus[3)]. Lower-limb blood pressure should be measured with an electronic (oscillometric) blood pressure meter. Once the posterior tibial artery is identified behind the medial malleolus, the cuff should be wrapped around the leg so that the ○ mark meets in this location. The start button on the blood pressure meter should be pressed after the patient is instructed to take a deep breath slowly and calmly. Blood pressure may be measured manually using a stethoscope instead of relying on automatic blood-pressure measurements obtained using an electronic blood pressure meter. If a medium cuff is used, the upper-limb systolic blood pressure can be estimated using the following formula (developed by a previous research group)[3)]:

Estimated upper-limb systolic blood pressure = 0.88 × (lower-limb systolic blood pressure + 8)

The German physician Dr. Jan Schulte-Hillen, himself a patient with TE, offers an Internet-based discussion of the findings of blood pressure measurements along with many helpful references[URL1)]. The site claims that systolic blood pressure is 20% higher when measured in the lower compared with the upper limbs, although the exact measurement may differ between Japanese people and Europeans.

(3) More information about lower-limb blood pressure

The following are applicable when the patient has severe lower-limb arteriosclerosis or peripheral artery disease (PAD)[3)]:

- Determining the ankle-brachial index should be considered for patients with severe arteriosclerosis but is not possible in patients with TE with marked upper-limb hypoplasia. These patients should be checked for a left–right difference in lower-limb blood pressure. If a difference is present, the popliteal and femoral arteries should be palpated to check for differences in pulse intensity. The findings may suggest lower-limb artery stenosis or obstruction.
- It must be remembered that patients with PAD often have low blood pressure readings, which makes it difficult to accurately evaluate blood pressure.
- If the blood pressure in the lower limbs differs, an upper-arm cuff can be fitted to an ankle to attempt measuring systolic blood pressure in the dorsalis pedis and posterior tibial arteries via a Doppler blood flow meter. With the higher reading taken to be the lower-limb blood pressure, patients should be checked for a

left–right difference. If no Doppler blood flow meter is available, an attempt can be made to measure systolic blood pressure in the dorsalis pedis and posterior tibial arteries by auscultation.

(4) Hypertension-related findings from comprehensive medical examinations

Comprehensive medical examination data on hypertension from the previous research group (FY2014–2016) is presented here.

Forty-one of those examined underwent upper-limb blood pressure measurement, and 50 underwent blood pressure measurement of either one or both of the lower limbs. Although some of the patients were on antihypertensive therapy, only 10 of the 57 patients had an upper-limb blood pressure measurement in the hypertensive range (≥140/90 mmHg). The previously discussed formula for estimating upper-limb systolic blood pressure developed by the prior research group was used to estimate the blood pressure of those unsuited for upper-limb measurement. Five of the 16 patients had an estimated upper-limb blood pressure of at least 140 mmHg. This formula appears to be applicable to patients unsuited for upper-limb blood pressure measurement because of upper-limb hypoplasia. After all, lower-limb blood pressure measurement was used to identify five (8.8%) of the 57 patients as possibly having hypertension. Upper-limb systolic blood pressure estimated from lower-limb systolic blood pressure readings, however, is 110.8±16.0% (right) and 107.8±13.6% (left) of actual upper-limb measurements, showing a tendency for the estimated value to be slightly higher than the actual value. Greater precision may require the estimation formula to be reevaluated.

(5) Treatment of hypertension

Hypertension should be treated by giving guidance on daily habits such as reducing sodium intake and selecting antihypertensive therapy according to the Guidelines for the Management of Hypertension[2]. No antihypertensive drugs are specifically contraindicated in TE. Routine treatment that factors in age, hypertension severity, and comorbidities is acceptable. Physicians, however, must put themselves in the shoes of the patient with TE with diseases other than hypertension because pharmacotherapy will require them to take more drugs. Since many thalidomide victims resist taking drugs, the physician must conscientiously convince the patient of the significance of medication and select an antihypertensive regimen that does not require the patient to take many dosage units. Pharmacotherapy must be selected to facilitate compliance in those few patients with TE with facial nerve palsy or dysphagia.

3 Cardiac Diseases

The general practitioner often encounters angina pectoris, myocardial infarction, cardiac failure, and other similar diseases in patients in their middle and later years. Since cardiac disease is more common in Europe than in Japan, a subject of intense concern among specialists there involves strategies to combat these diseases in patients with TE.

(1) Congenital heart disorders

It is widely known that thalidomide causes congenital heart diseases (e.g., valvular disease, atrial septal defect). Patients with TE complicated by a serious congenital heart disease generally die soon after birth or fortunately, the disease resolves by surgery. It is therefore rare for the disease to be found in middle-aged or older patients. Patients should nonetheless be examined by auscultation or echocardiography during visits to the doctor. This is to be sure that a mild to moderate congenital heart disease has not been overlooked.

Thalidomide has recently been shown to have wide reaching congenital manifestations. More specifically, some investigators claim that there is arrhythmia caused by congenital myocardial conduction disorders as well as directional and morphological abnormalities of the coronary arteries. All arrhythmias and ischemic heart diseases with abnormal electrocardiographic findings must be evaluated to determine if they have congenital origins.

(2) Ischemic heart disease and cardiac failure

Patients with TE are at high risk of developing CVD from lack of exercise, obesity, impaired glucose tolerance, dyslipidemia, hypertension, and CKD. Electrocardiography and echocardiography, in addition to blood pressure measurement, are needed to evaluate this risk. Patients with a clinically significant abnormal electrocardiographic or echocardiographic finding should be immediately referred to a cardiologist. Setting aside cases that are treatable with simple pharmacotherapy, patients requiring cardiac catheterization or another invasive procedure should be sent to a hospital with experience treating patients with TE whenever possible. Physicians who cannot readily identify any such hospital are welcome to consult with the Center Hospital of the National Center for Global Health and Medicine, where the Thalidomide Embryopathy Research Group is located, or with National Hospital Organization Kyoto Medical Center or Teikyo University Hospital. This is because some patients with TE have difficulty with stress electrocardiographic examinations owing to upper or lower limb disorders that impair their balance or limit their mobility. Communication disorders impair routine stress electrocardiographic examinations in patients with

TE with an auditory defect. Inexperienced technicians and nurses may encounter difficulty during the procedure.

Caution is also required for cardiac catheterization performed when ischemic heart disease is identified. Postural and balance problems are not the only hurdles, as blood vessels may be abnormally oriented. Catheterization is not impossible in patients with upper-limb defects, provided the hypoplasia is mild. However, finding a site in the upper arm to insert the catheter is elusive in those with moderate or severe defects. Moreover, damage to the artery of an upper limb could severely restrict the activities of a patient with TE. Such damage could also adversely affect shunt creation when needed in patients with TE with CKD. Particular caution is therefore warranted when catheterizing a patient via an upper limb. A femoral artery approach can also present concerns. The insertion site must be carefully considered in those patients with TE with femur malformation or hip abnormalities. Even if the catheter is successfully inserted, the coronary arteries may have slight anatomical discrepancies that could lead to a serious medical incident if overlooked. Extreme caution is therefore needed for catheterization and stent placement.

Caregivers must always remember that TE may involve vascular anomalies throughout the body in addition to the more well-known visually apparent anatomical anomalies (bone malformations and body shape in particular). Since these anomalies could seriously complicate treatment more than in typical patients if cardiac conditions are left unchecked, leading to myocardial infarction or severe cardiac failure, the physician must take responsibility for managing risk to keep the patient from these serious outcomes. Physicians must strive for the primary prevention of cardiac disease by giving smoking cessation guidance and thoroughly treating and managing obesity, glucose metabolism disorders, metabolic syndrome, dyslipidemia, hypertension, CKD, and other risk factors.

References

1) Evidence-based Clinical Practice Guideline for CKD 2018. Japanese Society of Nephrology (ed). Tokyo, Tokyo Igakusha, 2018
2) Guidelines for the Management of Hypertension 2019. Hypertension Management Development Committee of Japan (ed). Tokyo, Life Science Publishing Co., Ltd., 2019
3) Yoshizawa A, Nagase H, Seki H, et al. 6. Measuring and evaluating blood pressure. Q & A on Thalidomide-Impaired People. Yoshizawa A (ed). pp59-64, Tokyo, 2014

URL

1) Jan Schulte-Hillen. Measuring the blood pressure in patients with shortened arms due to thalidomide embryopathy. http://www.contergan-infoportal.de/ fileadmin/downloads/NEUDOWNLOADS/Medizinische_Beitraege/Blutdruckmessen/GB_blood_pressure_measurements_in_thalidomiders_with_upper_extremity_defects. pdf#search=%27SchulteHillen+thalidomide%27

[Fumihiko Hinoshita]

V Internal Medical Care

4 Preventing Respiratory Diseases and Infections



- No respiratory diseases or dysfunctions specific to patients with thalidomide embryopathy (TE) have emerged.
- In smokers, smoking cessation is important for preventing peripheral airway obstruction from progressing to chronic obstructive pulmonary disease (COPD).
- Strapless masks and masks for people with microtia are available to prevent the droplet transmission of infections.
- Alcohol disinfection is highly effective against the influenza virus. Alcohol disinfectants are sold as sprays and gels. Automatic hand sanitizers can be purchased for several thousand yen.
- Hand washing, disinfecting with sodium hypochlorite, and thoroughly heating shellfish are effective ways for preventing norovirus infections.
- Nicotine patches and oral varenicline therapy are effective pharmacotherapies for achieving smoking cessation.
- The out-of-pocket cost of insurance-covered smoking cessation therapy is about 250 yen per day, which is cheaper than a pack of cigarettes. Patients looking to quit smoking are more likely to achieve success if they begin treatment with determination.

1 Findings of Pulmonary Function Tests in 55-year-old Patients with TE

Thirteen patients (mean age: 55.5 years) underwent pulmonary function tests in the FY2017–2018 Health Screening Project. Percent vital capacity (%VC) was 111.5% and forced expiratory volume in 1 second (FEV_1%) was 79.1%. No respiratory diseases or dysfunctions specific to patients with TE have emerged. No abnormal findings suggestive of emphysema were made on chest computed tomography (CT), but most patients had peripheral airway obstruction that was more prominent among the smokers. Peripheral airway obstruction is attributable primarily to smoking and aging. In this investigation, the smokers had an estimated $\%V_{25}$ of <50%.

A total of 23% of those examined were smokers (vs. the national mean of 17.9%), and the smoking index was high, at 426, exceeding the threshold risk level for COPD. Since these patients could avoid progression to COPD by stopping smoking now, mainly the patients with TE who are smokers should undergo regular pulmonary function tests.

Those with COPD-related shortness of breath tend to be less physically active and venture outside less. Physical activity is strongly correlated with good outcomes, with relevant guidelines stressing the importance of regularly walking and otherwise keeping physically active. The physical pain experienced by patients with TE puts them at greater risk of low physical activity, which makes preventing COPD all the more important so that respiratory disease does not become an additional hurdle. As informing patients about the benefits of smoking cessation is important, all patients with TE should undergo a smoking survey that factors in e-cigarettes and be offered a smoking-cessation program.



Obstructive ventilatory defect, upper-limb defects, influenza virus, droplet transmission, contact transmission, vaccination, norovirus, sodium hypochlorite, smoking cessation, nicotine patch, varenicline, nicotine dependence

2 Preventing Respiratory Infections

[Focusing on prevention strategies aimed at the influenza virus and SARS-CoV2]

Influenza virus infections generally peak around February of each year, but current infection information should be monitored because in some years, infections begin emerging more early than normal in certain regions. Infections are generally transmitted via two routes. Droplet transmission occurs when someone inhales virus particles contained in droplets coming from the cough of an infected person. Contact transmission occurs when someone touches a doorknob or other surface touched by an infected person and then touches their nose or mouth. Strategies for influenza viruses are also applicable to SARS-CoV2. Strategies for preventing infections are listed here:



Figure 1 Mask with long straps



Figure 2 Strapless mask



Figure 3 Automatic hand sanitizer

(1) Preventing droplet transmission: Wear a mask and avoid going to crowded locations.
Masks for people with microtia are commercially available. Examples are masks with long straps (search for "mask for microtia," Figure 1) and strapless masks that are adhered to the cheeks with silicone tape (search for "strapless mask," Figure 2). These masks also help prevent pollen allergies.

(2) Preventing contact transmission: Wash and disinfect hands after going out.
Remember to wash your hands after returning home. Alcohol is highly effective against the influenza virus. Disinfecting the hands with an alcohol product is useful for people unable to rub their hands together. Alcohol sprays, such as Welpas, and gels, such as Softy Hand Clean, are available. Gel products can be dispensed and applied with one hand. Automatic hand sanitizers can be purchased for several thousand yen (search for "automatic hand sanitizer," Figure 3). They can be operated with one hand and can also be used for the feet.

(3) Maintaining optimal humidity levels: Breathing dry air reduces the defensive properties of the airway mucosa, which increases the chance of getting sick. A humidifier should be used to maintain proper humidity levels (50–60%).

(4) Getting enough rest and eating nutritious, well-balanced meals

(5) Getting a flu shot: Influenza vaccination reduces the chance of developing the flu and prevents influenza infections from worsening. Flu shots require about 2 weeks to become effective and should therefore be given by mid-December. Only one shot is needed. A shot is needed every year because the effects wear off after about 5 months and prevalent strains change from year to year. Flu shots contain an inactivated vaccine free of pathogens and therefore cannot cause influenza. Adverse reactions, which include redness and swelling at the injection site, fever, headache, and fatigue, normally resolve within 2–3 days. Shock and other severe adverse reactions are rare. Expert review revealed no death clearly causally related to vaccination. Most deaths occurred in older people with severe heart or kidney disease.

3 Preventing Infectious Gastroenteritis

[Focusing on prevention strategies aimed at norovirus]

Norovirus infectious gastroenteritis and food poisoning can occur year-round but are most prevalent in the winter. Norovirus infections occur when virus on fingers or food enters the mouth and propagates in the intestines, causing vomiting, diarrhea, and abdominal pain. Symptoms appear 24–48 hours after exposure.

Fever is mild, and symptoms generally resolve after 1–2 days. No vaccine or antiviral medication is available for norovirus. Symptomatic treatment with intravenous fluids may be necessary for severe dehydration. Antidiarrheal medications should not be used because they can prolong the disease.

Mechanisms behind acute viral gastroenteritis include (1) infection from virus particles that get on the hands from the feces or vomit of an infected person and (2) direct human-to-human transmission of droplets in a home or other location where people are in close proximity to one another. Viral food poisoning occurs (3) after eating contaminated food handled by an infected person, (4) after eating contaminated shellfish not heated, and (5) after consuming incompletely disinfected well water contaminated with norovirus. Strategies for preventing infections are listed here:

(1) Hand washing: This is the most effective way to reduce virus particles on the hands. The hands must be washed before preparing or eating a meal, after using the restroom, and after coming into contact with a patient with diarrhea. Although soap contains no ingredients that directly inactivate norovirus particles, thoroughly washing and rinsing the hands removes oils and other contaminants to physically eliminate virus particles.

(2) Disinfecting with sodium hypochlorite: Norovirus is highly infective when infected individuals develop symptoms. Virus particles can remain on doorknobs and curtains touched by an infected person. A chlorine-based household bleach that contains sodium hypochlorite will work just as well. Sodium hypochlorite corrodes metals and strongly damages proteins and should therefore be completely wiped away after cleaning so that it does not remain on the skin or get inhaled.

(3) Thoroughly heating shellfish: Since most viruses are highly susceptible to heat, heating is an excellent way to inactivate virus particles. Shellfish and other foods should be cooked so that the internal temperature reaches 85–90 °C for at least 90 seconds.

4 Commentary on Disinfection

Viruses are structurally different and must therefore be disinfected in different ways. The envelope that surrounds certain viruses is made up of lipids. Soap and alcohol dissolve lipids and therefore inactivate envelope-containing virus particles such as the influenza virus. Other viruses, such as norovirus, are bare and not surrounded by an envelope. Soap and alcohol cannot inactivate these viruses, but sodium hypochlorite, with its strong oxidizing activity, directly attacks virus particles.

5 The Importance of Smoking Cessation

Patients with TE smoke at a rate above the national average. Patients with TE who are smokers should be given smoking cessation guidance. Smoking (1) increases the risk of all cancers, (2) exacerbates arteriosclerosis, which can lead to ischemic heart disease and cerebrovascular disorders, and (3) can cause COPD and peptic ulcers. Smoking also has aesthetic effects. By promoting melanin pigment formation and breaking down collagen fibers, smoking can cause "smoker's face," which features skin darkening and wrinkles. Passive smoking can cause respiratory symptoms in children and increases the risk of lung cancer among those living with a smoker. On quitting, smokers regain their sense of taste after a few days, have a lower risk of ischemic heart disease after 2 to 4 years, and have a lower risk of developing cancer after 10 years. Quitting smoking at age 50 was found to prolong life by 6 years. The mean age of patients with TE as of 2019 was 58 years, meaning that quitting smoking would substantially reduce their risk of cancer.

Nicotine dependence hinders efforts to quit smoking. When a smoker smokes a cigarette, nicotine enters the bloodstream and arrives at nicotine receptors in the brain. Dopamine is released, temporarily creating a sense of satisfaction that is replaced by a desire for more as dopamine levels fall. This cycle, which perpetuates the desire to smoke, is called nicotine dependence.

Some refrain from advising smokers to stop out of concern that they will be met with rejection. A study, however, found that 90.1% of smokers reacted favorably when advised to quit smoking. Considerate, continued reminders are an excellent first step on the path of cessation guidance. In Japan, two types of pharmacotherapy are available to help smokers quit: nicotine supplementation with nicotine patches, and oral varenicline (Champix®) treatment. Varenicline blocks nicotine receptors in the brain to lower the satisfaction gained from smoking and stimulates the release of small amounts of dopamine to reduce the impulse to smoke. Around 50% to <70% of smokers are able to successfully quit, and the success rate for varenicline is about 10% higher. Medical insurance covers only one 3-month course of smoking cessation therapy per year. Medical insurance does not cover second and subsequent courses for patients failing the first course. The total out-of-pocket cost for a 3-month course is in the 20,000-yen range, which amounts to about 250 yen a day, or about half the cost of a pack of cigarettes. A simple Internet search will reveal medical institutions that provide insurance-covered outpatient smoking cessation programs.

Patients who do not wish to quit seldom succeed, even when given pharmacotherapy. The chance of success is better for patients who seek help when they are 50% sure of succeeding. Do not insist that the patient begin treatment immediately. Instead, start smoking cessation

therapy once the patient gains confidence in their ability to quit.

URL

1) Tuberculosis Infectious Diseases Division, Health Bureau, Ministry of Health, Labor and Welfare. Influenza Questions and Answers.
hou01/dl/leaflet20110208_01.pdf#search=%27%E3%82%A4%E3%83%B3%E3%83%95%E3%83%AB%E3%82%A8%E3%83%B3%E3%82%B6+%E4%B8%80%E5%95%8F%E4%B8%80%E7%AD%94+%E5%8E%9A%E7%94%9F%E5%8A%B4%E5%83%8D%E7%9C%81%E5%81%A5%E5%BA%B7%E5%B1%80%27
2) Health Bureau, Ministry of Health, Labor and Welfare. Q & A about norovirus.
http://www.mhlw.go.jp/file/06-Seisakujouhou-11130500-Shokuhinanzenbu/0000129187.pdf

[Hiroyuki Nagase]

5 Esophagogastroendoscopy (EGD) and Gastrointestinal Diseases



- To relieve the tension and anxiety that patients will feel, caregivers should work to create a relaxing environment and sufficiently inform and reach an understanding with patients before the examination, particularly if they have a auditory disability.
- Patients with thalidomide embryopathy (TE) can be prepped for transoral/transnasal endoscopy like other patients.
- Esophagogastroduodenoscopy (EGD) can be performed without sedation. To sedate a patient with an upper-limb reduction defect, secure a route and perform monitoring via the lower limbs, being mindful of the dose of sedative used.
- A total of 52.9% of those examined did not have a *Helicobacter pylori* (HP) infection.
- One patient, found to have unexplained stenosis of the descending duodenum, reported mild obstruction made evident depending on the food form the patient had consumed. It is unclear whether this condition is a manifestation of TE.

1 Status

From FY2012 to FY2018, 57 patients from 16 prefectures and Australia were examined at National Hospital Organization Kyoto Medical Center. (Ten of these patients were examined for a second time in or after FY2017.) A total of 53 patients underwent an endoscopic procedure.

2 Determining Patient Information

Determine the physical characteristics of the patient to undergo endoscopy in advance. Specific characteristics to check for include upper-limb reduction defects and deafness. Explanatory signs should be prepared for deaf patients.

3 Observable Areas in EGD

The term "upper gastrointestinal tract" refers to the esophagus, stomach, and duodenum. In addition to these locations, the mouth cavity, middle and lower pharynx, and larynx can be observed via a transoral approach, while a transnasal approach allows viewing of the nasal cavity on the side of insertion, upper, middle, and lower pharynx, and larynx. Widespread use of HP eradication and gastric cancer screening is bringing the annual number of deaths from gastric cancer down from 50,000 toward 40,000. Nevertheless, 2017 statistics indicate that gastric cancer resulted in the third most deaths in Japan behind lung and colorectal cancer. Caregivers are advised to factor in HP infection status in addition to tumorous lesion involvement and deliberate and implement eradication therapy for those infected.

4 Advantages and Disadvantages of Transoral and Transnasal Endoscopy and Route Selection

The transnasal approach is advantageous in that it does not trigger the gag reflex since pressure is not applied to the base of the tongue, the patient is able to converse in a relaxed manner, and the lower impact it has on breathing and circulation compared with a transoral approach means less of a physical burden on the patient[1]. Older devices suffered from low picture quality and a poor visual field, but the latest devices have picture quality on par with transoral devices. Compared with transoral scopes, however, transnasal scopes have poorer biopsy capabilities when inverted in the cardiac orifice or lesser curvature, have poorer imaging capabilities for the descending duodenum, and handle more poorly in patients with a severe cascade stomach or when twisted on their axis. Because of the nature of the air/water channels and suction of transnasal scopes, the procedure may take 20–30% longer, but this does not typically cause the patient greater discomfort. This approach can cause nasal pain and epistaxis and is therefore contraindicated in patients who are prone to bleeding.



Thalidomide embryopathy, esophagogastroduodenoscopy, Endoscopic Pretreatment, sedation, transoral endoscopy, transnasal endoscopy, selection of endoscope insertion route, *Helicobacter pylori* infection, epistaxis, nasal pain

It is also not usable in patients with obstructive disease of the bilateral nasal cavities or upper pharynx. The procedure is contraindicated in patients on a monoamine oxidase inhibitor because these drugs, when used with 0.05% naphazoline nitrate, can cause a sudden increase in blood pressure.

5 Sedation

The guidelines recommend that EGD for population-based gastric cancer screenings be performed without sedation[2]. Patients unable to undergo transoral EGD without sedation may also be able to undergo transnasal EGD without sedation. At our screening center, we successfully provide both transoral and transnasal EGD to all subjects without sedation, and this is also the case for our thalidomide screenings. When sedation is not used, the screener can perform the procedure in communication with the subject, and the subject can view the image on a sub-monitor.

Recently, many institutions have begun to perform EGD with sedation to reduce discomfort and anxiety and make the endoscopy procedure more tolerable for the subject. When used, sedation must be provided in conformity to the "Guidelines for sedation in gastrointestinal endoscopy"[3] of the Japan Gastroenterological Endoscopy Society. Blood pressure and other vitals must be monitored when sedation is used. Patients with upper-limb hypoplasia or aplasia can be monitored at the posterior tibial artery of the lower limb, and the route for the sedative can also be secured in a lower limb. The dose of sedative must be carefully decided in consideration of body weight.

6 Local Anesthesia

Xylocaine spray alone is normally sufficient for transoral EGD and can be administered per the rules of the particular medical institution. Transnasal endoscopy is contraindicated in patients with a lidocaine allergy because of the risk of anaphylactic shock. Transoral EGD can sometimes be performed without anesthesia, but transnasal EGD normally requires local anesthesia to block the nasal pain involved. Local anesthesia is also contraindicated with patients with aspirin-induced asthma because the paraben preservative in lidocaine jellies and lubricants can trigger aspirin-induced asthma.

7 Informing the Patient before the Procedure

Send the information sheet to the patient before the procedure so they can gain a certain level of understanding. Patients with an auditory defect should be fully informed about the endoscopy procedure in advance because they may not be able to read signs during the procedure.

8 Endoscopic Pretreatment

Patients with TE can be prepped for transoral and transnasal endoscopy according to the usual protocol. The practices normally used at the endoscopy facility need not be changed. The following is a list of the preparations we carry out for transnasal endoscopy:

(1) Alternately close the left and right nostrils. Select the side with better air passage.

(2) Orally administer 5 mL of dimethicone syrup, 150 mL of lukewarm water, 20,000 units of pronase, and 1 g of sodium bicarbonate just before providing local anesthesia.

(3) Inject, spray, or apply as drops approximately 0.2 mL of 0.05% naphazoline nitrate to dilate the nasal cavity, prevent bleeding, and extend the duration of anesthesia. Apply to both sides in case the scope cannot be inserted into the originally selected side. Wait 10 minutes. Anesthetize the side with better airflow.

(4) Anesthesia can be administered with sticks (single- or two-stick method), with a spray, with both sticks and spray, or via injection. We administer anesthesia with a single stick at this medical institution. Specifically, 2 mL of a 2% xylocaine jelly (or viscous lidocaine solution) (20 mg of lidocaine hydrochloride per mL) is injected into the selected side, a 16-Fr stick is inserted, and then removed. The patient is asked to swallow xylocaine jelly flowing into the pharynx to anesthetize the pharynx. Forcing the stick in when there is resistance could cause pain or bleeding. Anesthetize the opposite side if there is resistance. Even if inserting the stick is difficult, the scope, with its angling mechanism, may be insertable. Add anesthesia if the patient complains of pain following insertion. Minimize the amount of lidocaine used, taking care not to exceed a total dose of 200 mg. Switch to a transoral approach (with the patient's consent) if the scope cannot be inserted into either side.

9 Transnasal Insertion

Insert via the wider of the middle concha or inferior concha routes. Have the patient breathe through the nose. After locating the upper pharynx, guide the scope to the middle pharynx. Have the patient stick out the tongue for a better view of the vallecula of epiglottis. After this, the route is the same as that with the transoral approach. In our thalidomide screenings, 29 of the 53 patients opted for transnasal EGD. Only one of those patients had to be switched to transoral EGD because the nasal cavity was too narrow.

10 Guidance

If the patient so wishes, allow the caregiver to be present in the room to put the patient at ease. Physical contact by a nurse (or the endoscopic technician) will help reassure the patient.

11 Diagnosis of helicobacter pylori (HP) Infections

At this medical center, we endoscopically assess HP infection status according to the Kyoto Classification of Gastritis[4], factoring in interview findings, and then diagnose the HP infection status of our patients in overall consideration of the results of a gastric cancer risk stratification test. Our thalidomide screenings have included this gastric cancer risk stratification test since FY2014.

12 Handling Epistaxis and Nose Pain from Transnasal Endoscopy

Keep the tip of the endoscope away from Kiesselbach's area during insertion. When the route is narrow, gently guide the scope forward while twisting it back and forth. Add about 1 mL of viscous xylocaine as needed. If there is resistance or the patient experiences severe pain, stop inserting the scope and switch to the other side. Switch to the transoral approach if you are unable to insert the scope via the other side. If the curved portion of the scope catches on the mucosa of the nasal concha during removal, apply a lubricant and guide it in to lubricate the area. Then, gently remove the scope, twisting it back and forth. Check for bleeding during the removal process and take a still image. Mild bleeding can be stopped by applying pressure by pinching the nasal wing for about 5 minutes with the patient in a slightly forward-leaning position. Pressure is normally sufficient to stop the bleeding. If the bleeding does not stop, insert a cotton ball soaked in 0.1% topical adrenaline diluted by a factor of 5 to 10 into the nasal cavity. This will often stop the bleeding. Profuse bleeding such as this, however, is a rarity that we have not encountered in our screenings of patients with TE.

13 Findings

The transnasal approach was used for 28 of the 53 patients, and the transoral approach for 25 (one patient with narrow nasal cavities was switched from a transnasal to transoral approach, but the narrowing was not associated with TE). One patient, found to have unexplained stenosis of the descending duodenum, reported mild obstruction made evident depending on the food form the patient consumed. It is unclear whether this condition is a manifestation of TE. No other anatomical anomalies were identified.

No patient had gastric cancer. Of the patients, 30 had a gastric mucosal atrophy classification of C0, two C1, six C2, two C3, six O1, seven O2, and none O3. Since FY2015, 36 patients with TE have undergone both endoscopy and gastric cancer risk stratification testing and received an overall HP infection status assessment. All but two patients (34 patients) did not use a proton pump inhibitor. Of these, 18 (52.9%) were not infected, nine (26.7%) had a current infection, five (14.7%) were previously infected and had undergone eradication, and two (5.9%) were previously infected but had not undergone eradication (i.e., incidental eradication). Since FY2018, we have performed HP culture for five patients with a current infection confirmed by endoscopy. All cultures were positive. Resistance was somewhat high, with clarithromycin resistance seen in 40% (2/5) and metronidazole resistance in 40% (2/5). Further investigation is needed, however, because the sample size was small. There were no accidental symptoms.

References

1) Yoshino J, Kobayashi J : Role and Significance of Small Diameter Endoscope in Gastric Cancer Screening. Manual for gastric cancer screening using transnasal endoscope. Japanese Society of Gastrointestinal Cancer Screening. IGAKU-SHOIN, 2-9, 2014 (in Japanese)
2) Narisawa R : Endoscopic Pretreatment. Gastric endoscopic examination manual for population-based gastric cancer screening. Japanese Society of Gastrointestinal Cancer Screening, Nankodo, 47-48, 2017 (in Japanese)
3) Obara K, Haruma K, Irisawa A, et al : Guidelines for sedation in gastrointestinal endoscopy. Gastroenterological Endoscopy 55:3822-3847, 2013 (in Japanese)
4) Kyoto Classification of Gastritis, 2nd Edition. Nihon Medical Center, 2018 (in Japanese)

[Nobuko Shima, Takama Maekawa]

1 Diagnosis and Assessment/Testing



- The age-related musculoskeletal disorders that thalidomide victims experience are attributable to overuse and misuse.
- Common musculoskeletal disorders are arthritis, arthralgia, and myalgia of the limbs, pain in the back and neck, and neuropathic pain and numbness.
- Congenital musculoskeletal malformations contribute to musculoskeletal disorders occurring later in life.

1 Congenital Musculoskeletal Malformations

Aplasia or hypoplasia of the limbs is the most common manifestation of thalidomide embryopathy (TE). Morphologically, these manifestations (1) occur as preaxial longitudinal hypoplasia, (2) have left–right symmetry, and (3) feature upper limb domination[1–3]. (1), preaxial longitudinal hypoplasia, appears as upper-limb aplasia on the radial (thumb) side and lower-limb aplasia on the tibial (great toe) side. Those with severe preaxial longitudinal hypoplasia of the upper limbs, for example, may have no radius and no thumb and other radial-side digits. Less severe cases feature thumb and thenar hypoplasia or triphalangeal thumbs (i.e., thumbs with proximal, middle, and distal phalanges like the other fingers) (Figures 1 and 2). Severe hypoplasia leads to phocomelia with shortening or agenesis of the humerus. The ulnar fingers and ulna show hypoplasia but are conserved (Figure 3). The most severe form is called amelia. (2), left–right symmetry, is another characteristic of TE, but there may exist some left–right differences in limb hypoplasia (Figure 4). (3), upper limb domination, indicates that lower-limb hypoplasia is generally milder than upper-limb hypoplasia. When present, lower-limb hypoplasia almost always accompanies upper-limb



Figure 1 Severe preaxial longitudinal hypoplasia of the upper limbs
The radius is missing, the ulna is shortened, the thumb is missing, the index finger shows hypoplasia, and the carpal bones are hypoplastic and fused. The wrist is bent toward the radial. This is known as club hand. The elbow shows hypoplasia.



Figure 2 Mild preaxial longitudinal hypoplasia of the upper limbs
The thumbs are triphalangeal. The left hand has a rudimentary metacarpal on the radial side.



Musculoskeletal disorder, tenosynovitis, peripheral neuropathy, osteoarthritis, carpal tunnel syndrome, overuse, misuse

hypoplasia. Hypoplasia of the lower limbs very rarely occurs in isolation. Japanese patients with TE have lower-limb hypoplasia less frequently than their European counterparts[3].

Limb hypoplasia may manifest aplasia, dislocation, and subluxation of the joints. In the upper limbs, hypoplasia of the humeral head and arm muscles with associated acromioclavicular joint protrusion is frequently seen in the shoulders (Figure 5). Even those without signs of lower-limb hypoplasia may have dislocation or subluxation of the hips, acetabular dysplasia, or hypoplasia of the femoral head (Figure 6)[1,2]. In the elbow, patients sometimes have proximal radioulnar synostosis or fusion of the ulna and humerus[2] that severely limits the range of motion.

In the spine, anomalies of the vertebral end plates and intervertebral discs are common and sometimes progress to vertebral fusion. Such fusion often occurs in the area of transition between the thoracic and lumbar vertebra. Scoliosis is also often present, and in some cases, features progressing deformity[2,4].

Congenital musculoskeletal malformations in patients with TE are evaluated with visual palpation and mainly plain X-ray. But now that the age-related changes discussed below are emerging, medical professionals must pay close attention to determine whether a malformation is congenital, acquired, or a combination of the two. Imaging with computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound may be warranted as necessary.

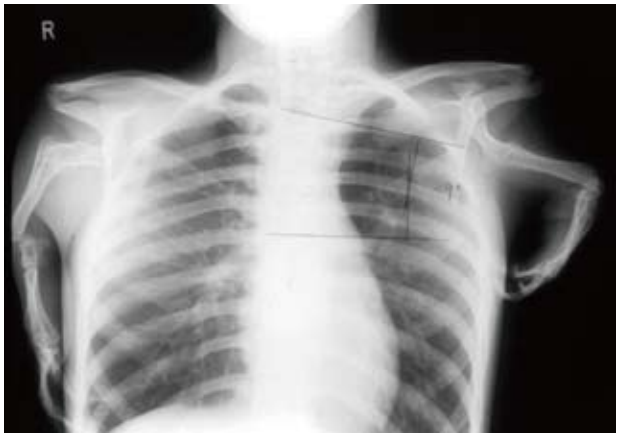


Figure 3 Phocomelia
Both humeri and radii show hypoplasia. Hands are present but have hypoplastic thumbs.



Figure 4 Upper-limb hypoplasia with left-right asymmetry
Both patients appear to have normal right upper limbs, but thumb hypoplasia is present.



Figure 5 Shoulder subluxation and acromioclavicular joint protrusion caused by bilateral humeral hypoplasia



Figure 6 Bilateral hip hypoplasia and coxarthrosis

2 Age-related Musculoskeletal Disorders

As an age-related health issue that patients with TE face, musculoskeletal disorders occur as frequently as psychiatric issues. Common musculoskeletal disorders are arthritis, arthralgia, and myalgia of the limbs, and pain in the back and neck, and neuropathic pain and numbness are also associated with TE[5]. The mechanisms behind musculoskeletal disorders associated with upper-limb hypoplasia, which is most common in Japanese patients with TE, are summarized in Figure 7. Patients with relatively mild upper-limb hypoplasia normally use their upper limbs to carry out activities of daily living (ADLs). As age-related changes from overuse and misuse accumulate, arthropathy, tenosynovitis, and peripheral neuropathy of the upper limbs occur. The term overuse refers to proper yet excessive use, while the term misuse refers to use in a non-normal fashion. An example of the latter is the use of the fingers for grasping by a patient with TE with no thumbs. Patients with relatively severe upper-limb hypoplasia, on the other hand, normally use their lower limbs to carry out ADLs. They develop spinal disorders and lower-limb arthropathy as age-related changes from overuse and misuse accumulate. Those who use the lower limbs to eat or wash their faces must bend their spine, which can be a source of spinal disorders. Overuse and misuse, however, are not the only causes of these disorders. The congenital limb and spinal malformations mentioned in the section "Congenital Musculoskeletal Malformations" above may also contribute.

Common examples of age-related upper-limb disorders are shoulder pain and osteoarthritis[6] and weakness and induration of the muscles of the upper limbs, and shoulder hypoplasia and soft-tissue anomalies are related to these conditions[7]. Pain attributable to instability and overuse of the elbows and wrists and tenosynovitis of the fingers may also occur (Figure 8).

A common form of peripheral neuropathy of the upper limbs is carpal tunnel syndrome, which is caused by median nerve compression in the wrists[8]. This condition, which is often secondary to radial aplasia, is attributed to a smaller cross sectional area of the carpal tunnel due to carpal hypoplasia[9]. Diagnosing TE-related carpal tunnel syndrome through studies of sensory disturbance and nerve conduction velocity is complicated by thumb hypoplasia. Ultimately, the diagnosis must be made in overall consideration of sensory disturbance in the index and middle fingers and the results of other tests (Tinel and Phalen signs) and neurophysiological tests[10].

Common age-related spinal disorders are neck pain, back pain, and cervical and lumbar radiculopathy[4,5,8,11]. The congenital anomalies of the vertebral end plates and intervertebral discs mentioned above, in addition to changes from overuse and misuse, contribute to these conditions, which show signs of degenerative spondylosis in X-ray imaging (Figure 9).

Osteoarthritis of the hips and knees is a common lower-limb disorder[6,12]. Coxarthrosis appears as secondary osteoarthritis due to congenital hip dysplasia (Figure 6). Although many with knee involvement have hypoplasia of the lateral condyle and intercondylar fossa as well as knock knee, most patients with TE without hypoplasia of the proximal femur have only mild arthrosis that is mostly asymptomatic[12].

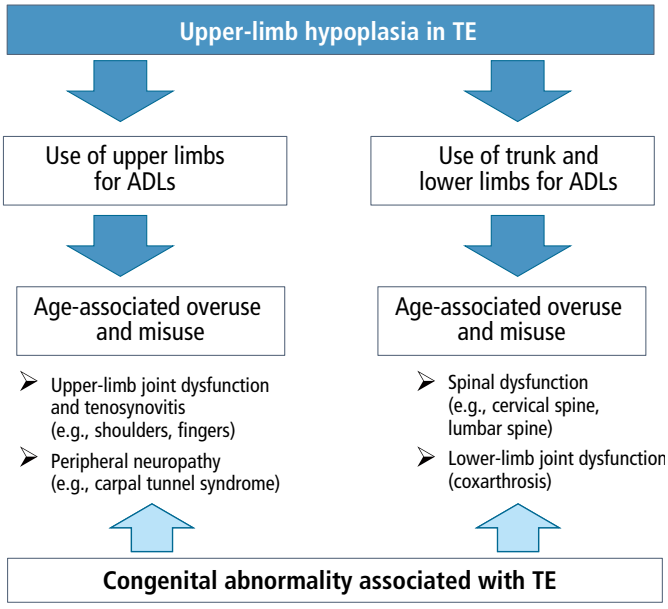


Figure 7 The mechanism of musculoskeletal dysfunction caused by upper-limb hypoplasia in TE



Figure 8 Thumb and thenar hypoplasia, with tenosynovitis of the other fingers due to overuse



Figure 9 Narrowing of the intervertebral space and spondylolisthesis in the lower lumbar spine

References

1) Vargesson N: Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today 105: 140-156, 2015.
2) Smithells RW, Newman CGH: Recognition of thalidomide defects. J Med Genet 29: 716–723, 1992
3) Ryooji Kayamori Post-Thalidomide Syndrome at 50 Years. Jpn J Rehabil Med 50: 957-961, 2013
4) Edwards DH, Nicholas PJR: The spinal abnormalities in thalidomide embryopathy. Acta Orthop Scand 48: 273-276, 1977
5) Newbronner E, Atkin K: The changing health of Thalidomide survivors as they age: A scoping review. Disabil Health J 11: 184-191, 2018
6) Bent N, Tennant A, Neumann V, et al: Living with thalidomide: health status and quality of life at 40 years. Prosthet Orthot Int 31: 147-156, 2007
7) Merkle TP, Beckmann N, Bruckner T, et al: Shoulder joint replacement can improve quality of life and outcome in patients with dysmelia: a case series. BMC Musculoskelet Disord 17: 185, 2016
8) Nicotra A, Newman C, Johnson M, et al: Peripheral nerve dysfunction in middle-aged subjects born with thalidomide embryopathy. PLoS One 11: e0152902, 2016
9) Kimura H, Ikuta Y, Ishida O: Carpal tunnel syndrome in radial dysplasia. J Hand Surg Br 26: 533-536, 2001
10) Oshima Y, Okutsu I, Hamanaka I, et al: Carpal tunnel syndrome accompanying radial dysplasia due to thalidomide embryopathy. J Hand Surg Br 31: 342-344, 2006
11) Ghassemi Jahani SA, Danielsson A, Ab-Fawaz R, et al: Degenerative changes in the cervical spine are more common in middle-aged individuals with thalidomide embryopathy than in healthy controls. PLoS One 11: e0155493, 2016
12) Ghassemi Jahani SA, Danielsson A, Karlsson J, et al: Long-term follow-up of thalidomide embryopathy: malformations and development of osteoarthritis in the lower extremities and evaluation of upper extremity function. J Child Orthop 8: 423–433, 2014

[Nobuhiko Haga]

2 Treatment and Support [1] Drug Therapy



- Administer drug therapy for pain and numbness while monitoring for side effects.

The age-related musculoskeletal disorders that patients with TE suffer can be broadly classified as pain caused by osteoarthritis and degenerative spondylosis, numbness and pain caused by peripheral neuropathy in a broad sense that includes the nerve roots, and pain attributable to another cause.

The complex mechanisms behind pain caused by osteoarthritis and degenerative spondylosis involve not only inflammation within joints, but also the spread of inflammation to surrounding tissues and bone marrow lesions[1)]. Drugs traditionally used include acetaminophen (an antipyretic analgesic with the Japanese brand name Calonal®) and nonsteroidal anti-inflammatory drugs (NSAIDs). The dose and duration of use of NSAIDs, however, must be carefully considered because long-term users risk gastrointestinal bleeding, cardiovascular events, and renal impairment. COX-2 selective inhibitors such as celecoxib are one type of NSAID with a more favorable gastrointestinal safety profile, but the risks of cardiovascular events and renal impairment they pose must be remembered. Non-narcotic opioids (tramadol, Japanese brand name: Tramal®) minimally damage the gastrointestinal tract and are sometimes used to treat chronic pain refractory to non-opioid analgesics. A tramadol-acetaminophen combination product (Japanese brand name: Tramcet®) is also available, but must be used with caution because of the nausea, vomiting, constipation, dizziness, and sleepiness it can cause. Serotonin-noradrenaline reuptake inhibitors (duloxetine, Japanese brand name: Cymbalta®), which relieve pain by improving the function of neurotransmitters in the brain, are sometimes used to treat osteoarthritis-associated pain. Topical products indicated for osteoarthritis include NSAID-containing compresses, gels, and lotions. Sodium hyaluronate and steroids are injected into joints to relieve osteoarthritis-associated pain. Sodium hyaluronate relieves pain by lubricating the joints but is indicated only for knee osteoarthritis. (Some products are also indicated for shoulder periarthritis.) Steroids have anti-inflammatory and analgesic effects but can destroy cartilage by inhibiting cartilage metabolism. Many experts believe that repeated steroid injections should be avoided.

Mecobalamin, a form of the coenzyme vitamin B_{12} that promotes repair of the peripheral nerves, is used to treat numbness and pain associated with peripheral nerve damage. Pain associated with peripheral nerve damage falls under the category of neuropathic pain, for which pregabalin (Lyrica®) and mirogabalin (Tarlige®) are indicated.

Other types of pain are often caused by tissue inflammation or peripheral nerve abnormalities and can be treated with the drugs mentioned above. Low back pain in the general adult population, however, occurs as unexplained "nonspecific lumbar pain" in 85% of cases. First-line treatments include nondrug treatments such as exercise therapy.

[Nobuhiko Haga, Ryoji Kayamori, Yasuhiro Maehara]



Drug therapy, osteoarthritis, degenerative spondylosis, pain, peripheral neuropathy, numbness

2 Treatment and Support [2] Surgery and Indications



- Arthroplasty is performed to treat osteoarthritis of the shoulders and hips.

Surgery is sometimes indicated for musculoskeletal conditions not treatable with conservative therapies such as drug therapy and rehabilitation. Patient eligibility, however, must be assessed with a full grasp of the congenital morphological anomalies associated with thalidomide embryopathy (TE).

Arthroplasty may be performed to treat osteoarthritis of the shoulders and hips[2,3]. Replacement of only the humerus side of the joint in a procedure called hemiarthroplasty may be used instead of standard shoulder replacement because of the hypoplasia of the shoulder components seen in patients with TE. This procedure was found to relieve pain and improve the range of joint motion[2]. No detailed studies of hip arthroplasty have been conducted.

Carpal tunnel syndrome is generally first treated with braces and other conservative therapy. The literature, however, does not mention the effects of conservative therapy in TE-associated carpal tunnel syndrome. Endoscopic carpal tunnel release can be performed when the response to conservative therapy is poor. A Japanese study found this procedure to be effective[4].

[Nobuhiko Haga, Ryoji Kayamori]

References

1) Ishida T, Sekiguchi T, Kihito Kawasanada: Mechanism of pain caused by arthritis and the latest advances in drug treatment. Journal of Japan Pain Clinic Society 25: 53-62, 2018
2) Merkle TP, Beckmann N, Bruckner T, et al: Shoulder joint replacement can improve quality of life and outcome in patients with dysmelia: a case series. BMC Musculoskelet Disord 17: 185, 2016
3) Ghassemi Jahani SA, Danielsson A, Karlsson J, et al: Long-term follow-up of thalidomide embryopathy: malformations and development of osteoarthritis in the lower extremities and evaluation of upper extremity function. J Child Orthop 8: 423–433, 2014
4) Oshima Y, Okutsu I, Hamanaka I, et al: Carpal tunnel syndrome accompanying radial dysplasia due to thalidomide embryopathy. J Hand Surg Br 31: 342-344, 2006



Artificial joint replacement, carpal tunnel syndrome, carpal tunnel release

2 Treatment and Support [3] Properly Interacting with People with Thalidomide Embryopathy (TE): A Physical and Occupational Therapy Perspective

Key Points

- Give patients lifestyle-focused guidance centered on activities of daily living instead of fixating on their body function and body structures.
- Consider giving guidance on correcting movement, finding creative approaches to movement, and making movement easier to people with limited reach due to upper-limb defects.
- For people who have difficulty grasping and pinching due to finger defects, consider giving guidance on identifying tools to help keep things from slipping out of grasp or reshaping or forming items to suit the grip of the people.
- Consider giving guidance about utilizing the features of smartphones (Android™, iPhone™) for people with auditory defects. (See the section on "Otolaryngology" for more information.)
- People with TE need guidance on how they can best live their lives, guidance that is unrestricted by the stereotypes of upper-limb and auditory defects.

1 Introduction

A basic picture of the morphological, body function and body structures seen in those with TE is given in other sections of this publication. This section, by contrast, presents approaches for addressing lifestyle issues related to activity and participation among people with TE.

2 Characteristics of Upper-limb Defects and Approaches to Guidance

The characteristics of TE in Japan include limb defects (e.g., amelia, phocomelia, ectromelia, thumb triphalangia) and auditory defects (e.g., deafness, anotia, microtia)[URL1)].

Those with upper-limb defects have a shorter reach because of their shortened upper limbs and must compensate to require the trunk forward(flexion), backward(extention), lateral bending and rotation. The typical extent of reach of the upper limbs is shown in Figure 1. Those with a shortened reach must compensate

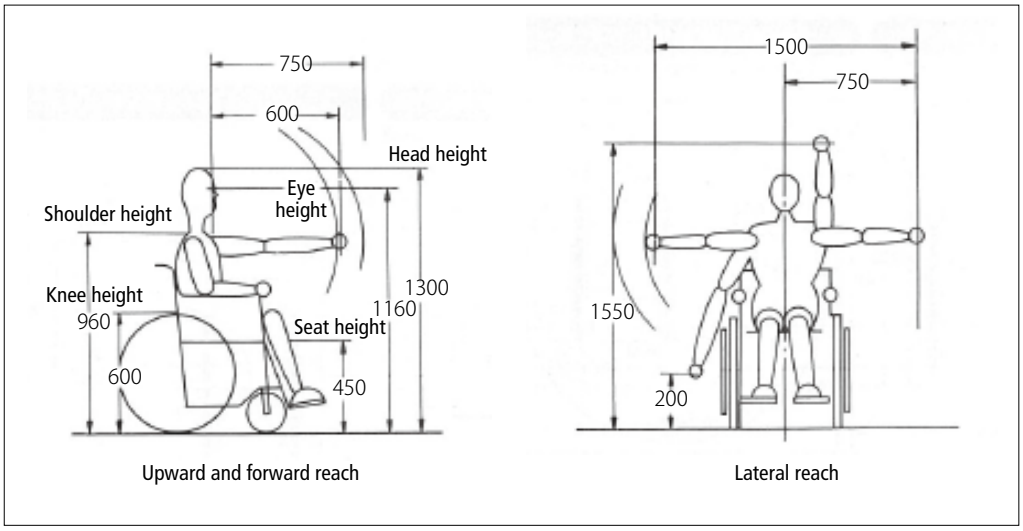


Figure 1 Reach of the upper limbs of a person seated in a wheelchair (TOTO Ltd.[2)], 1977) (dimensions are in millimeters)

Keywords

Reach, grasping and pinching, creative uses of tools, utilizing new devices

Table 1 Examples of difficulties in daily activities caused by a shorter reach of the upper limbs

◆ Picking up things that have fallen (or are dropped) on the floor
◆ Tearing off toilet paper from the toilet paper holder while on the toilet
◆ Raising and lowering pants and underwear while changing or using the toilet
◆ Taking items from high and low shelves while shopping
◆ Swiping prepaid transportation cards while using public transportation
◆ Retrieving items from the back of the refrigerator

with the trunk to perform daily activities (Table 1). People with TE and other with congenital defects grow up learning compensatory movements. On mastering these movements, they often do not realize the strain these movements create. People with TE have a higher incidence of cervical spondylosis compared with healthy individuals[1], and compensatory movements can result in overuse or misuse.

People should be fully informed that compensatory movements can lead to overuse and misuse, and be instructed about how to correct or refine their movements.



Figure 2 Using a reacher

Examples:

- ○ Correct movements to reduce the strain they cause by moving closer to light switches on the wall or squatting when picking up something from the floor.
- ○ Utilize tools to compensate for reduced reach by using a reacher to pick things up from the floor or using a long-handled brush when bathing (Figure 2).
- ○ Replace tools (or the living environment) with easier-to-use tools by selecting a dining-room chair with a higher back (and that is light and easy to grab) that helps the people better reach things or selecting a see-through glass desk so people who use their toes to operate their computer's keyboard and mouse can see their feet.

3 Characteristics of Finger Defects and Approaches to Guidance

Finger defects such as thumb triphalangia make it hard to bring the thumb together with the other fingers because certain digits are elongated and the opposable motion of the thumb is restricted. Those affected are often unable to manipulate their hands to grab or pinch things and must adopt compensatory hand shapes to, for example, sandwich things with the fingers (Figure 3). These hand shapes can cause substantial strain in frequent daily activities, such as holding a heavy item such as a tablet or book or holding chopsticks or a pen.

Kamakura[3] classifies uses of the hands in daily activities into eight categories. Since people with TE have difficulty correcting hand function, they benefit from guidance on replacing or creatively modifying the tools they use that is informed by the categories of Kamakura.



Figure 3 How people with TE hold the hands when grasping things (left: rolled paper, middle: chopsticks, right: pen)

Examples:

- When doing office work, find ways to stop the fingers from slipping, such as by using finger sleeves to make things easier to hold.
- Find ways to make instruments like chopsticks less slippery and easier to hold by selecting those with a nonslip or thick shaft.
- Modify chopsticks and pens to suit the grip of the user by reshaping or forming the shaft so it is easier to hold (Figure 4). Select instruments for longer activities, such as eating or writing, that have a rubber grip to reduce fatigue. Such instruments are also easier to carry around (Figure 5).



Figure 4 Molded handles
Left: A handle reshaped for the each user's hand with thermoplastic resin and added an effect of a non-slipp by a rubber bands.
Right: This handle makes gripping and holding easier for the user who grasps it between the index and middle fingers.
(Courtesy of Shizuka Yoshida, Occupational Therapist, National Center for Global Health and Medicine)



Figure 5 A bespoke reacher
Reachers can be made from the leg of a camera tripod so they can be shortened when carried and extended when used. A custom tip has been added to this reacher to make it easier to use for the user.
(Courtesy of a person who asked to be referred to as "A")

4 Characteristics of Auditory Defects and Approaches to Guidance

The communication difficulties from deafness in those with auditory defects face are a major hurdle to daily activities. See the section on "Otolaryngology" for more information. Several solutions are presented here.

Examples:

- When conversing with those with an auditory disorder, face the listener, speaking slowly and moving the mouth.
- Magnetic writing boards and word processing applications (e.g., Word™) of smartphones (Android™, iPhone™) are convenient tools for written conversation.
- Voice recognition and text tracing applications for smartphones (Android™, iPhone™) are useful in different situations. Examples are Google Docs™ and Siri™ on the iPhone.

5 Conclusions

Kobayashi[4] suggests that many people with TE suffer from chronic stiff shoulder and lumbar pain and lifestyle diseases and other medical conditions from a variety of factors in addition to overuse and misuse and have workplace and age-related stress at subjectively perceived levels higher than in the general population. In his paper, Kobayashi notes that dizziness is a complaint of not only people with auditory defects, but also those with upper-limb defects, proposing from the results of postural sway testing that thalidomide victims with upper-limb defects may have labyrinthine equilibrium disturbances[5]. Caregivers must appreciate the fact that people with TE, who are now in or approaching their 60s, have difficulty with daily activities because of many factors in addition to more obvious age-related declines in body function and body structures. Each of their complaints must be taken seriously so that multidimensional guidance can be given not only on maintaining body function and body structures, but also on refining their living environment.

References
1) Shadi A. Ghassemi Jahani, Aina Danielsson, Rana Ab-Fawaz, et al.:Degenerative Changes in the Cervical Spine Are More Common in Middle-Aged Individuals with Thalidomide Embryopathy than in Healthy Controls. PLoS One 11(5): e0155493, 2016
2) TOTO Ltd. (TOTO): Equipment and devices for the physically handicapped, mainly those who use wheelchairs. TOTO Ltd. (TOTO), P8, 1977
3) Kamakura N: Hand shape Hand movement. Ishiyaku Publishers, Inc., p4-p9, 1989, Tokyo
4) Kobayashi T: From the results of a survey of the living conditions of thalidomide embryos. Ministry of Health, Labor and Welfare Grant-in-Aid for Scientific Research Pharmaceuticals and Medical Devices Regulatory Science Research Project "Study on Health and Living Conditions of Thalidomide Embryonic Disease Patients (H23-Pharmaceuticals-Designation-023)" 2013 Summary / Shared Research Year Completion Report, May 2014
5) Kobayashi T, Suzukamo Y, Idee S: Equilibrium function of thalidomide embryonic disease. 52nd Annual Meeting of the Japanese Society of Rehabilitation Medicine, 2015

URL
1) Ishizue Foundation:Thalidomide and Drug-induced sufferings
http://ishizue-twc.or.jp/thalidomide/damage-01/

[Takeshi Kobayashi, Junko Fujitani]

2 Treatment and Support [4] Addressing Musculoskeletal Pain and Inconveniences in Daily Living Through an Ergonomic Approach



- To relieve nonspecific musculoskeletal pain, it is required to reduce the physical strain of daily activities by refining the patient's environment based on assessments of their physical function and living and working environments.
- It is recommended to provide lifestyle guidance gently and considerately on personal time management (i.e., limiting smartphone use) and health management (e.g., cigarette cessation), which are effective ways to reduce fatigue.
- Ergonomic devices and tools can be used to eliminate inconveniences in daily living.

1 Introduction

The "Lifestyle Survey of Thalidomide Victims"[1] revealed that those with thalidomide embryopathy (TE) "are more likely to have shoulder stiffness and lumbar pain than their healthy peers" and that "people with upper limb defects have difficulty doing chores, cleaning, and other household tasks but lack supportive services." Now that many patients with TE are in their 50s, musculoskeletal conditions (pain) secondary to their underlying pathology have begun to emerge and are likely to worsen over time.

We previously built a team consisting of a proffetional ergonomist, physical therapists, doctors, and nurses to address the needs of individual patients (who included thalidomide victims, victims of the Morinaga Milk arsenic poisoning incident, people with drug-induced muscle contracture, patients with refractory diseases, and people with other physical disabilities). The team interviewed and observed patients in their homes and workplaces to determine what musculoskeletal and other issues they faced. The team then redesigned their environments in consideration of their physical capabilities to reduce the strain of their daily activities, thereby alleviating their musculoskeletal symptoms. Refining their environment to be appropriate for their posture and movements often reduced the physical strain they experienced, alleviated musculoskeletal symptoms, and eliminated their inconveniences in daily living thanks to adjustments made to the devices and tools they used.

2 Disabilities in Daily Activities due to Musculoskeletal Impairment by Upper-limb Hypoplasia

(1) Effects of shortened limbs

Those with shortened limbs have a shorter reach often accompanied by muscular weakness. These hindrances frequently force them to bend forward or even twist their trunk when they do kitchen chores or use a computer. These awkward postures have little impact over short times. Chores and computer work, however, normally take several hours to complete. The small momentary strain due to awkward postures can build up over time, leading to disabling fatigue as well as stiff shoulders and lumbar pain.

The neck pain caused by the extended use of smartphones and other devices has become an issue in the general population. Those with shortened limbs are forced to adduct their shoulders as they hold their smartphone in one hand while operating it with the other. This is a risk factor of shoulder and upper back pain. Those with upper-limb hypoplasia likely have thoracic outlet stenosis that could be a risk factor of numbness.

(2) Shoulder hypoplasia

Carrying luggage with the upper limbs or backpack on shoulder causes the shoulders and shoulder girdle to drop, which can stretch or compress the brachial plexus, causing pain.

(3) Hypoplasia of the upper-limb musculature

Atrophy of the upper-limb musculature combined with disuse syndrome that can affect people with upper-limb hypoplasia leaves them prone to fatigue and pain when they are overly active or carry heavy things.



Nonspecific pain, secondary disorders, ergonomics, living environment refinements, reducing the strain of daily activities, posture and motion

(4) Spinal column symptoms

Poor posture from cervical spondylosis, block vertebrae, left–right asymmetry, and spinal distortions often lead to stiff shoulders, lumbar pain, osteoarthritis, and joint instability.

(5) Wrist pain

Thalidomide victims have a normal median nerve but narrower than normal carpal tunnels because of wrist bone hypoplasia. This narrowness leaves the median nerve prone to compression, which is a cause of carpal tunnel syndrome.

3 Identifying Issues in Interviews

Most patients with TE have complicated feelings about medical institutions. The issues they face can be identified by considerately asking them about their daily life.
Key matters to address in interviews:

- What are the burden and difficulty faced in daily life and work, and how much time do these consume (for work, how long are working hours, overtime, and breaks)? What are the environments and conditions like? What is your posture like? What your body sites are strained?
- Do the physical limitations of being a thalidomider influence the burden and difficulty faced (e.g., limited range of joint motion, muscular strength, reach)?
- How are the lifesyle habits (e.g., quantity and quality of sleep, smoking status, exercise habit)?

Try to identify the problem, keeping in mind the likely effects of unapparent carpal tunnel and thoracic outlet stenosis that affect many patients with TE.

4 Ergonomic Remedies

Generally, elevating the working plane reduces the strain on those with shortened limbs. Several examples are presented here.

(1) In the first example, improving the environment where a laptop computer was used and the posture of the user helped alleviate shoulder stiffness, lumbar pain, and upper-limb numbness. To improve the sitting posture (forward-leaning trunk, kyphosis, scoliosis), the monitor was raised, and a knitted mesh cushion with a viscoelastic consistency similar to muscle and a form-fitting memory-foam back support with microbeads were added (Figure). A handle was attached to the top of the mouse to allow one-handed manipulation even by those with little grip strength (Photograph 1). Surface electromyography showed reduced muscle load on the trapezius and erector spinae, and his symptoms improved.

(2) A holder that lets people with shortened limbs operate their devices more easily is shown in Photograph 2.



Photograph 1 A computer mouse with a handle

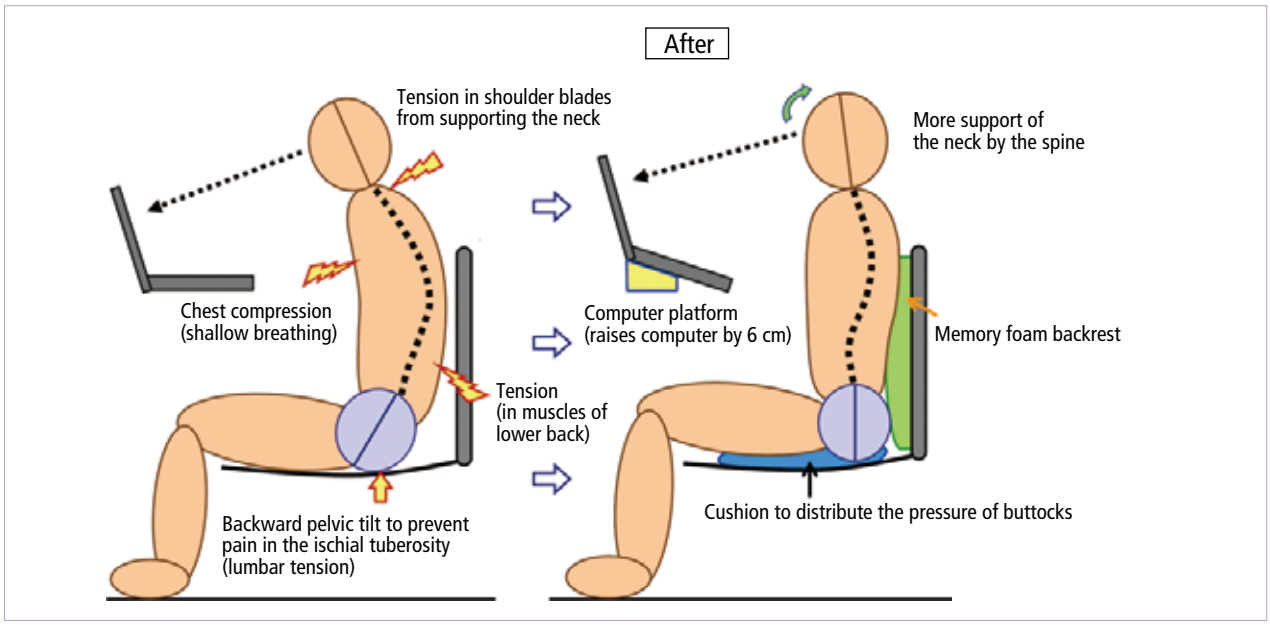
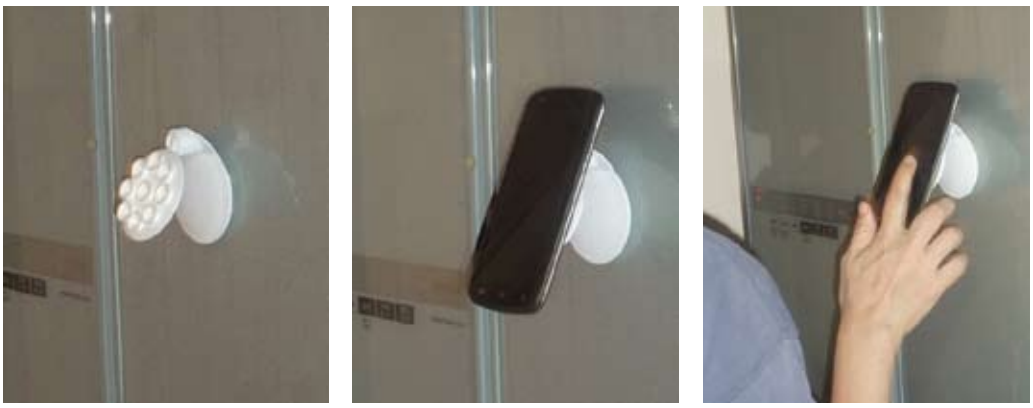


Figure An improvement of working environment for easier operation of a computer user



Photograph 2 A cellphone holder



Photograph 3 An assistive device to help a thalidomide victim open and close the refrigerator

(3) A short-limbed person with muscular weakness kept getting hit in the face when straining to open the refrigerator door. An assistive device for resolving this problem is shown in Photograph 3. The lengths of the ring to put the hand through and the straps that hold the ring are adjustable.

5 Recommendations for Health Management

Musculoskeletal symptoms arise from the accumulation of daily strain, even without a specific contributing disease, leading to nonspecific musculoskeletal pain. Guiding on developing good lifestyle habitst is effective in order to reduce stress without compromising anything and to eliminate fatigue due to daytime act on the day. Patients, of course, must not be forced into anything. Conscientiously tell the patient what they can easily do and what their efforts will produce.

A specific recommendation is personal time management, such as limiting the time spent on electronic devices. Some recommendations for health management are smoking cessation, daily exercise sufficient to make the patient break a sweat, stretching, and calisthenics. Relieving fatigue is also important, and to this end, relaxing in a warm bath and using ergonomic sleep products should prove helpful.

These ergonomic approaches should help alleviate the musculoskeletal symptoms of patients. Caregivers unable to offer them should refer their patients to the consultation center of the Ishizue Foundation for a consultation that includes ergonomic solutions.

6 Conclusions

Even simple ergonomic interventions informed by occupational health practices have proven effective in reducing musculoskeletal pain. Assessment of the physical function and environment of patients with TE with an understanding of the physical and mental characteristics of TE and providing interventions (improving posture, modifying working style) based on the findings should reduce the physical strain they experience.

References

1) Yoshizawa A, Kimura I, Kayamori R, etc. A study on the health and living conditions of thalidomide embryonic disease patients nationwide. Regulatory Science Comprehensive Research on Pharmaceuticals and Medical Devices 2015.

[Hiroji Tsujimura, Shin-ichi Shirahosi]

VII Radiological Examination and Evaluation

- The "Q&A on Thalidomide-impaired People" provides useful information for preparing for radiological procedures.
- Technicians preparing to perform a chest X-ray must determine how they will give the patient instructions and be careful that the patient does not fall.
- Dual-energy X-ray absorptiometry (DXA) should be used for bone mineral density (BMD) analysis of the lumbar spine and femoral neck.
- For mammography, sufficiently informing a patient about the procedure and communicating with the patient in addition to identifying her physical characteristics is essential to ensuring that the procedure goes smoothly and produces the imaging necessary to make a diagnosis.
- To facilitate a magnetic resonance imaging (MRI) scan, patient details should first be collected to allow a plan (e.g., equipment, patient positioning, imaging conditions) to be formulated. The patient should be continually monitored during the scan so that any issues can be dealt with on the spot.

1 Preparing for Radiological Procedures

(1) Interviewing and informing the patient before the procedure

Radiological procedures require a cooperative patient. Radiology technicians must know the physical characteristics of individual patients with thalidomide embryopathy (TE) and how best to give them instructions. When the patient has auditory hypoplasia, the technician needs to determine if a sign-language interpreter is necessary or if the patient can lip-read. Conveying the steps of the procedure to a patient with TE via an interpreter before the procedure, if available, will help the procedure go smoothly and put the patient at ease. Signs with instructions and information about the procedure for the patient to read are also helpful. Photographs and illustrations can be added to these signs to give the patient a better idea of the procedure (Figure 1). Sometimes patients with TE must assume awkward postures or limb positions for imaging. Patients with upper-limb hypoplasia may find raising their arms or holding their arms up particularly difficult. The physical characteristics and level of mobility of the patient must be conveyed to each imaging team to allow them to provide proper assistance.

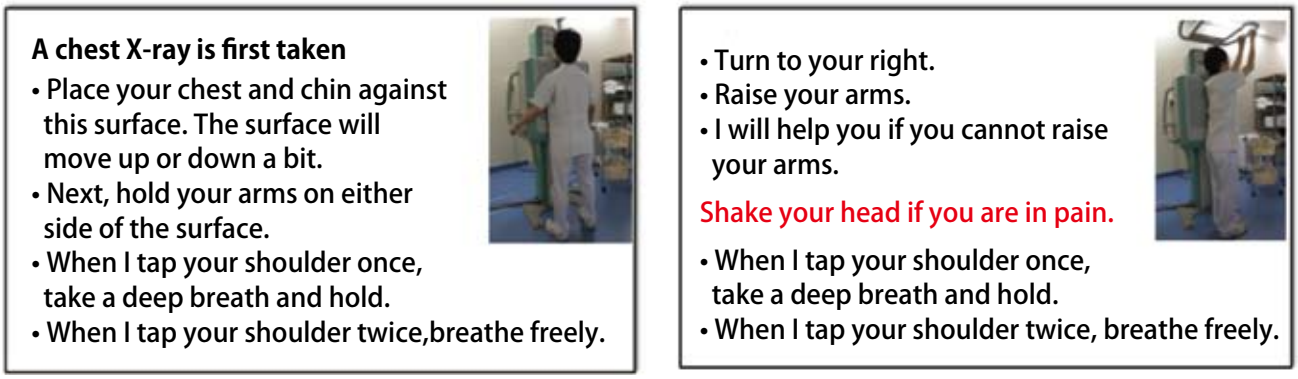


Figure 1 Signs with patient instructions for a chest X-ray

Changing clothes, front-tying gown, patient with upper-limb hypoplasia, patient with auditory hypoplasia, chest X-ray, bone mineral density analysis, osteoporosis, lumbar spine, femoral neck, dual-energy X-ray absorptiometry, mammography, breast cancer, positioning, computed tomography, magnetic resonance imaging, diagnostic imaging, image assessment

(2) Changing into gown and preparation

Radiological imaging often requires the patient to change clothes, so the imaging team must determine whether the patient needs help changing before the procedure. Gowns that are tied in the front (Figure 2) and slip-on gowns (Figure 3) are available. Patients should be allowed to choose the type they can most easily change into. A slip-on gown should be offered to patients with TE with upper-limb hypoplasia because they may not be able to tie a front-tying gown.



Figure 2 Front-tying gown



Figure 3 Slip-on gown

[Azusa Minagawa]

2 1. General Imaging: Chest X-rays

Chest X-rays are the most commonly performed radiological procedure. This is also true for patients with TE. Discussion begins with this basic procedure to provide a foundation for a patient-centered approach to other radiological procedures.

(1) Chest X-rays for TE patients with upper-limb hypoplasia

The biggest concern during the imaging procedure is falls. Comfortably position the patient, giving voice commands and monitoring all the while. Allow patients to reposition themselves or raise their upper limbs on their own as much as they can. Patients are particularly prone to falling during side X-ray imaging because they can lose their balance when raising their upper limbs (Figure 4). Have patients unable to raise their upper limbs extend their upper limbs forward, offering assistance as needed (Figure 5).

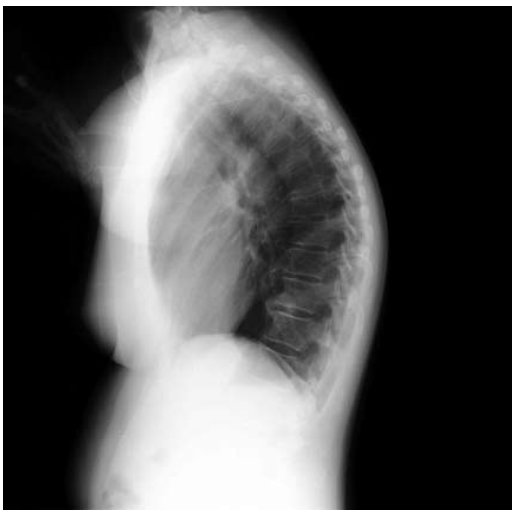


Figure 4 Lateral chest X-ray image



Figure 5 Upper-limb assistance for a patient undergoing a lateral chest X-ray

(2) Chest X-rays for TE patients with auditory hypoplasia

The technician must determine how the patient will be instructed to breathe. As in the section on interviewing and informing the patient, the technician will need to determine how to convey instructions. If the patient can lip-read, the technician should remove their mask and speak slowly, making large mouth movements. If written communication is to be used, the technician should prepare signs with instructions and information about the procedure in advance and point to these signs to facilitate the imaging procedure (Figures 6 and 7). Written communication could be used to tell the patient to hold their breath when the technician taps their shoulder once and to breathe out when the technician taps their shoulder twice. For each of these means of communication, the technician should monitor the patient's face while standing in front of them.

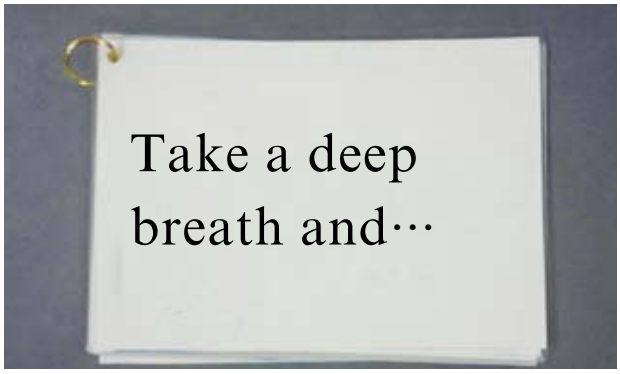


Figure 6 A sign with instructions



Figure 7 A patient is instructed with the sign

[Azusa Minagawa]

2 2. General Imaging: Bone Mineral Density (BMD) Analysis

Loss of BMD in osteoporosis increases the risk of fractures, which can substantially reduce quality of life (QOL). Secondary prevention is in order for patients with TE because they are more likely to have low BMD. BMD should be regularly analyzed and evaluated to prevent the deterioration in daily function and reduction in QOL that fractures can cause. Patients with congenital functional and morphological disorders of the upper limbs are limited in the activities they can perform and therefore suffer, in addition to insufficient bone development and muscular weakness, secondary dysfunction as they age. BMD is an important parameter to determine regularly in order to help prevent fractures that can reduce QOL. Monitoring for risk factors and lifestyle guidance are also necessary.

(1) Definition of osteoporosis

The WHO defines osteoporosis as "A disease cThe World Health Organization (WHO) defines osteoporosis as "A disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk." Diagnostic categories (criteria) for osteoporosis are shown in Table 1.

Table 1 Diagnostic categories of WHO based on BMD[2)]

Normal	Hip BMD greater than the lower limit of normal, which is taken as 1 SD below the young adult reference mean (T score ≥–1).
Low bone mass (osteopenia)	Hip BMD between 1 and 2.5 SD below the young adult reference mean (T score less than -1 but above –2.5).
Osteoporosis	Hip BMD 2.5 SD or more below the young adult reference mean (T score ≤–2.5).
Severe osteoporosis	Hip BMD 2.5 SD or more below the young adult reference mean in the presence of one or more fragility fractures (T score ≤–2.5 plus fracture).

(2) BMD analysis

Microdensitometry (MD), DXA, quantitative ultrasound, and other procedures are used to determine BMD. Patients with TE with upper-limb hypoplasia are unsuited to MD and radius-based DXA, which are relatively easy procedures. As recommended by the Japanese Society for Bone and Mineral Research, DXA of the lumbar spine and proximal femur should be used for diagnosing osteoporosis[1)]. Our medical institution determines BMD using DXA of L1 to L4, imaged from the front, and DXA of one proximal femur.

(3) Characteristics of BMD in patients with TE

About 60% of the 40 patients with TE tested at our medical institution had low BMD. An even higher proportion of the patients with upper-limb hypoplasia had low BMD, and the reduction was more prominent in the femoral neck than in the lumbar spine. For details, see Question 3-3 ("Determining bone mineral density in patients with TE" by Mochigi et al.[2)]) in the "Q&A on Thalidomide-impaired People." Proximal femur fractures are one type of non-vertebral fracture that directly adversely affects activities of daily living (ADL) and can leave patients bedridden. Regular BMD analysis is particularly important for patients with TE with upper-limb hypoplasia because they may use their lower limbs

to perform some daily activities normally performed with the upper limbs.

(4) Considerations for BMD analysis for patients with TE

DXA of both the lumbar spine and femoral neck is recommended since the BMD in these two locations may differ. Some patients with TE may experience pain when in a supine position. Adjusting the height of the pillow or putting a cushion under their legs could help reduce their suffering. Any adjustments made should be conveyed to future technicians in charge so the patient can be imaged in an identical position to ensure reproducibility.

[Azusa Minagawa]

2 3. General Imaging: Mammography

Breast cancer has a surging incidence in Japan and affects more women in the country than any other cancer. Breast cancer deaths are also growing. Unlike typical types of cancer that increase in incidence with age, female hormones play a large role in breast cancer onset. In Japan, breast cancer incidence peaks in women in their late 40s to early 50s, but as in Western countries, in recent years, a growing number of women in their 60s develop breast cancer. Breast cancer is therefore a concern in patients with TE. Patients are often the first to discover their breast cancer, but some patients with TE with upper-limb hypoplasia may not be able to do self-palpation over the entire area and should therefore undergo mammography.

(1) Mammography

"Guideline for Conducting Cancer Prevention Priority Health Education and Cancer Screenings" (Notification No. 0331058 of the Director-General of the Health Service Bureau, Ministry of Health, Labour and Welfare) provides the following guidance for general screening:

- Perform for: Women aged ≥40 years
- Frequency: From left or right once every 2 years (from left and right for women in their 40s)
- Parameters: Interview, mammography
  Inspection and palpation, although not recommended, should be done with mammography if performed.

For voluntary screening mammography, left–right medio-lateral oblique (MLO) and craniocaudal (CC) imaging with a breast ultrasound are often performed.

(2) Mammography imaging techniques for patients with TE

Mammography for patients with TE should be performed per the Third Expanded Edition of "Mammography Guideline" (published in Japan). For CC imaging, the patient should be instructed to stand with the trunk squarely against the device and the face oriented to the side[3] (Figure 8). Patients with upper-limb hypoplasia undergoing CC imaging should be quickly positioned, as maintaining a certain posture is uncomfortable for them. The upper limbs should be checked before exposure to ensure that they do not interfere with imaging. For MLO imaging, the angle of the imaged field is adjusted based on the outer edge of the pectoralis major, but the angle of the outer edge of the pectoralis major viewed from behind may not agree with the angle for the side. The angle should be adjusted with the palms on the center of the pectoralis major and latissimus dorsi. The height of the upper limbs is normally adjusted so that the limbs are parallel to the breast support platform, but this is difficult for patients with TE with upper-limb hypoplasia since their upper limbs narrow distally and are not parallel. This can result in wrinkles near the pectoralis major at the armpits (Figure 9).

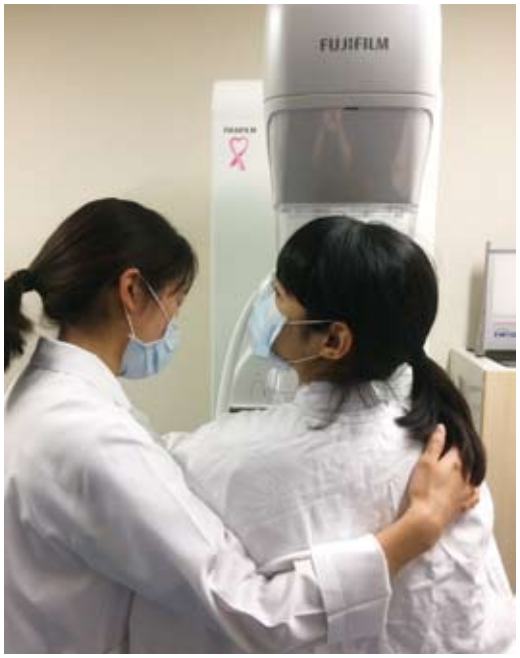


Figure 8 Craniocaudal imaging

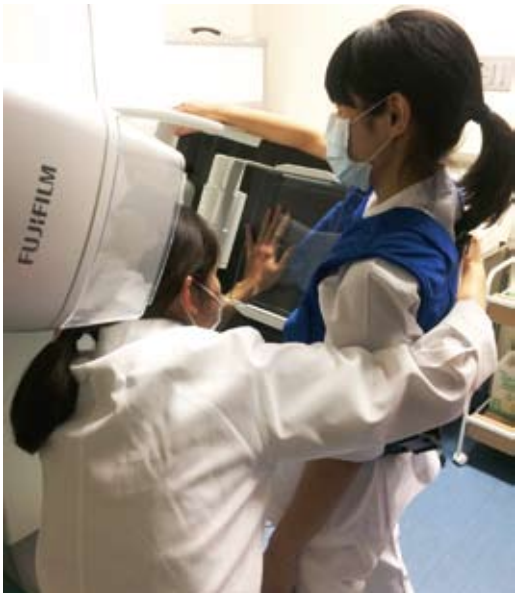


Figure 9 Medio-lateral oblique imaging

(3) Considerations for mammography for patients with TE

Falls are the most important risk to consider during mammography. The devices at most medical institutions are set to automatically release after the end of imaging, but release can cause the patient to lose her balance. The patient should therefore be warned in advance of the procedure. In digital breast tomosynthesis, the face guard moves with the X-ray tube. Even greater caution is required when the tube is in motion in CC imaging. Seated imaging is an option for patients not able to remain standing well (Figure 10). Both patients with and without TE must be cooperative for mammography to conclude successfully. Sufficiently informing a patient about the procedure and communicating with the patient is essential to ensuring that the procedure goes smoothly and produces the imaging necessary to make a diagnosis.



Figure 10 Patient chair for mammography

[Azusa Minagawa]

3 Computed Tomography (CT)

(1) Significance of CT

CT is an important modality for the temporal bone, cervical vertebrae, and trunk (chest to abdomen and to the pelvis). Patients with TE may have wide-ranging disorders of the auditory, skeletal, vascular, and digestive systems. Imaging conditions must be optimized to properly detect these conditions. For more information, see section 5 "Diagnostic Imaging: Tips and Warnings for Radiographic Evaluation."

(2) Positioning

For imaging, the patient should be in a supine position with the hands on the abdomen. Communicating with the patient, position them so that they can maintain a supine position for the duration of the procedure. A belt may be used if necessary to restrain the arms of the patient. A pillow may be placed under the knees to make the patient more comfortable.

(3) Imaging protocol

The images are not contrast-enhanced and use conditions for abdominal imaging of an adult man. The procedure involves a helical scan from the top of the head to the groin. The hands, held at the sides, are in the field of view (FOV). The axial cross sections have a slice thickness of 5 mm. Attenuation coefficients for soft tissue, bone, and lung tissue are used. These reconstructed images show 0.5- or 0.6-mm axial slices and 1.0-mm coronal slices of the left and right inner ear. The FOV includes the foramen magnum and all cervical vertebrae. An axial 1-mm slice and 1-mm sagittal and coronary slices are shown. An attenuation coefficient for bone reconstruction was used. The FOV includes all thoracic, lumbar, and sacral vertebrae. An axial 1-mm slice and 1-mm sagittal and coronary slices are shown. An attenuation coefficient for bone reconstruction was used.

Figure 11 shows proper positioning and the FOV.

The images are not contrast-enhanced and use conditions for abdominal imaging of an adult man. The procedure involves a helical scan from the top of the head to the groin. The hands, held at the sides, are in the FOV.

Figure 12 shows images reconstructed from a full-body CT scan.

The axial cross sections have a slice thickness of 5 mm. Attenuation coefficients for soft tissue, bone, and lung tissue are used.

Figure 13 shows reconstructed images of the inner ear.

These reconstructed images show 0.5- or 0.6-mm axial slices and 1.0-mm coronal slices of the left and right inner ear.

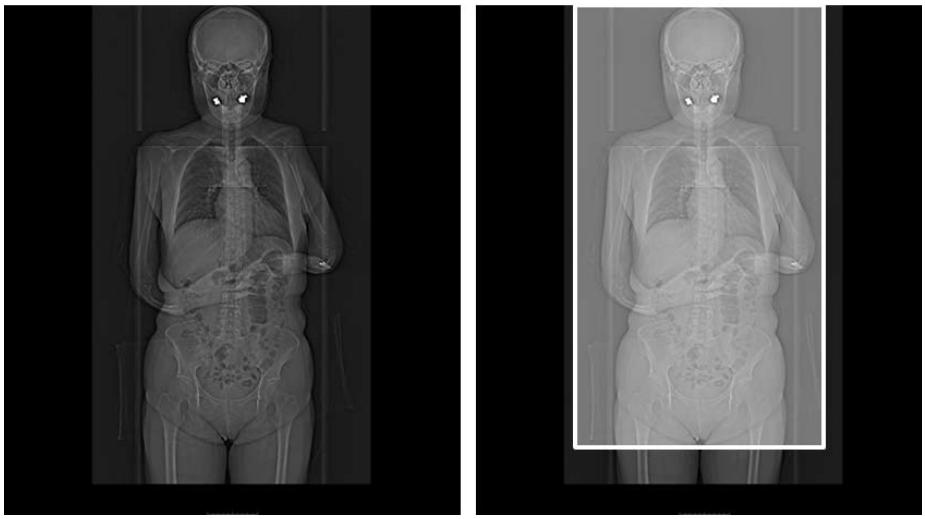
Figure 14 shows reconstructed images of the cervical vertebrae.

The FOV includes the foramen magnum and all cervical vertebrae. A 1-mm axial slice and 1-mm sagittal and coronary slices are shown. An attenuation coefficient for bone reconstruction was used.

Figure 15 shows reconstructed images of the thoracic, lumbar, and sacral vertebrae.

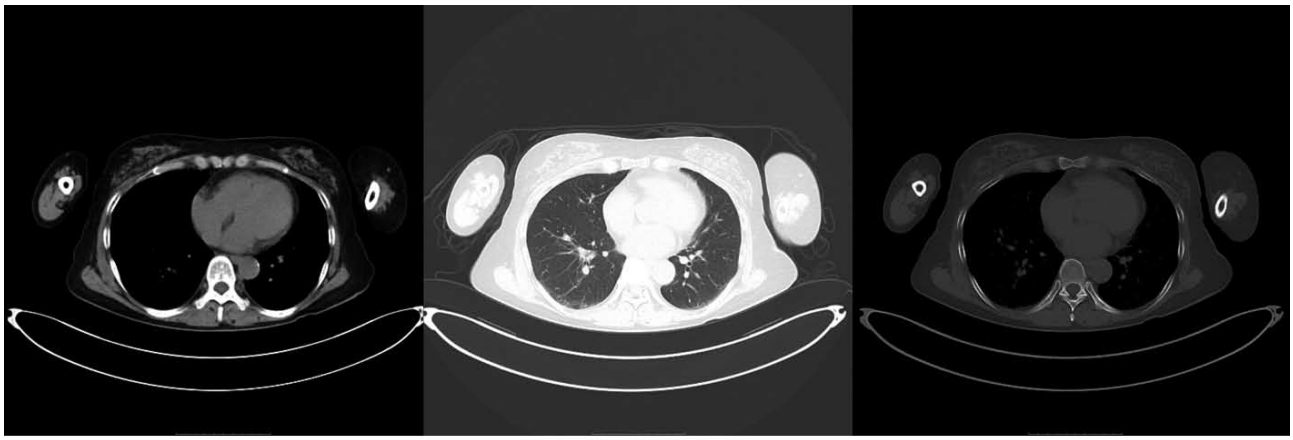
The FOV includes all thoracic, lumbar, and sacral vertebrae. A 1-mm axial slice and 1-mm sagittal and coronal slices are shown. Attenuation coefficients for bone reconstruction were used.

[Masafumi Shinozaki]



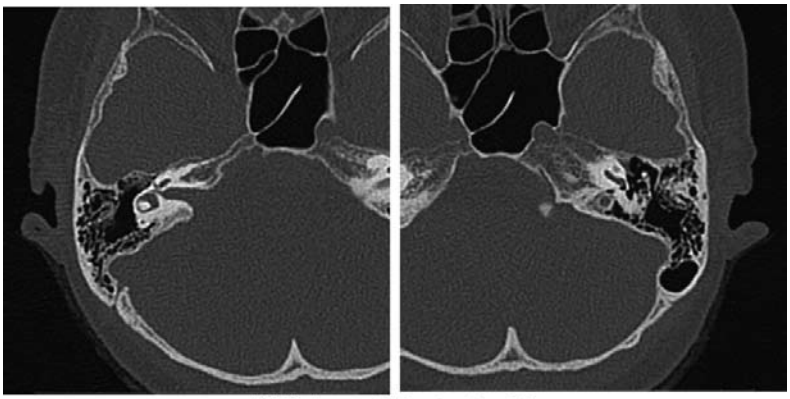
Positioning Field of view (within white rectangle)

Figure 11 Positioning and field of view

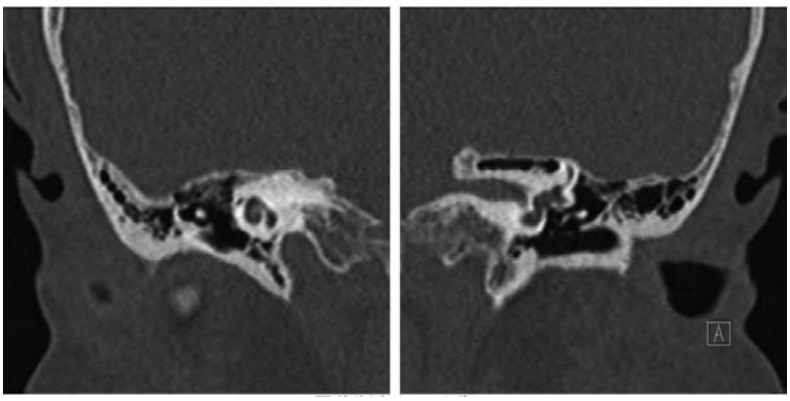


Soft tissue conditions (5 mm thickness) Lung tissue conditions (5 mm thickness) Bone conditions (5 mm thickness)

Figure 12 Reconstructed images of the trunk

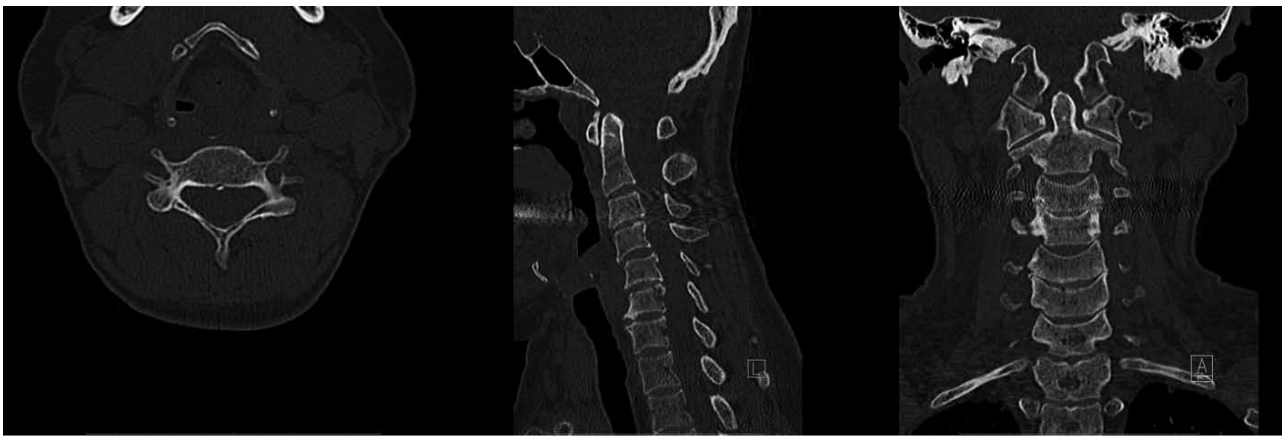


Axial (0.5 mm or 0.6 mm thickness)



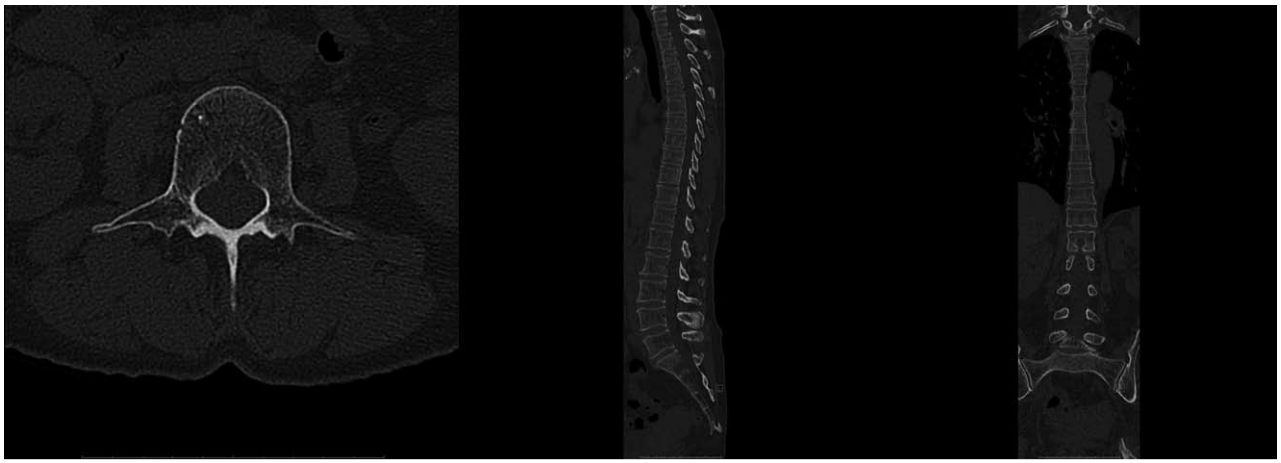
Coronal (1.0 mm thickness)

Figure 13 Reconstructed images of the inner ear



Axial (1 mm thickness) Sagittal (1 mm thickness) Coronal (1 mm thickness)

Figure 14 Reconstructed images of the cervical vertebrae



Axial (1 mm thickness) Sagittal (1 mm thickness) Coronal (1 mm thickness)

Figure 15 Reconstructed images of the thoracic, lumbar, and sacral vertebrae

4 Magnetic Resonance Imaging (MRI)

(1) Interviewing the patient before the procedure

Manifestations of TE include muscular weakness, auditory defects, and chronic kidney disease (CKD). How medical radiology technicians must prepare for an MRI scan will depend on the manifestations in the particular patient. The patient must be interviewed before the procedure to collect information relevant to changing clothes before, and positioning, device, and imaging conditions during the procedure.

(2) Informing the patient before the procedure

Patients undergoing MRI must stay still, maintaining a position in a confined space for an extended time. Patient cooperation is necessary. This is why patients must be informed before the procedure. Points to raise include the possession of metals, whether the patient needs to change clothes, a description of the procedure, the time needed, the fact that the device will make noise, whether the patient needs to be restrained, positioning, and emergency protocols. The scan should not proceed until the patient fully understands all these points. Sign language or written communication may be used to inform patients with an auditory or language defect.

(3) Changing clothes and preparation

Since patients with metal in their bodies may not be able to undergo MRI, check with the patient's physician to determine surgical history and whether the patient can undergo MRI (by having the patient bring the radiology appointment form). Referring to the pre-MRI checklist, the medical radiology technician must make sure that no metals or valuables are brought into the scanner room. The particular procedure may require the patient to change into a gown. If available, a large changing room should be provided to protect patients from falls caused by muscular weakness. At our medical institution, we have the caregiver clothe the patient in a front-tying gown.

(4) During the procedure

Multiple technicians should move the patient to the scanner bed. A substantial number of patients feel uneasy from having to remain still in a cramped space for a long time during MRI. Restraining the patient in a particular position may result in better imaging but can also cause uneasiness. Communicating with the patient, select a position that is as comfortable as possible. The emergency call button for patients to use in an emergency may not be suitable for patients with TE because of muscular weakness, auditory defects, language defects, or other conditions. Decide in advance on a way they can signal the technician, such as by moving their feet or hands or calling out. A technician should remain in the scanner room during the procedure to handle any unexpected events. In preparation for sudden changes in a patient's condition, the patient should be fitted with a pulse oximeter to provide oxygen saturation and heart rate readings.

Some patients with TE have CKD and may be on hemodialysis (HD). Realize that contrast agents are contraindicated in people on HD and in those with advanced renal impairment constituting stage 4 or 5 CKD (GFR<30 mL/min/1.73 m^2).

[Jun Harada]

5 Diagnostic Imaging: Tips and Warnings for Radiographic Evaluation

Tips and warnings for the image-based diagnosis of patients with TE are presented here based on the findings of health screenings performed by this and the previous research group[4].

(1) MRI of head and sinuses

1. As with evaluations of normal individuals, first evaluate the scan in T1WI, T2WI, FLAIR, and T2*WI primarily to screen for intracranial lesions (cerebrovascular disorders and neoplastic lesions).
2. In the posterior cranial fossa and using thin-slide T2WI, check for hypoplasia or aplasia of the 7th and 8th cranial nerves (reported incidence of 23% by present research group). Patients may have narrow or missing inner ear canals, which should be checked for with temporal bone CT.
3. In head-and-neck magnetic resonance angiography, patients may have various arterial anomalies, such as abnormal branching from the internal carotid artery (duplicate middle cerebral arteries, internal carotid artery branching level abnormality, subclavian vein anomaly). Select a wide enough FOV and check for artery hypoplasia or agenesis, duplication, and branching level anomalies.
4. Check closely for chronic cerebral ischemic disease, lacunar infarcts, and other chronic cerebrovascular disorders in this aging population of patients with TE.

(2) Temporal bone CT: Evaluate the following on axial and coronal images

(Figures in parentheses are frequencies identified by the present research group.)

1. Hypoplasia/agenesis of the semicircular canals (36%), vestibule (23%), cochlea (18%), and auditory ossicles (23%)
2. Stenosis of the inner ear canal (18%), outer ear canal (14%), and facial canal (5%)

(3) Cervical vertebral CT: Evaluate the following with a focus on reconstructed sagittal images

1. Block vertebrae is a frequently observed abnormality in which multiple vertebrae are partially or completely fused (reported incidence of 23% by present research group). Remembering that fusion often involves the vertebral arches as well as vertebral bodies, evaluate the range of fusion and degree of intervertebral foramen stenosis.
2. Monitor closely for cervical spondylosis and slipped cervical disks in this aging population of patients with TE.

(4) Trunk CT: Evaluate the following with a focus on axial images

1. Gallbladder agenesis is a frequently observed abnormality (reported incidence of 27% by present research group).
2. Abnormal fusion of the liver (e.g., fusion of the left lobe lateral section and quadrate lobe, agenesis/hypoplasia of liver round ligament, right liver round ligament)
3. Urinary and reproductive organ malformations (e.g., abnormalities of the kidneys/bladder, vaginal hypoplasia)
4. Gastrointestinal tract malformations
5. Thoracic cavity hypoplasia
6. Large vessel abnormalities (duplicate superior vena cava, directional abnormality of azygos vein)
7. Heart malformations: These are often difficult to evaluate in non-contrast-enhanced CT.

(5) Presentation of radiology images

Following are radiaology images typical of TE.

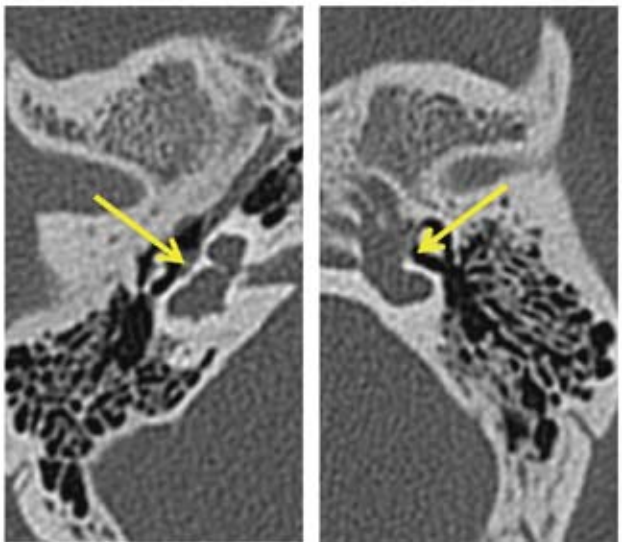


Figure 16 Bilateral hypoplasia of the semicircular canals, vestibule, and cochlea
Axial CT scans of the temporal bone. The images show bilateral hypoplasia of the semicircular canals, vestibule, and cochlea, with one cystic area (arrow).

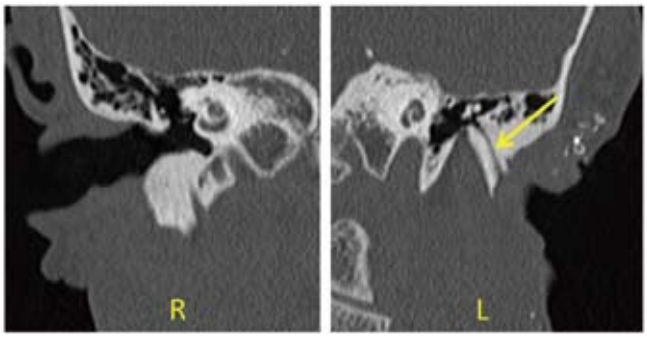


Figure 17 Stenosis of the outer ear canals
Coronal CT scans of the temporal bone. The left outer ear canal (arrow) features much more stenosis than the right.

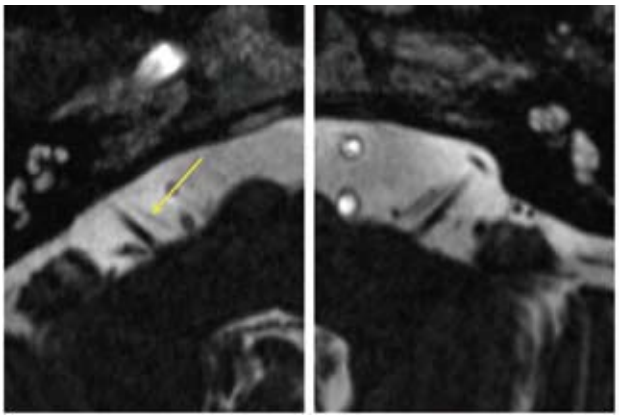


Figure 18 Facial nerve hypoplasia
Axial T2-weighted MRI scans. The right facial nerve (arrow) features more hypoplasia than the left. Both auditory nerves are normal.

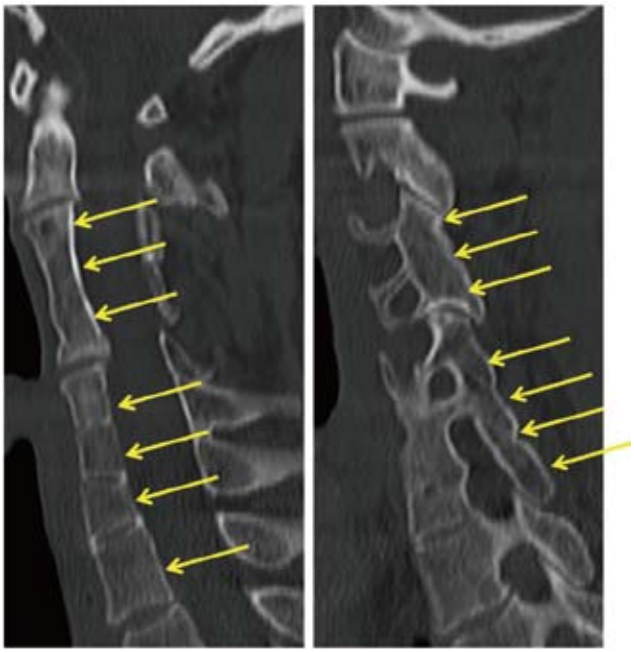


Figure 19 Block vertebrae
Reconstructed sagittal CT scan without contrast. The bodies and arches of the cervical and thoracic vertebrae (C3–C5 and C6–T2) are fused (arrows).

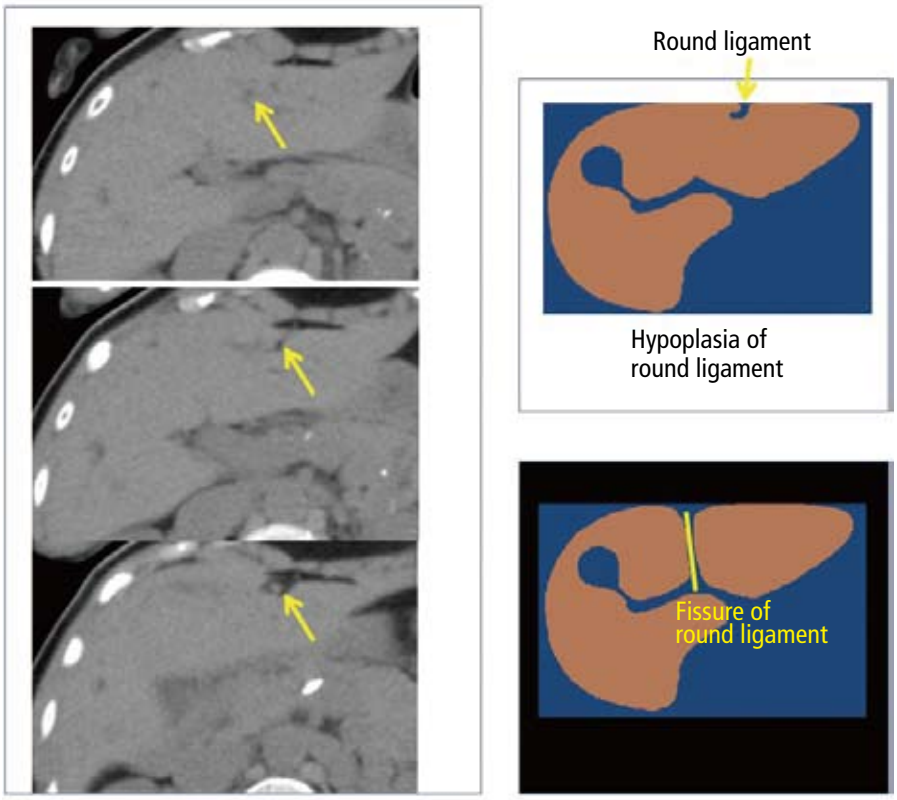


Figure 20 Lobulation defect of the superior and inferior lateral segments of the left lobe of the liver
Axial image of unenhanced CT. The barely visible fissure of round ligament indicates hypoplasia (arrow).

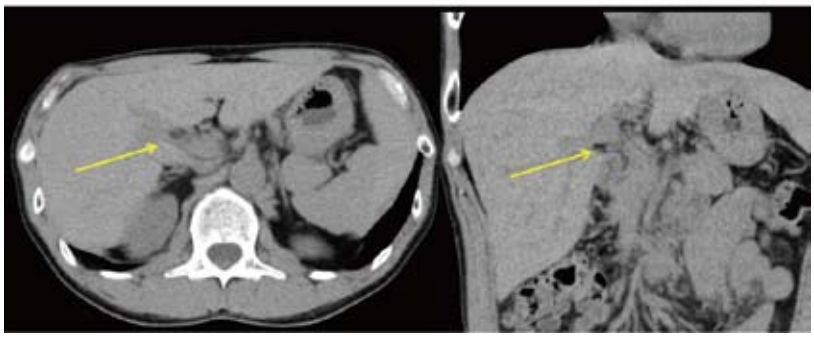


Figure 21 Gallbladder agenesis
Axial and coronal CT scans without contrast. No gallbladder is present (arrow). No gallbladder fossa is visible (arrow). Biliary dilatation is indistinct. These findings indicate gallbladder agenesis.

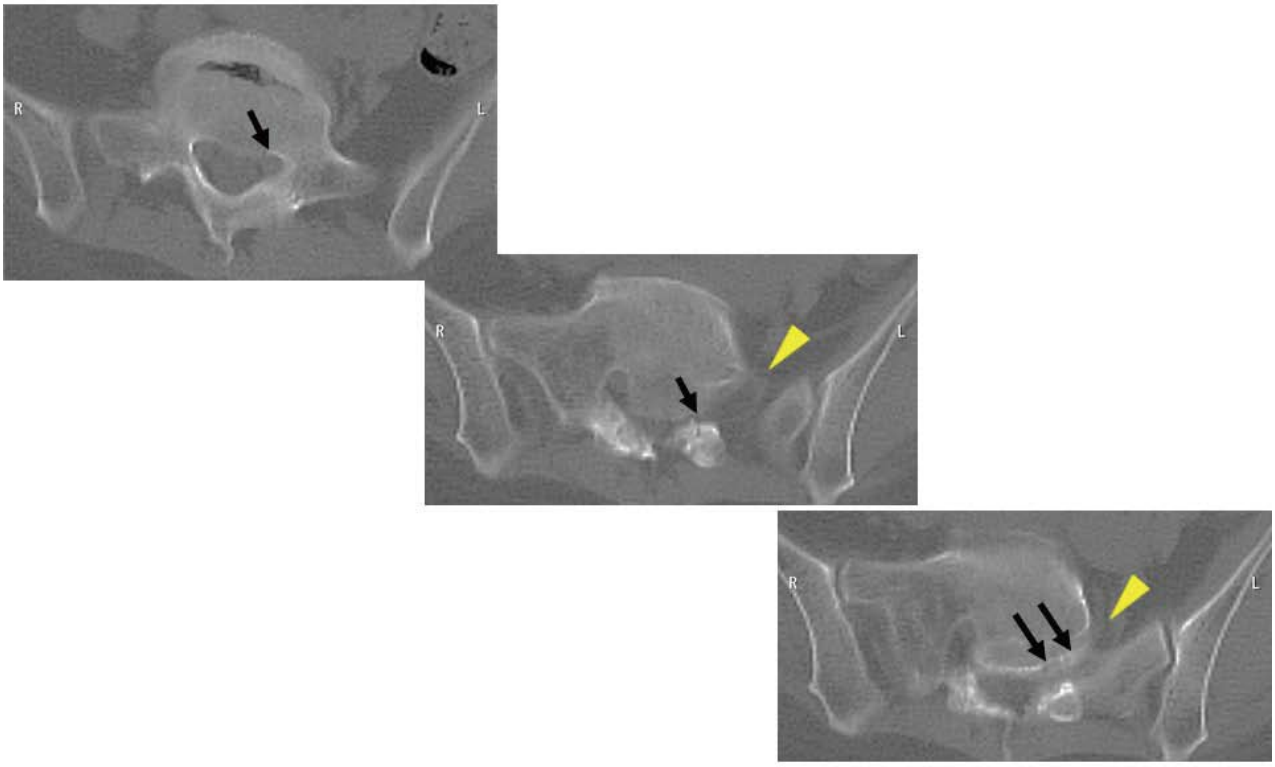


Figure 22 Sacral vertebra aplasia

Axial CT scans without contrast. Hypoplasia (arrowhead) with intervertebral foraminal stenosis (arrow) is seen on the left side of the sacral vertebra at the S2 level. These findings suggest narrowing and hypoplasia of the sacral nerves.



Sagittal MPR scan　　Axial CT scan

Figure 23 Aplasia of the sacrum and coccyx

Axial CT scan and sagittal MPR scan. Taken together, these findings indicate aplasia of the fourth to fifth sacral vertebrae and coccyx.

[Tsuyoshi Tajima]

References
1) Mochiki K, Sasaki T, Wada T, et al .: 3. Comments from radiological technologists,Q & A on Thalidomide-Impaired People. pp26-31,Tokyo,2014
2) Japan Osteoporosis Society, Japan Bone Metabolism Society, Osteoporosis Foundation: Osteoporosis Prevention and Treatment Guidelines 2015 Edition, Life Science Publishing Ltd.,Tokyo,2015
3) Koyama T: Mammography shooting that you can understand in your hand-Positioning that you can understand immediately-, Vector core,Tokyo,2015
4) Tajima T, Wada T, Yoshizawa A, et al:Internal anomalies in thalidomide embryopathy: results of imaging screening by CT and MRI. Clin Radio 71:1199.e1-7, 2016

VIII Otorhinolaryngology



- Outer ear canal stenosis and upper-limb hypoplasia can make it difficult for patients with thalidomide embryopathy (TE) to remove earwax. Intervention is required.
- Patients with TE have varying degrees of hearing loss. Speak clearly and slowly, allowing the patient to see your mouth.
- Communication with patients with TE with severe hearing loss can be achieved through sign-language interpreting, written communication, or lipreading.
- Little is known about the clinical course of hearing loss in patients with TE. Regular hearing tests should be encouraged.
- Consult an otolaryngologist who specializes in hearing aids if the patient has an outer-ear deformity unsuited for a normal hearing aid.

1 Auditory Defects

There are three types of TE, a short-arm type (upper-limb hypoplasia), a hearing-loss type (auditory hypoplasia), and a mixed type that has the manifestations of these two types. Three-quarters of patients have the short-arm type, and the other quarter have the hearing-loss and mixed types. Deformations of the inner, middle, and outer ear can result in sensorineural, conductive, or mixed hearing loss. Tanaka identified a hearing defect of some type in 83 of 137 patients (about 60%). He explains that hearing defects begin at the high-pitch, 8-kHz range, extending into lower ranges as severity increases, and that sensorineural deafness (inner ear disorders) is somewhat independent from outer ear malformations in that embryologically, while the inner ear develops from the otocyst, the outer ear develops from the branchial arch, which is why these two locations are sensitive to thalidomide at slightly different times[1)].

The variation of hearing-loss type TE often involves agenesis or hypoplasia of the abducens or facial nuclei and associated peripheral nerves.

Although most patients will have already undergone evaluations of the severity of their hearing loss, aging will likely impact the hearing defects of patients as they grow older. Patients should undergo regular hearing follow-up because the clinical course of hearing loss in TE is unclear. Patients may benefit from hearing aids depending on the severity of their hearing loss and should be referred to a hearing-aid specialist.

(1) Outer ear malformations

Auricle deformations take many forms. A substantial number of patients have already undergone otoplasty. Auricle deformations not only have aesthetic consequences, but also can affect lifestyle, leaving patients unable to put on a mask or glasses. Outer ear canal deformations increase in prevalence with increasing severity of auricle deformations. Patients with stenosis or closure of the outer ear canal, a cause of conductive hearing loss, are unsuited for normal hearing aids and require the attention of a specialist to consider the use of a bone-conductive hearing aid, bone-anchored hearing aid, meatoplasty, or tympanoplasty.

(2) Middle ear malformations

The middle ear cavity, although present, is often flattened, and the auditory ossicles are often deformed, appearing as a clump. Stapes malformation is also common. TE, however, has no specific auditory malformations. Temporal bone computed tomography is needed to make a definitive diagnosis.

(3) Inner ear malformations

Although no malformations are thought to be unique to TE, absence of the tympanic bone occurs more in TE than in association with other causes. In this situation, the temporomandibular joint directly abuts the mastoid process. Patients with an inner ear malformation often



Auditory defect, outer ear malformation, middle ear malformation, inner ear malformation, abducens nerve palsy, Duane syndrome, facial nerve palsy, crocodile tears syndrome, vestibular dysfunction, earwax, hearing aid, hearing aid specialist

have severe hearing defects that impair communication during examinations.

2 Facial Nerve Palsy

Facial nerve palsy occurs as a result of failure of the facial nuclei to develop or hypoplasia of the facial canal. Paralysis present in early childhood spontaneously resolves in some people. Persisting paralysis can lead to secondary conditions such as eye dryness or teary eyes owing to incomplete eyelid closure or crying on eating (crocodile tears syndrome).

3 Abducens Nerve Palsy

Aplasia or hypoplasia of the abducens nuclei and its peripheral nerves can lead to innervation of the lateral rectus muscle by the oculomotor nerve. The result is a condition called Duane syndrome. Duane syndrome features severely limited abduction, eyeball retraction during adduction, and accompanying narrowing of the palpebral fissure. The eyeball may deviate upward during adduction. Often, the face turns toward the side of the affected eye (abnormal head posture).

4 Vestibular Dysfunction

Evaluating 18 patients with TE with an auditory anomaly, Takemori identified deafness in 15 and vestibular hypofunction or afunction in 15[2].

5 Orofacial Abnormalities

Reported nose abnormalities include saddle nose and shortening of the nasal apex. Other abnormalities include hemangioma of the upper lip, cleft palate, cleft uvula, and aplasia or hypoplasia of the palatine tonsils and palatoglossal arch. Patients with severe dysfunction will have likely already undergone corrective surgery, even if they have not been diagnosed as having TE.

6 Other Comment

Since no deformations of the lower pharynx or larynx are observed, TE is not thought to involve specific disorders of speaking or swallowing.

7 Relationship Between Otolaryngological Deformation and Limb Malformation

TE is classified into short-arm, hearing-loss, and mixed types because the tissues of the head and limbs are sensitive to thalidomide in different phases of organogenesis.

8 Other Considerations for Patient Care

The auditory defects some patients with TE have may hamper communication during medical care. Sign language, gesticulating, writing, lipreading, or other means of communication suited to the patient should be used. Signs with instructions and a description of the flow of tests should be prepared for patients scheduled to undergo tests[3].

References
1) Tanaka Y: T Thalidomide-induced Otolaryngological Defects. Otolaryngology 58(1): 35-44, 1986
2) Takemori S, et al:Thalidomaide anomalies of ear. Arc Otolaryngol 102: 425-427, 1976.
3) Yoshizawa A,Nagase H,Seki H,etc.Q & A on Thalidomide-Impaired People.Tokyo,2014

[Niro Tayama]

IX Dentistry and Oral Surgery Examination



- Patients have difficulty maintaining oral hygiene. Concerns go beyond just dental caries, extending to loose and tooth fracture and missing tooth.
- Check artificial teeth for cleanliness.
- Check the color and condition of the gingiva, tongue, lips, and oral mucosa.
- An oral examination is necessary because thalidomide embryopathy (TE) sometimes involves trismus, sound and other conditions of the temporomandibular joint, and articulation disorders.

1 Oral Examination

The upper-limb movement disorders that many patients with TE have may affect oral cleanliness (brushing) more than anything else. Patients find using an electric toothbrush to clean the teeth much more effective and easier than using a normal toothbrush. The patients that the authors have examined had generally good oral hygiene, but often had teeth crowding and wear of the dental cervix (wedge-shaped defect).

Maintaining oral health and keeping oral bacterial counts as low as possible have gained attention as being useful in significantly reducing the incidence of stomatitis, aspiration pneumonia, and other infections[1].

(1) Teeth

Dental caries (cavities), discoloration, tooth fracture, and congenital aplasia or malformation of the wisdom and other teeth are associated with TE[2].

People who hold items with their teeth to assist upper limb movement are prone to dental abrasion and chipping. This necessitates monitoring of the condition of the teeth and crown prosthesis as well as tooth looseness.

Imbalances in pressure applied during brushing can result in a worn, wedge-shaped dental cervix, which in turn leads to hyperesthesia of the cervical enamel and pain when drinking cold water.

(2) Tooth alignment

Thalidomiders often have difficulty properly cleaning their teeth and therefore frequently have dental caries, periodontitis, and high oral bacteria counts. Excessive dental caries in the deciduous teeth can lead to crown destruction and early tooth loss, which in turn lead to crowding of the permanent teeth, malocclusion, and poor oral hygiene. Poor maintenance, even in those who regularly receive dental care, can lead to dental caries, worsening periodontitis, and even tooth extraction. Proper prosthodontic treatment is needed following tooth loss to prevent gaps and a consequent worsening of alignment.

Partial tooth loss can result in stomatitis owing to accidental biting of the tongue or buccal mucosa. Decreases in the vertical dimension of occlusion can cause disorders of the chewing muscles and motor pain of associated joints.

(3) Fillings, artificial teeth, and dental implants

Fillings and crowns are applied to treat dentin damage from dental caries, abrasion, or chipping. The resin used to secure fillings and cement used to attach prosthesis, however, degrades over time and must therefore be maintained on an ongoing basis after treatment.

A bridge or artificial teeth are used to fill the gaps left following tooth extraction. Patients fitted with a bridge experience little discomfort, but may have trouble cleaning the area because of its complicated shape. Artificial teeth can be removed for cleaning but must be carefully removed and reinserted to keep their metal fittings from injuring the lips or buccal mucosa. Care is needed to ensure that the artificial and remaining teeth remain clean.

Dental implants are very useful but require a relatively invasive surgical procedure to implant and are expensive for the patient because they are not covered by medical insurance.



Oral cleaning, electric toothbrush, dental caries, wedge-shaped defect, tooth fracture, crowding of the teeth, temporomandibular joint disorders

Moreover, a greater level of oral hygiene management is required to maintain them properly.

(4) Periodontal tissues

Dental plaque and tartar caused by less than satisfactory cleaning can result in gingivitis and periodontitis. The color and condition of the gingiva should be evaluated, and bleeding, gingival recession, and tooth looseness should also be checked.

(5) The tongue, lips, and oral mucosa

Gargling is an effective way to keep the tongue from becoming coated. A tongue brush can be used to remove coloration and adhesion, but excessive brushing should be avoided. The sharp edges of a chipped tooth can injure the lips and buccal mucosa. Malocclusion from tooth loss can injure the tongue and buccal mucosa. Patients tend to have lip dryness, which can lead to cheilitis and angular cheilitis. Patients with a small mouth opening tend to have trismus and multiple dental caries.

2 Jaw and Other Bone Disorders

The manifestations of TE include abnormal jaw development, a high-arched palate, cleft palate, and soft palate palsy. Abnormalities may also appear in the outer ear and the temporomandibular joint, which shares its embryological origins with the outer ear. Affected patients may have trismus, joint sound, and other temporomandibular symptoms. Training the patient to properly open the mouth and fitting the patient for a splint (mouthpiece) should prove effective.

Dyslalia, a relatively rare condition, may occur in patients with soft palate palsy or cleft palate.

(1) Jaw

Morphological complications include micrognathia, malformation (hypoplasia) of the body of the jaw, cleft palate, high-arched palate, and palatal torus. Functional complications include protrusion or retraction of the upper or lower jaw[2].

Coronoid hyperplasia, mandibular deviation, and mandibular torus, which may also be present, do not feature bone quality abnormalities.

(2) Temporomandibular joint

Morphological anomalies may also occur in the mandible, which shares some of its embryological origins with the outer ear. Relatively common morphological anomalies of the mandibular condyle include hypoplasia, bone spurs (osteophyte), surface concavities, cortical bone rupture, and flattening of the joint surfaces. Displacement of the articular disc in the temporomandibular joint is also common. This often leads to clicking, cracking, and other joint sound when the mouth is opened, as well as trismus. Conservative therapy is indicated, with nonsteroidal anti-inflammatory drugs given for pain as needed, a splint (mouthpiece) used to stabilize occlusion, and rehabilitation therapy provided to increase jaw mobility.

References
1) Yoneyama T, Yoshida M, Matsui T, et al:Oral care and pneumonia. Oral Care Working Group. Lancet. 354: 515, 1999
2) Kikuchi S: Congenital Anormalies of oro-facial region on Thalidomide Embryopapthy, Teikyo Medical Journal 9: 223-234, 1988

[Yutaka Maruoka]

X Ophthalmologic Care



- Patients in the short-arm group may have microphthalmos, uveal coloboma, cataracts, and corneal opacity. The severity of these eye conditions tends to increase with increases in the severity of upper-limb hypoplasia.
- Ophthalmologic manifestations specific to thalidomide embryopathy (TE) include Duane syndrome, facial nerve palsy, and crocodile tears syndrome.
- Many patients with TE with auditory hypoplasia or deafness also have ophthalmologic manifestations.
- Duane syndrome often appears bilaterally as type III.

1 Introduction

Ophthalmologic dysfunction in TE is nonspecific but involves visual impairment. Patients in the short-arm group may have microphthalmos, uveal coloboma, cataracts, and corneal opacity. The severity of these eye conditions tends to increase with increases in the severity of upper-limb hypoplasia. Uveal coloboma is frequent, and aniridia and microphthalmos typically affect both eyes. By contrast, patients in the hearing-loss group (auditory hypoplasia) often have Duane syndrome, facial nerve palsy, crocodile tears, vertical gaze palsy, and dermoid cysts (dermoids) (Table 1)[1].

2 Malformations of the Eyes and Their Symptoms

Microphthalmos, uveal coloboma, congenital aniridia, and other ocular malformations are reported in patients with TE. In the general population, these conditions are rare genetic or sporadically occurring congenital anomalies. Their associated malformations and symptoms are discussed here.

(1) Microphthalmos

Typically, severe hypermetropia is present in both eyes, and vision must be corrected with +8D to +25D glasses.

Table 1 Ophthalmologic comorbidities in 132 patients with thalidomide embryopathy
These figures are for 81 patients with deafness (hearing-loss group), 32 in the short-arm group, and 10 in the mixed group

	Hearing-loss Group	Short-arm Group	Mixed Group	Total
Microphthalmos	1	2	0	3
Uveal aplasia	1	2	0	3
Cataract	2	4	0	6
Lens dislocation	0	1	0	1
Corneal opacity	1	3	0	4
Chorioretinal atrophy	1	1	1	3
Eyeball	0	0	1	1
Dermoid	2	0	0	2
Duane syndrome	27	1	3	31
Abducens paralysis	0	1	0	1
Facial nerve palsy	33	3	2	38
Vertical gaze palsy	2	0	0	2
Crocodile tears syndrome	1	2	1	4
Strabismus	2	14	1	17
Amblyopia	8	1	1	10

(from reference 1).



Microphthalmos, uveal coloboma, cataract, corneal opacity, Duane syndrome, congenital facial nerve palsy, crocodile tears, thalidomide embryopathy

The eyeballs are smaller than normal (axial length ≤20 mm), and the palpebral fissure is also narrowed. The lens accounts for a large volume of the eye (Figure 1). The risk of angle closure glaucoma increases as the volume of the lens increases with age (Figure 2, top). Reconstructive surgery of the lens (cataract surgery) is sometimes performed to treat angle closure glaucoma (Figure 2, bottom). The abnormal structure of the eye can result in surgical complications that, in the worst of cases, can cause blindness (Figure 3).



Figure 1 MRI scan of a patient with microphthalmos
The volume of the lens accounts for a larger than normal share of the volume of the eye.

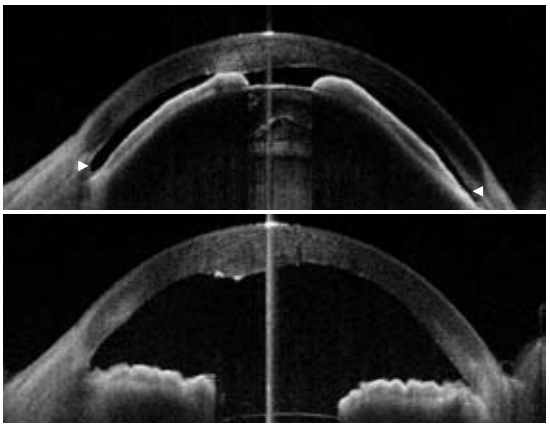


Figure 2 Cross-sections of the anterior eye of a patient with microphthalmos
The axial length of the eye is 17 mm, higher lens volume results in severe narrow angle (arrow heads), and the iris and cornea are adhered around the pupil (top). In lens reconstruction, the ≥4-mm thick lens was replaced with a 1-mm artificial lens, which normalized the position of the iris, opening the angles (bottom).



Figure 3 Postoperative complications in a patient with microphthalmos
The abnormal eye structure in microphthalmos makes surgery risky. Blindness may result from complications such as retinal detachment and corneal opacity (bullous keratopathy).

(2) Uveal coloboma

Uveal (iris, ciliary body, choroid) coloboma always affects the lower half of the eye because it arises during eye formation. Those with iris coloboma are often photophobic because the pupil is larger than normal (Figure 4). Ciliary body coloboma features partial absence of the zonule of Zinn that supports the lens and may also have a deformity at the equator of the lens. Choroidal coloboma leads to severe visual impairment if the range of the defect extends to the macular area. Although people become more prone to retinal detachment as myopia progresses, those with choroidal coloboma often fail to notice any symptoms, which delays detection.

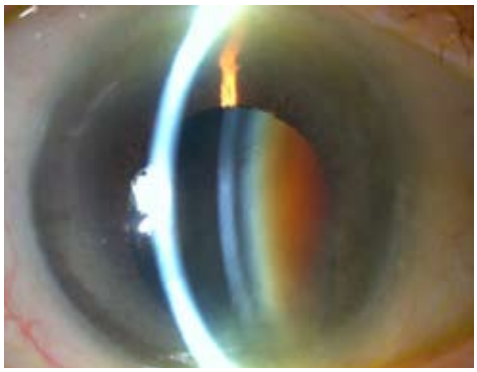


Figure 4 Uveal coloboma (iris coloboma)
Uveal coloboma always affects the lower half of the eye. Those with iris coloboma are often photophobic because the pupil is larger than normal. When ciliary body coloboma is present, the equator of the lens becomes deformed.

(3) Congenital aniridia

A mutation in the *PAX6* gene causes this condition. Since this condition is a developmental disorder of the eye, people born without this condition can later acquire aniridia. Complications include cataracts (Figure 5, top), glaucoma, corneal pannus, amblyopic nystagmus, macular hypoplasia, and eyelid ptosis. Contact lenses with an iris pattern and artificial irises have been used in attempts to reduce the photophobia associated with aniridia, but often cause complications. Hyperemia and reduced visual acuity from corneal pannus are also problematic. Treatments include lens reconstruction for cataracts (Figure 5, bottom) and conventional outflow reconstruction surgery (Figure 6) and filtration surgery for glaucoma.

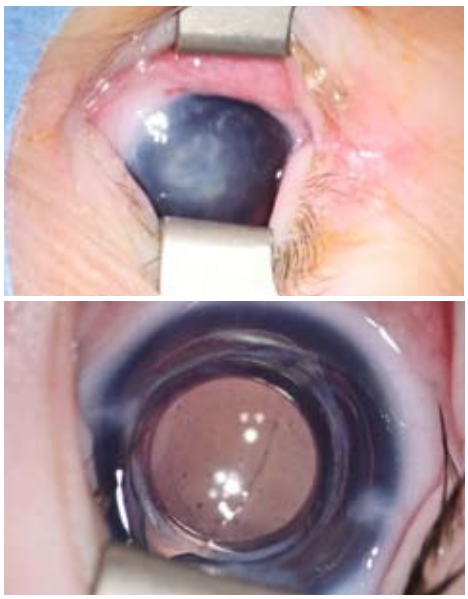


Figure 5 Aniridia (with congenital cataracts)
This 3-month-old patient has bilateral cataracts (top). Six months after lens reconstruction, the artificial lens is fixed within the capsule (bottom).

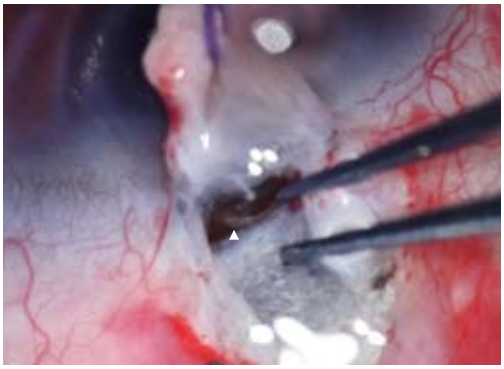


Figure 6 Glaucoma surgery (trabeculectomy)
Schlemm's canal is opened from the outside of the eye, and the trabecular meshwork (arrow head), which is the primary resistance to aqueous humor outflow, is removed. The procedure may be modified according to findings made during surgery.

References

1) Arimoto, Y: Ophthalomology in thalidomide embropatyy, Thalidomide embropatyy in Japan (Kida M. ed), pp143-153, Kodansha, Tokyo, 1987

[Miyuki Nagahara]

XI Psychiatric Care



- Patients with thalidomide embryopathy (TE) should be examined with the realization of a higher prevalence of depression or other psychiatric disorders compared to the general population.
- The difficulty that patients with TE with auditory defects have communicating with others can put them at greater risk of psychiatric problems.
- People with TE are expected to face more difficulty performing activities of daily living as they age.
- Patient care must be flexibly handled in consideration of what areas are affected, disease severity, and the patient's background and personality.

1 Psychiatric Issues in Patients with TE

The "National Study on the Health and Living Situations of Thalidomide-Impaired People" was conducted in people with TE in Japan in 2012[1]. Of the 201 respondents, 130 (64.5%) reported being in poor physical condition (i.e., having subjective symptoms) because of a disease or injury, 23 (11.4%) insomnia, 21 (10.4%) irritability, and 18 (9.0%) forgetfulness. A total of 21 (10.4%) responded that they were "visiting a medical institution for depression or another mental illness." This figure is more than five times greater than the 2.0% of respondents in the general population answering affirmatively to this question in the FY2010 Comprehensive Survey of Living Conditions in Japan (age 50–54 years, n=7659).

Saito[2] used the General Health Questionnaire-28 (GHQ-28), an instrument designed to evaluate mental health, to evaluate people with TE in Japan. Higher scores on this instrument indicate poorer health. Around 20–35% of people in the general population have a high GHQ-28 score (cutoff value of 6/7). A total of 26% of thalidomide victims with limb defects were above this cutoff in 2002. This figure is comparable to that for people in the general population. By contrast, 56% of thalidomide victims with auditory defects were above this cutoff. This indicates that thalidomide victims with auditory defects have poor mental health, although the sample size was small. Mean GHQ-28 total scores were 4.9 (SD=5.2) in thalidomide victims with limb defects and 8.9 (SD=6.6) in victims with auditory defects. The significantly higher score in the victims with auditory defects indicates they have poorer overall mental health (Table 1). Saito[2] attributed this to the double hit of communication difficulties caused by auditory defects and communication disorders caused by difficulty showing expressions, reasoning that many of the people in this group have auditory disorders as well as facial nerve palsy.

Table 1 GHQ-28 total and subscale scores in people with limb and auditory defects

Year of data	2000		2002	
Type of defects	Limb manifestations	Auditory manifestations	Limb manifestations	Auditory manifestations
Number of subjects	N=97	N=25	N=97	N=25
GHQ total score (SD)	4.8(5.2)	8.5(6.3) **	4.9(5.2)	8.9(6.6)**
Somatic symptoms	1.7(1.8)	2.3(1.8)	1.8(1.7)	2.9(2.0)
Anxiety and insomnia	1.9(1.9)	3.2(2.2) **	1.7(1.8)	3.5(2.5)**
Social dysfunction	0.7(1.2)	1.4(1.9)	0.8(1.4)	1.1(1.7)
Depression	0.6(1.4)	1.6(2.0) **	0.6(1.6)	1.4(2.1)**

Notes: **P<0.01, adapted from Saito (2005).



Anxiety, insomnia, somatic symptoms, depression, auditory defects, communication disorders, quality of life, pain, General Health Questionnaire-28, the 12-Item Short Form Health Survey, World Health Organization quality of life, drug-related injury

2 Quality of Life (QOL) of Patients with TE

The 12-Item Short Form Health Survey (SF12) was conducted to evaluate QOL in 50 patients with TE in the UK[3]. Compared with the general public, the patients with TE had much poorer QOL scores on questions related to physical functioning and bodily pain. A questionnaire survey using the World Health Organization quality of life (WHOQOL) assessment was conducted to evaluate QOL in 900 patients with TE in Germany[4]. The patients with TE had significantl poorer QOL scores than members of the general public of the same age group (50s). The QOL of the patients with TE was comparable to members of the general public in their 80s, which suggests that they are aging than there actual age subjectively.

The physical aspects of QOL in patients with TE have been shown to be poorer than those of the general population, but this is not true for the mental aspects of QOL. Newbronner and colleagues[3] found no substantial differences between the mental QOL of patients with TE and the general population. Ghassemi Jhani and colleagues[5] investigated the relationship between QOL and the severity of physical malformations in 31 patients with TE. They found a correlation between physical malformations and physical QOL, with the patients with TE having poorer physical QOL than the general population, but the mental QOL of the patients with TE was comparable to that of the average member of the general population.

Although these studies cannot be treated as equivalent because of differences in the country involved, sample size, and instrument used, they consistently find that patients with TE have poorer physical QOL than the general population. The same, however, cannot be said about mental QOL. Nevertheless, the impact of decreasing physical QOL with aging on mental QOL must be remembered, as Kruse and colleagues[4] recently found that 92% of the participants in their study reported noticing decreased motor function due to a secondary sequela or pain.

3 Tips for Caring for Patients with TE

Although the name of a single condition, TE features many affected sites and levels of disease severity, and the environment and social circumstances of patients differ. Some affected people are able to carry out daily and social activities by themselves, while others are not. Caregivers engaging with the patient with TE must work flexibly in consideration of the affected areas, disease severity, and the patient's background and personality. Horton[6] notes that victims with the same level of severity may present superficially with different clinical manifestations of pain because of differences in personality, problem-solving abilities, lifestyle, career, support network, and other background factors. people who have listened to their bodies and adjusted to its limitations, who have accepted care when they needed and coped in a conscious, have mostly seem to be in less pain. Thalidomide victims that handle life in this way will probably be more accepting of the changes associated with the difficulties that aging brings.

Many patients with TE are able to live life day-by-day despite their physical disabilities and social handicaps. Healthcare professionals should interact with their patients with TE with a constant respect for their abilities to live with, and even in spite of, their disabilities. Interaction also requires remembrance of the historical backdrop of this drug-induced tragedy, which may cause some to distrust healthcare. This makes carefully explaining the side effects of a drug being prescribed to a patient with TE all the more important.

From the perspective of the patient, routine psychiatric care is all that is needed because there are no special psychiatric drugs or treatments for TE. Healthcare professionals need not flaunt their knowledge of the drug-induced nature of TE or its limb and auditory defects. Instead, they should keep an open ear to all that their patient has to say, proceeding at his or her pace. It is important not to fixate exclusively on mental issues because pain and other somatic symptoms are also relevant.

References

1) Yoshizawa A: 2012 Ministry of Health, Labor and Welfare Science Research Grant (Regulatory Science Research Project for Pharmaceuticals and Medical Devices) Research on the health and living conditions of thalidomide embryonic disease patients nationwide, 2013
2) Saito T: Grant-in-Aid for Scientific Research 2002-2004 (Basic Research (C) (2)) Clinical Psychological Study of Thalidomide Embryonic Disease Patients in Middle Ages, 2005
3) Newbronner L, Chamberlain R, Borthwick R, et al : Firefly IL-LUMINATING RESEARCH, Looking to the Future:Evaluation of the Health Grant to Thalidomide-Impaired People, Year 2 Final Report, York, 2012
4) Kruse A, Baiker D, Becker G, et al : THALIDOMIDE Inquires to be carried out repeatedly with regard to problems, specific needs and support deficits of thalidomide victims. pp52-59, Institute of Gerontology of the University of Heidelberg, Heidelberg, 2012
5) Ghassemi Jahani S A, Karlsson J, Brisby H, Danielsson A J : Health-related quality of life and function in middle-aged individuals with thalidomide embryopathy. Journal of children's Orthopedics 10(6):691-703, 2016
6) Horton A : The Thalidomide Trust's approach to supporting thalidomide individuals in pain – a personal perspective. Pain News 13:94–95, 2015

[Ken Otomo, Hanae Sone, Yuki Nakano, On Kato]

XII Problems Encountered in Clinical Settings

1 Blood Sampling



- Upper and lower limb malformations often complicate blood collection.
- When preparing to collect blood, have the patient identify a site from which blood has previously been collected successfully and aim to collect from that site.
- When blood collection does not proceed well, observe all areas of the limbs to find an appropriate site for needle insertion. Then take various approaches, such as warming the insertion site or placing a towel under the arm to facilitate insertion.

1 Blood Collection: Being Prepared

Patients with thalidomide embryopathy (TE) must be cared for with the understanding that many are anxious about medical procedures. When collecting blood, speak calmly and proactively work to reduce tension and calm anxiety. As will be discussed later, it is important to warm the room at cold times and spend time relieving tension in patients with congenital limb malformation to overcome the difficulties involved in collecting blood. When possible, an experienced and skilled caregiver should collect blood. When collection efforts do not go well, another caregiver should be asked for assistance or a doctor should be contacted.

Selecting a site to collect blood from patients with TE with auditory defects is rarely complicated, but the communication difficulties they may have must be remembered. A sign-language interpreter or family member, if available, should be consulted. If no one is available, explain the process slowly, using gestures. Temporarily remove your mask when communicating with patients with TE who can lip-read.

2 Technical Challenges of and Techniques for Collecting Blood

Patients with TE (and particularly those with upper-limb defects) generally have small peripheral blood vessels with an abnormal arrangement. Collecting blood from the medial cubital vein is therefore often unfeasible. The patient should thus be asked from where blood has successfully been collected in the past so that site can be used. If the patient knows of no such vein, or if blood is not successfully collected from the site the patient names, carefully observe the entirety of the upper and lower limbs. Possible sites for collection include the upper arm, dorsal region of the hands, wrists, knees, dorsal region of the feet, and around the toes.

Veins that appear difficult to insert the needle into can be dilated with a hot pack. If blood is to be collected from a lower limb, the patient could first warm his or her feet in a bathtub.

In cases where the patient has a small upper limb owing to hypoplasia, a tourniquet could be gently tied around it. When collecting blood from a site of arm deformation, the angle or direction of the limb could be optimized for collection by placing a folded towel under the arm. For some insertion sites, the wings of the butterfly needle need not be placed tightly against the skin. Blood could be collected from the groin if collection from other sites is unsuccessful.

Coagulation could occur when collection from a narrow vessel takes time. When the collection site of a patient with upper-limb defects does not stop bleeding, as often happens, an attendant or medical assistant should remain with the patient for 5 or so minutes to help stop the bleeding.



Blood collection, being prepared, blood sampling kit

3 Blood Sampling Kits

The Safe-touch PSV Set with Luer Adapter by Nipro Corporation has been used to collect blood from patients at the Center Hospital of the National Center for Global Health and Medicine[1] (Figure 1). When this set is used, air in the line is aspirated into the first collection tube, so blood from the second or later tube should be used to obtain blood counts and perform coagulation tests.

Photographs of the kit in use are shown in Figures 2–4[1]. Although personnel wear gloves as a standard precaution, those shown in Figures 2 and 3 have no gloves on so as to better indicate how the line is held and how the fingertips should be oriented.

References
1) Yoshizawa A. 5. Blood collection. Q & A on Thalidomide-Impaired People. Yoshizawa A (ed). pp55-58, Tokyo, 2014

[Fumihiko Hinoshita]

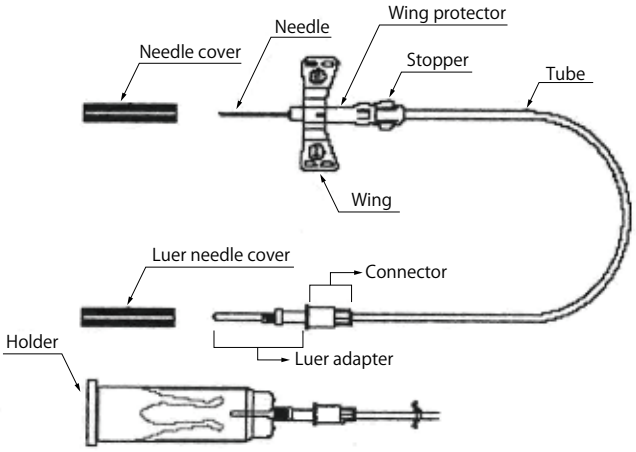


Figure 1 Names of the components in the Safe-touch PSV Set with Luer Adapter

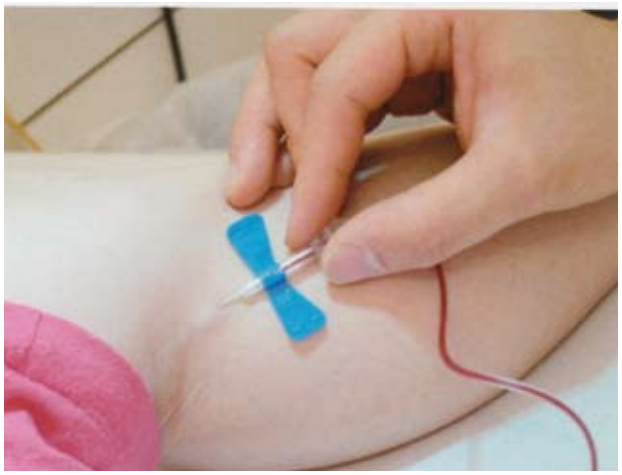


Figure 3 Patient from whom blood can be collected only from behind the left knee (24 gauge)



Figure 2 Patient from whom blood can be collected only from the inside of the first right toe (24 gauge)



Figure 4 Patient from whom blood was successfully collected from a vein of the upper right limb (22 gauge)

Figures 1 to 4 are from "Q&A on Thalidomide-impaired People"[1] by the previous research group.

XII Problems Encountered in Clinical Settings

2 Measuring Blood Pressure



- Properly prepare the environment prior to measurement.
- Carefully decide which of the limbs of patients with thalidomide embryopathy (TE) to use to measure blood pressure.
- Select an appropriate cuff size.
- When upper-limb blood pressure measurement is not possible, measure lower-limb systolic blood pressure and use the reading to estimate upper-limb systolic blood pressure.
- Be sure to determine if the patient has peripheral artery disease (PAD).

Measurement by Healthcare Professionals

1 Before Measuring Blood Pressure

Have the patient remain still for 2 to 3 minutes in a supine position on the bed to calm any tension that could elevate blood pressure.

2 Selecting a Site to Measure Blood Pressure

Measure blood pressure with an electronic (oscillometric) blood pressure meter. Many patients with TE have upper-limb defects (e.g., short arms, forearm deformities, upper-limb hypoplasia, phocomelia). These defects sometimes require blood pressure measurements to be attempted at different sites, including those in the lower limbs. Excluding those with lower-limb deficits, to measure blood pressure, the pulse of the posterior tibial artery is normally identified by palpation near the medial malleolus and then used as the measurement site. In health examinations at the Center Hospital of the National Center for Global Health and Medicine, we measure blood pressure twice at each of four locations of the upper and lower limbs. We use the average of the two readings unless the first reading is abnormally high because of tension, in which case, we use the second reading. When a patient has upper-limb aplasia, we do not measure the blood pressure at those sites.

3 Cuff Placement on the Upper and Lower Limbs

The ○ mark on the outside of the cuff is normally aligned over the brachial artery when measuring upper-limb blood pressure. The marks should be aligned over the posterior tibial artery to obtain a proper reading in lower-limb blood pressure measurement. To do this, carefully palpate for the posterior tibial artery behind the medial malleolus and place the cuff there. Alternatively, auscultation can be used when measuring lower-limb blood pressure.

4 Selecting the Appropriate Cuff Size (particularly relevant to patients with upper-limb hypoplasia)

The second research group found no substantial differences in readings when comparing small and medium cuffs. Basically, we now use a medium cuff to measure blood pressure at four locations. The blood pressure can be underestimated when a poorly fitting medium cuff is used for a patient with upper-limb hypoplasia (because the upper arm is too small or the cuff is too large). A small cuff should be used in these cases. A small cuff, if it is indicated, should be used at all measurement sites.

There are various controversies about cuff sizing and measurement sites. The recommendations of an overseas expert are informative[URL1)].



Blood pressure measurement, cuff, lower-limb systolic blood pressure, regression formula, peripheral artery disease

5 Evaluating Lower-limb Systolic Blood Pressure

The previous research group developed a regression formula for predicting upper-limb blood pressure from lower-limb blood pressure using the data of 1,892 people in the 1999–2000 National Health and Nutrition Examination Survey, an American survey that contains analysis data including upper- and lower-limb blood pressure measurements[1]. The group derived the following formula for medium cuffs: Upper-limb systolic blood pressure = 0.88 × (lower-limb systolic blood pressure + 8). The group then used the upper- and lower-limb measurements of 17 people with TE evaluated in health examinations to test the validity of the formula. The fit was relatively good. This formula is now recommended for estimating upper-limb blood pressure[1]. However, there was a report that indicated lower-limb blood pressure was 20% higher than upper-limb blood pressure[URL1], so further examination with a larger sample size is needed to evaluate the validity of the formula.

6 Evaluation When peripheral arterial disease (PAD) Is Suspected

PAD, a result of arteriosclerosis, makes it difficult to estimate blood pressure based on the reading of a lower-limb vessel with stenosis. Stenosis may affect both lower limbs. Patients with diabetes mellitus or cardiovascular disease should have blood pressure measured at all four limbs. However, if only lower-limb measurements are possible, the ankle-brachial index cannot be determined for patients with no upper limbs. For these patients, determine whether the blood pressure measurements of the left and right lower limbs differ. If they do, palpate for the femoral and popliteal arteries and check by touch whether the intensity of the pulse on the left and right sides differs. If it seems to, an upper-arm cuff can be fitted to an ankle to use to measure systolic blood pressure in the dorsalis pedis and posterior tibial arteries via a Doppler blood flow meter. Taking the higher of the two readings to be the lower-limb blood pressure, check for a left–right difference. Auscultation can be used to measure the systolic blood pressure of the posterior tibial and dorsalis pedis arteries if no Doppler blood flow meter is available. This, however, may not work if the patient has PAD, so PAD cannot be ruled out with an auscultation approach.

7 Recommendations of an Overseas Expert on Blood Pressure Measurement

The German-born Swiss physician, Dr. Schulte-Hillen, himself a thalidomide victim, published recommendations for blood pressure measurement on the Internet[1].

8 Other Information

Patients will need a blood pressure meter with buttons large enough to operate with the toes and a cuff that can be applied with the feet. Some patients with TE report having a favorable experience with the UA-621® upper-arm blood pressure meter (Smart Mini Blood Pressure Meter) by A&D Company, Limited[2]. The procedures for home-based blood pressure measurement are provided here for those interested.

Home-based Blood Pressure Measurement Procedures

People with upper-limb defects can measure blood pressure on their own at home as follows:

(1) Be seated. Gently fit the cuff to the upper ankle.
(2) Align the ○ mark on the outside of the cuff over the posterior tibial artery.
(3) Be still in a supine position for 2 to 3 minutes.
(4) Raising only the head, press the start button with the big toe of the opposite leg.
(5) Check the reading.

References

1) Yoshizawa A, Nagase H, Seki H, et al. 6. Measuring and evaluating blood pressure. Q & A on Thalidomide-Impaired People. Yoshizawa A (ed). pp59-64, Tokyo, 2014

URL

1) Jan Schulte-Hillen. Measuring the blood pressure in patients with shortened arms due to thalidomide embryopathy. http://www.contergan-infoportal.de/fileadmin/downloads/NEU-DOWNLOADS/Medizinische_Beitraege/Blutdruckmessen/GB_blood_pressure_measurements_in_thalidomiders_with_upper_extremity_defects.pdf#search=%27blood+pressure+schulteHillen+thalidomide%27

[Fumihiko Hinoshita]

XII Problems Encountered in Clinical Settings

3 Surgery for Patients with Thalidomide Embryopathy (TE): Considerations for Perioperative Management



- Thoroughly determine what external and internal anomalies the patient has before operating.
- Identify blood vessels and blood flow with ultrasonography to allow blood pressure measurement and vascular access.
- Thoroughly prepare for airway management if the patient has facial or neck malformations.
- Thoroughly prepare for waking the patient and extubation, checking for neurological changes and delirium after the patient wakes.

Patients with TE are likely to require more operations as they age. Issues surrounding perioperative management and solutions to these issues are discussed in this section.

1 General Preoperative Issues

First, know what type of abnormality the patient has.

Patients with TE have a diverse array of manifestations[URL1)] that must be thoroughly considered. Computed tomography and magnetic resonance imaging often show a range of internal anomalies in addition to the more obvious external anomalies[1)]. Caregivers must identify the severity and sites of congenital anomalies (e.g., upper limbs, lower limbs, face [eyes, ears, lacrimal glands], organs [heart, kidneys/urinary tract, reproductive organs]) and know well whether any neurological disorders are present. A preoperative management plan should be formulated based on the anomalies identified.

2 What Range of Preoperative Tests is Possible?

Any medical institution will want to try to perform routine preoperative tests. Blood sampling, however, may be difficult because of abnormal distribution of peripheral limb veins associated with the above congenital anomalies. Problems may also be encountered during respiratory function tests and electrocardiography. The condition of the patient may require some tests to be eliminated or alternative tests to be performed.

However, blood tests, electrocardiography, chest X-ray, limb X-ray, and ultrasonography of the heart and limbs (to determine blood vessel distribution) should be conducted over the range possible regardless of the condition of the patient. The patient's airway, moreover, should be observed by an otolaryngologist (or oral surgeon). Since many patients with TE, now advanced in age, have cervical vertebral disc deformation[2)], X-ray imaging of the cervical spine is also warranted.

3 Issues Facing Anesthesia and Intraoperative Management

(1) Measuring blood pressure and ensuring venous access

Measuring blood pressure is the greatest difficulty encountered in intraoperative management. There are several publications on intraoperative blood pressure measurement techniques[URL2–4)]. Measuring blood pressure with a normal cuff is unfeasible in patients with bilateral upper-limb reduction defects. Blood pressure can be measured with a children's cuff if the upper limbs are of a certain length, but accurate readings may not be determinable if the blood vessel distribution is abnormal. Lower-limb blood pressure measurement can be attempted if upper-limb measurement is not possible. When intraoperative management based on lower-limb blood pressure is performed, it must be remembered that lower-limb readings are generally somewhat higher (10–20 mmHg higher) than upper-limb readings (see section XII.2 Measuring Blood Pressure). Shiga and colleagues[5)] discuss the usefulness of a cuff to measure lower-limb blood pressure and present differences between cuff-based readings and direct arterial blood pressure monitoring. Another publication discusses the usefulness



Preoperative tests, perioperative management, blood pressure measurement, direct arterial blood pressure monitoring, vascular access, ultrasonography, airway management, cleft lip, cleft palate, muscle relaxation

of devices developed to measure blood pressure with a finger cuff[6]. Relevant to all measurement techniques is the degree of blood flow at the measurement site. Preoperative ultrasonography and Doppler imaging are needed to evaluate vessel distribution and blood flow at candidate sites.

The nature of the scheduled surgery and comorbidities of the patient may require direct arterial blood pressure monitoring during surgery. To allow this, ultrasound should be used to characterize arterial distribution and locate arteries where cannulation is possible.

(2) Airway management and intubation

Particular caution is required when administering general anesthesia in a patient with facial malformations with airway involvement. The degree of cleft lip and cleft palate must be preoperatively determined whenever possible to inform the selection and preparation of assistive devices for intubation. Users of a laryngeal mask airway, gum-elastic bougie, video laryngoscope (e.g., McGRATH™, Airwayscope™), and fiber optic larynx/bronchoscope should have appropriate expertise. Similar preparations are needed even if the patient has undergone cleft palate repair, because adhesions and other remnants of deformity repair could be present. Conscious intubation is an option.

(3) Options other than general anesthesia

Anesthesia options for patients with TE include local anesthesia, regional anesthesia (including subarachnoid spinal block and epidural anesthesia), and general anesthesia, and no anesthetics are contraindicated in this population. The procedure to use should be selected in consideration of the type and duration of surgery and any comorbidities present. Epidural anesthesia and subarachnoid spinal block require particular caution, and the patient should be evaluated for spinal and other neurological anomalies. To ensure that an overdose of muscle relaxant is not given, the degree of muscle relaxation should be monitored since patients with limb reduction defects often have less muscle mass than other patients. Consider placing the monitoring electrodes on the corrugator supercilii or orbicularis oculi since placement on the ulnar nerves as in normal monitoring is not often possible in patients with TE.

(4) Maintaining body positioning during surgery

When the patient must be restrained in a certain body or limb position during surgery, use assistive devices to prevent decubitus from excess pressure on a certain area.

4 Postoperative Management

Normal postoperative management procedures are generally useful for patients with TE. Since 80% of patients with limb reduction defects also have sensorineural defects at the affected areas[URL1)], patients must be monitored for prolonged muscle relaxant effects and unintended neurological changes. In addition, since patients with TE with facial malformations with airway involvement or who have undergone repair surgery may experience ventilatory insufficiency following substandard extubation, they should be extubated after they are fully conscious and after precautions have been taken (e.g., tube exchanger insertion). When necessary, the patient, while still unconscious, can be transferred to the intensive care unit. Once awake, the patient should be closely monitored for sensory disturbances and paralysis and the range of conduction/local anesthesia. Patients with TE are likely to have psychiatric complications[7)] and must therefore be monitored for postoperative cognitive function level and delirium.

References

1) Tajima T, Wada T, Yoshizawa A, et al. Internal anomalies in thalidomide embryopathy: results of imaging screening by CT and MRI. Clinical Radiology 71: 1199.e1-1199.e7,2016
2) Ghassemi Jahani S.A., Danielsson A, Ab-Fawaz R, et al. Degenerative changes in the cervical spine are more common in middle-aged individuals with Thalidomide Embryopathy than in healthy controls. PLOS One. 11: e0155493, 2016
3) Kumar CM. Anesthesia and thalidomide-related abnormalities. Anaesthesia 43: 613-614, 1988
4) Grayling GW, Young PN. Anesthesia and thalidomide-related abnormalities. Anaesthesia 43: 69, 1988
5) Shiga Y, Nojiri F, Yoshizawa A, et al. Measurement of blood pressure in a thalidomide-impaired patient who required ovarian cystectomy: A case report. Int J of Surg Case Reports 5:428-430, 2014
6) Earle R, Vaghadia H, Shanahan E, et al. Real-time measurement of blood pressure with Nexfin in a patient with thalidomide-related phocomelia. J of Clinical Anesth 34: 244-246, 2016
7) Imai K, Iida T, Yamamoto M, et al. Psychological and mental health problems in patients with thalidomide embryopathy in Japan. Psychiatry and Clinical Neuroscienses 68: 479-486, 2014

URL

1) WHO 2014. Thalidomide Embryopathy Report of a meeting of experts (PDF). http://apps.who.int/medicinedocs/documents/s21639en/s21639en.pdf
2) Jan Schulte-Hillen. Measuring the blood pressure in patients with shortened arms due to thalidomide embryopathy. http://www.contergan-infoportal.de/fileadmin/downloads/NEU-DOWNLOADS/Medizinische_Beitraege/Blutdruckmessen/GB_blood_pressure_measurements_in_thalidomiders_with_upper_extremity_defects.pdf#search=%27SchulteHillen+thalidomide%27

[Yasuhiro Maehara]

XII Problems Encountered in Clinical Settings

4 Nursing



- The care of thalidomide embryopathy (TE) patients should be conducted with a thorough knowledge of the disease, an understanding of their social circumstances, and a considerate attitude.
- A good understanding of the individual disorders of each patient, and considerate nursing practices and care are necessary to ensure that testing proceeds smoothly.
- Patients must be adequately briefed prior to testing.
- Carefully decide how to communicate with patients with an auditory defect (e.g., sign language, written communication, lipreading, use of assistive forms) on an individual basis.
- Care requires a multidisciplinary approach by healthcare professionals from various disciplines, who should be closely partnered together.

Based on past experience, we have have listed below some precautions for the testing of TE patients at detailed medical examinations.

The roles of nurses in detailed medical examinations include maintaining safety and examination quality assurance.

For maintaining safety, protecting patients from falls is particularly important. Since unfamiliar settings and medications can put patients at greater risk of falls, nurses must structure the facility environment so that tests proceed safely.

Nurses must also observe the overall condition of each patient to evaluate the situation. In relation to examination quality assurance, it must be remembered that precise examination results facilitate treatment. To ensure that the tests are properly performed, nurses should begin examinations with a briefing and provide support for holding the patient in the required postures, assist with the tests, and monitor the patient before and after the tests. Nurses must therefore have an informed understanding of the disease and its individual manifestations to properly provide assistance.

1 Urinalysis

If standard urine collection procedures are acceptable, patients should be asked to collect urine on their own. A toilet insert or urine container should be provided to patients unable to collect urine in a cup because of an upper-limb defect, or devise another method of collection. Assist patients who have difficulty transferring their urine to the Spitz tube or in fastening and refastening their pants.

2 Abdominal Ultrasonography

Assist patients who are unable to keep their upper limbs raised. Assist patients who are unable to maintain a side-lying position. Wipe away any residual gel after testing.

3 Electrocardiography

Use tape-on electrodes rather than the standard gripped electrodes for the upper limbs depending on their severity.

Tape-on electrodes should be attached to the shoulders instead of the upper limbs.

4 Computed Tomography (CT)

Before imaging, instruct the patient how to position themselves and help them assume the proper posture. If necessary, secure the upper limbs with a belt and help them maintain a comfortable and effective posture.

5 Hearing Tests and Otolaryngology Examinations

Before the patient is examined, remove any excess earwax that the patient cannot remove because of upper-



Toilet insert, urine container, maintaining posture, earwax, upper-limb defect, auditory defect, communication, considerate attitude

limb defects. Make sure that the hair does not cover the ears.

6 Gynecological Examinations

Before the examination, brief the patient about the tests and how they will proceed. Adjust the gown so that the top does not cover the midriff when the patient sits on the exam table. Communicate with the patient during the exam, being mindful of the embarrassment she may be feeling. Observe the patient for post-exam bleeding and inform her about how to manage the condition.

7 Breast Surgery Examinations

Some patients may experience pain when raising their upper limbs in certain positions. Assist the patient with changing positions as necessary. Wipe away any residual gel after testing.

8 Upper Gastrointestinal Endoscopy

Before the procedure, inform the nurse in the exam room about the status and severity of the patient's deafness and upper-limb defects. TE Patients with upper-limb defects tend to strain more than others and may therefore have difficulty breathing. Provide emotional support during the procedure by, for example, gently rubbing the patient's back. Assist patients who are unable to maintain a side-lying position. When a sedative or other intravenous drug is to be used, ask the patient if they have a preferred blood vessel. Secure a peripheral venous route if needle insertion proves difficult. Inform patients with an auditory defect about the flow of the test in advance, telling them to raise their hand if they experience discomfort. Use signs to explain the test procedure and give instructions during the test. (Brightly colored signs with big writing will be more legible in a darkened exam room.)

9 Examinations and Nutritional Guidance

If the patient has a hearing defect, inform testing personnel in advance about how the patient should be communicated with (e.g., sign language, written communication, lipreading) to facilitate smooth communication. For nutritional guidance, ask the nutritionist to provide pamphlets and other written materials.

10 Others

(1) Collect any information available on the degree of the patient's disability to assist in the preparation of necessary materials.
(2) If the patient needs to change into a gown, provide a slip-on or other type of gown that is easier to put on and take off than a gown with buttons or straps. Assist patients who need help putting on or taking off their gown.
(3) To facilitate testing, determine if the patient has previously undergone the test. Explain the test as necessary to ease the concerns of the patient.
(4) Ask patients with an auditory defect how they wish to communicate (e.g., sign language, written communication, lipreading) and use the patient's preferred method of communication.
(5) Before the test, inform testing personnel about whether the patient has an upper-limb or auditory defect and the severity of that defect.
(6) Patients may experience pain if they must maintain a certain posture for an extended time. In such situations provide towels or other padding to reduce suffering.
(7) Provide assistance to patients who need help lying down or sitting up.
(8) Serve meals on nonslip plates or in cups with handles when necessary.
(9) Many thalidomide victims tire easily and may require a wheelchair.
(10) Be especially considerate, as the patient may be anxious or resistant because of previous bad experiences in healthcare situations.
(11) Note that some thalidomide victims are uneasy around others. Be mindful of the time required, routing, and locations when informing patients about moving and waiting between tests.
(12) It is important to approach patients with awareness of their disease, understanding of their social circumstances, and a considerate attitude.

[Keiko Tanaka, Chika Kuge]

5 Information on Supporting Patients with Auditory Defects

Information on Hearing Aids

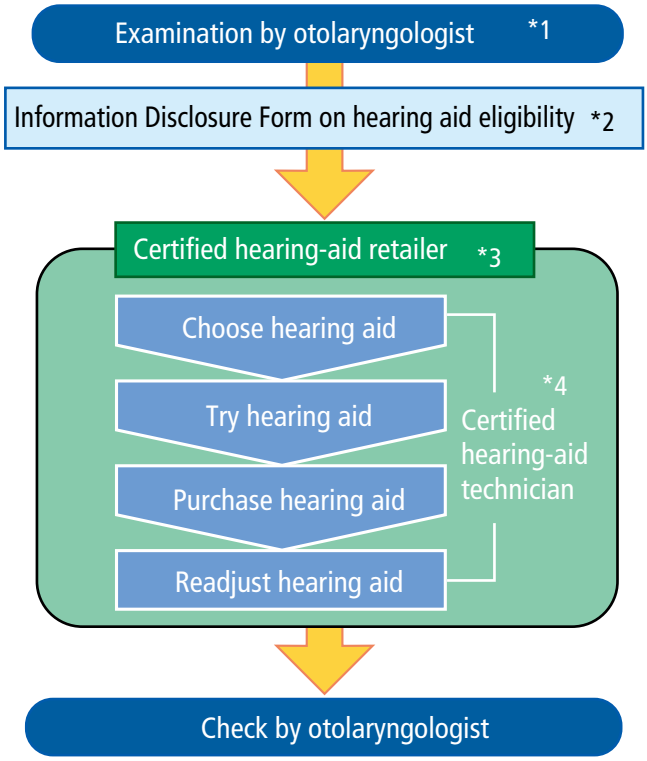
1. The Oto-Rhino-Laryngological Society of Japan, Inc.:
   :http://www.jibika.or.jp
   Easy explanation of hearing aids:
   http://www.jibika.or.jp/citizens/hochouki/yasasii.html
   List of hearing-aid specialized ENT doctors:
   http://www.jibika.or.jp/members/nintei/hochouki/hochouki.html
2. Japan Hearing-aid Industry Association, Inc.:
   http://www.hochouki.com
3. Association for Technical Aids, Inc.:
   http://www.techno-aids.or.jp
   List of Certified hearing-aid retailers:
   https://www5.techno-aids.or.jp/shop/map.php
4. Japan Hearing Instruments Technician's Association, NPO:http://www.npo-jhita.org
   Certified hearing-aid technicians of your town:
   http://www.npo-jhita.org/tech/
5. Japan Hearing Instruments Despensers Association, Inc.
   http://www.jhida.org

Smartphone Apps

Speech-to-text conversion application
  Android: Google play™
  iPhone:Siri™
Voice translation application
  VoiceTra™

[Niro Tayama]

Process of purchasing a hearing aid



*1 This examination by a hearing aid consultant physician is needed to determine whether the patient is eligible to be fitted with a h
*2 The patient must submit this "Information Disclosure Form" to qualify for coverage of healthcare expenses.
*3 The hearing aid must be purchased at a certified hearing-aid retailer staffed by a certified hearing-aid technician (*4).



XIII Care for Thalidomide Embryopathy (TE) in Germany



- Dr. Lenz devoted himself to diagnosing and caring for patients with TE, practicing in Nordrhein-Westfalen and Hamburg, Germany.
- Healthcare services for thalidomide victims are still offered in these locations. Victims living in Nordrhein-Westfalen are served by the Dr. Becker Rhein-Sieg-Klinik located in the suburb of Cologne, and those living in Hamburg and its environs by the Thalidomide Clinic Hamburg (Contergansprechstunde Hamburg).
- The Outpatient Center for Contergan Victims (das Ambulante Zentrum für contergangeschädigte Menschen) was opened at the Dr. Becker Rhein-Sieg-Klinik in September 2017. The Center accepts outpatient visits by patients with TE from Monday to Thursday. Patients receive alternative treatments including acupuncture, moxibustion, aquatic therapy in a pool, foot acupressure, and sling table care. Psychotherapy consultations by the University of Cologne are offered on Wednesdays.
- Opened in 2013, the Contergansprechstunde Hamburg offers standard disability evaluation care as well as alternative treatments such as yoga and Pilates instruction.

Members of the TE research group visited Germany and the UK as the "Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-impaired People in Japan" in August 2016 and the "Research Group on Grasping the Health and Living Situations as well as Creating the Support Infrastructure for Thalidomide-impaired People in Japan" in September 2018. While in Germany, they visited two facilities that provide focused care for many thalidomide victims[1,2]. One facility, located in Nordrhein-Westfalen, is the Dr. Becker Rhein-Sieg-Klinik, which provides care in central Germany, where more patients with TE live than anywhere else. The other is Thalidomide Clinic Hamburg (Contergansprechstunde Hamburg), which offers comprehensive care for patients with TE in Hamburg and other areas in northern Germany. Each clinic is dedicated to supporting patients with TE. To inform TE care in Japan, the services they offer are presented here.

1 Dr. Becker Rhein-Sieg-Klinik

The Dr. Becker Rhein-Sieg-Klinik is located in Nümbrecht, a suburb of Cologne in Nordrhein-Westfalen. It opened the Outpatient Center for Contergan Victims in September 2017. There to cut the ribbon at the opening ceremony was Udo Herterich, the leader of the International Contergan Thalidomide Alliance (ICTA), a group of about 800 thalidomide victims in the state of Nordrhein-Westfalen (Figure 1).

The leader of the Center is Dr. Kraus M. Peters (at the left in Figure 1). Patients receive outpatient care 4 days a week from Monday to Thursday, with an optional examination by a psychotherapy specialist at the University Hospital of Cologne on Wednesday. Patients can opt for a 3-day schedule without the Wednesday examination (Table 1). The services include a welcome address by the coordination team, a doctor examination, acupuncture, moxibustion and other evaluations, as well as routine physical therapy (which includes aquatic therapy in a large pool), physiotherapy, and occupational therapy (Table 2).



Figure 1 Ribbon cutting ceremony at the launch of the Outpatient center for thalidomide-damaged people in the Dr. Becker Rhein-Sieg-Klinik (Ambulantes Zentrum für contergangeschädigte Menchen in der Dr. Becker Rhein-Sieg-Klinik)



Nordrhein-Westfalen, Hamburg, Outpatient Center for Contergan Victims, alternative medicine

In Germany, physical therapy is called *physiotherapie* (English: physiotherapy). Dr. Becker's facility distinguishes physiotherapy from physical therapy.

*Sling table (Figure 2): A sling table is used to bear some of the weight of the body to facilitate exercise of the limbs and trunk.

Table 1 Schedule of the Outpatient Center for Contergan Victims

	Category	Caregiver
Monday	Welcome address	Coordination team
	Physical examination	Doctor
	Lunch	
	Physical therapy	PT
	Physiotherapy	PT
	Occupational therapy	OT
	Acupuncture, moxibustion	Doctor
	Follow-up	Coordination team
Tuesday	Consultation	Visiting specialist
	Lunch	
	Physiotherapy	PT
	Occupational therapy	OT
	Physical therapy	PT
Wednesday	Psychotherapy consultation	University of Cologne
Thursday	Physiotherapy	PT
	Physical therapy	PT
	Occupational therapy	OT
	Lunch	
	Acupuncture, moxibustion	Doctor
	Closing discussion	Doctor
	Farewell remarks	Coordination team
	PT = Physical therapist	
	OT = Occupational therapist	

PT = Physical therapist
OT = Occupational therapist

Table 2 Therapeutic treatments

Physiotherapy	Mobilization, sling table*, cognitive and motor training/physical exercise
Physical therapy	Craniosacral therapy, foot reflexology (foot acupressure), interstitial massage, ultrasound therapy, aquatic therapy, acupuncture, moxibustion
Occupational therapy (ergotherapy)	Mobilization of the hands, upper limbs, and shoulders, brace consultations
Evaluation	Evaluation + recommended approaches



Figure 2 A patient is treated on a sling table

• Following is a list of questions we asked Dr. Peters and his staff along with their answers.

1) What do your conferences involve?

We begin by telling the patient about their condition and our approach. We then write a prescription for therapy with our team of physical and occupational therapists. We evaluate the effects of the therapeutic approach at the next visit. Since some patients are unable to make a follow-up visit, we can pass along our recommended approach and prescriptions to the referring doctor.

2) Do you offer telemedicine?

Having considered the comments of our psychologist Mr. Alexander, we do not offer it now because of problems in the system for connecting individual patients with TE, but we will offer it in the future. Dr. Peters was asked in 2019 to diagnose a new claimer from Brazil. From faraway Germany, Dr. Peters confirmed that the patients satisfied the diagnostic criteria in the British diagnostic algorithm for thalidomide embryopathy based on the dates of birth, affected limbs, other disease characteristics, and family history of the claimers.

3) How do you psychologically evaluate chronic pain?

Since our patients are so susceptible to psychosomatic pain, we work hard on our evaluations in this area. On Wednesdays, we offer psychotherapy consultations at the University of Cologne. Holding meetings for thalidomiders to exchange opinions about pain and anxiety have been found to be effective.

4) Are there any new approaches to pain?

Thalidomiders in general (1) do not like medications, (2) have bones and tissues different from healthy people, and (3) have chronic pain. For these reasons, here in Nümbrecht, we focus on acupuncture, moxibustion, and aquatic therapy, and use a range of other approaches (see Table 2).

2 Thalidomide Clinic Hamburg

(Contergansprechstunde Hamburg) at Schön Klinik Hamburg Eilbek

In Hamburg, Dr. Rudolf Beyer (of the Schön Klinik Hamburg Eilbek) established the Thalidomide Clinic Hamburg (Contergansprechstunde Hamburg) in the Schön Klinik Hamburg Eilbek in 2013. There, patients are treated through a comprehensive, multidisciplinary approach (Figure 3). The Center served fewer than 20 patients in 2014, but more patients began to visit as word spread. A total of 181 patients visited a total of 309 times from 2014 to 2017. The data of patients who have visited even once are stored in electronic medical records so that they can be easily retrieved if the patient must be hospitalized. Although Dr. Beyer is an anesthesiologist, visiting patients can be seen by specialists, including a pain specialist, orthopedic surgeon, psychiatrist, and physical therapist, as well as an internist or surgeon when needed. The Center uses X-ray devices, computed tomography (CT), and magnetic resonance imaging (MRI) to identify problems that are treated with the necessary medication, pain therapy, physical therapy, psychotherapy, and rehabilitation. When indicated, patients are referred for care to an otolaryngologist, ophthalmologist, or dentist. Patients can also receive hospitalized care managed by a surgeon, physical therapist, or psychologist when needed. The focuses of the Center are (1) orthopedic issues, (2) pain, (3) hypertension and cardiovascular risk factors, (4) entrapment neuropathy, (5) digestive diseases, and (6) psychiatric diseases. The Center caregivers organically partner and work with other hospital departments to address these conditions. Instruction in yoga, Pilates, and other alternative therapies are also offered. These programs appear to be arranged for patients with TE because even healthy people find them difficult.

- Research activities

1) Application of digital health apps for TE

In partnership with the Institute of Technology and Innovation Management at the Hamburg University of Technology, the Center is using an Internet survey service called Survey Monkey to determine what kinds of digital health apps are needed for TE. They identified a certain amount of interest in individualized yoga and Pilates instruction and remote instruction for rehabilitation and exercise. Unexpectedly, however, the greatest amount of interest was expressed in flexible home care. Specifically, survey respondents expressed interest in a digital app they could use to seek a supporter when they require care (e.g., for shopping or going to the movies). Such an app would help thalidomiders live more independently.

2) Evaluation of congenital vascular and organ anomalies using non-contrast-enhanced magnetic resonance angiography

The Center evaluated 78 patients with TE in partnership with the University Hospital Hamburg Eppendorf. The investigators found a higher incidence of double renal arteries and other renal vascular anomalies than in healthy individuals, but noted that these vascular malformations did not cause renal impairment[3)].

3) New attempts to measure blood pressure

Investigators are studying methods for measuring blood pressure by looking at changes in pulse oximetry determined with a finger cuff and measuring blood pressure at the buccal artery, but these methods have not yet been applied for patients with TE because the former method requires reference measurements and is expensive, and the latter method requires mathematical modeling to produce blood pressure values.

4) Other studies

In a partnership with the University of Hannover Medical School, the Center began investigations in June



Figure 3 Schön Klinik Hamburg Eilbek (left) and Dr. Rudolf Beyer giving a presentation (right)

2016 to serve as a foundation for helping patients with TE maintain their range of motion and be independent, and, under an initiative called the "E-Health Project," is developing a way to allow easy, on-demand access to the healthcare information of thalidomide victims when they visit other medical institutions by importing digitized healthcare information into computers. The Center is also working with the Hamburg University of Technology to provide remote instruction for rehabilitation and exercise via the Internet.

References

1) Hinoshita F, Kayamori R, Shiga T. III. Summary Report on the end of the research year 4. Visits / tours in Europe, exchanges with experts. Health and Labor Sciences Research Grant (Pharmaceutical / Medical Equipment Regular Science Research Project) Designation-003) "2016 Summary / Shared Research Report. 2017 (in Japanes)
2) Hinoshita F, Haga N, Kayamori R, et al. II. General Report 3. Visit to Europe Report: Visit / Visit to Europe, Exchange with Experts. Health and Labor Science Research Grant (Pharmaceutical / Medical Equipment Regular Science Research Project) "Study on understanding the health and living conditions of patients with salidamide embryos and building a support base (H29-Pharmaceutical-Designation-006)" 2018 Summary / Shared Research Report. 2019 (in Japanese)
3) Weinrich JM, Beyer R, Well L, et al: Assessment of Congenital Vascular and Organ Anomalies in Subjects With Thalidomide Embryopathy Using Non-Contrast Magnetic Resonance Angiography. Circ J 82(9):2364-2371, 2018

[Ryoji Kayamori, Fumihiko Hinoshita]

XIV Related Information

1. Network of Healthcare Providers Serving Thalidomide Survivors

The Network of Healthcare Providers Serving Thalidomide Survivors was established in 2015 by the previous research group, the Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-impaired People in Japan. This network consists of dozens of members who are physicians, nurses, physiotherapists, researchers, pharmacists and other healthcare professionals, with experience providing care for or otherwise involved in activities with thalidomiders. This network aims to facilitate access to healthcare for thalidomiders even in local areas. Moreover, this network is useful for consultations among physicians, caregivers and researchers and for the exchange of clinical and research information.

The list of this network is omitted here because it is written in Japanese.

2. Website of the Thalidomide Embryopathy Research Group

The website of the Thalidomide Embryopathy Research Group of Japan was created in March 2016, and is available at http://thalidomide-embryopathy.com/.

3. Information on the Ishizue Foundation

The Public Interest Incorporated Foundation, the Ishizue Foundation, was founded in 1974 for thalidomide victims living in Japan, and continues to actively work on various issues.

（http://ishizue-twc.or.jp/）

4. Notable Sites for Information on Thalidomide Embryopathy Outside Japan

- Conterganstiftung für behinderte Menschen. Contergan Infoportal. (Germany)
  https://www.contergan-infoportal.de/
- Contergan. Wiederholt durchzuführende Befragungen zu Problemen, speziellen Bedarfen und Versorgungsdefiziten von contergangeschädigten Menschen (A survey on the living situations of German thalidomiders)
  https://silo.tips/download/wiederholt-durchzufhrende-befragungen-zu-problemen-speziellen-bedarfen-und-verso
- Damage to Health, Psychosocial Disorders and Care Requirements of Thalidomide Victims (Survivors?) in North Rhine Westphalia from a Long-Term Perspective. Expert opinion commissioned by LZG.NRW.
  https://www.thalidomidetrust.org/wp-content/uploads/2016/10/The-Cologne-Report.pdf
- The Thalidomide Trust (The UK)
  https://www.thalidomidetrust.org/
- A Securer Future - Evaluation of the Health Grant to Thalidomide-Impaired People Year 3 Final Report – July 2013
  http://www.fiftyyearfight.org/images/Health_Grant_Evaluation_Year_3_Final_Report_July_2013_.pdf
- The Swedish Thalidomide Society (Sweden)
  http://www.thalidomide.org/web/welcome/
- EX-Center (Sweden)
  http://www.ex-center.org/web/home/
- Thalidomide victims association of Canada (Canada)
  http://www.thalidomide.ca/the-canadian-tragedy/

* The information above was obtained in 2020.

XV Index

A

Aachen 12
abdominal ultrasonography 31
abducens nerve palsy 78, 79
abnormal glucose metabolism 35
acetaminophen 56
activities of daily living 54
affinity bead 16
age-related 52
a hearing defect 78
a high-arched palate 81
airway involvement 93
airway management 92
alcohol product 45
Alsdorf 13
alternative medicine 98
angle closure glaucoma 83
aniridia 82
ankle-brachial index 40, 91
anotia 58
anticancer effects 16
anxiety 86
A patient is treated on a sling table 99
aplasia 79
arteriosclerosis 31
arthralgia 52
arthritis 52
arthropathy 54
artificial joint replacement 57
artificial teeth 80
aspirin-induced asthma 49
auditory defect 38, 42, 78, 86, 94
auditory hypoplasia 22, 26
auditory ossicles 78
auricle deformations 78
Australia 23
avoidable cases of TE 11

B

basal metabolism 35
bath 64
being prepared 88
bend forward 62
bilaterally 25
Blessed Drug 22
block vertebrae 30, 32
blood access 39
blood collection 88
blood pressure at home 32
blood pressure cuff 38, 40
blood pressure in the dorsalis pedis 91
blood pressure measurement 40, 90, 92
blood pressure measurement technique 38
blood sampling kit 88
bone-anchored hearing aid 78
bone-conductive hearing aid 78
bone mineral density 34, 66
bone mineral density analysis 66
braces 57
brachial plexus 62
Brazil 11
breast cancer 66

C

calisthenics 64
cardiac catheter 38
cardiac failure 38
cardiovascular disease 38
Carl Schulte-Hillen 8, 10
carpal tunnel release 57
carpal tunnel syndrome 52, 54, 57
cataract 82
Celgene 12
central obesity 31
cereblon 16
cervical spondylosis 59, 63
cervical vertebral CT 73
cervical vertebral disc deformation 92
changing clothes 66
chemical biology 16
chemical formula of thalidomide 8
chest X-ray 66, 67
chipping 80
chronic kidney disease 34, 38
ciliary body coloboma 83
CKD 34
classifications of deafness in auditory hypoplasia 26
cleft lip 92, 93
cleft palate 92
cleft uvula 79
clinical symptoms of SALL4-related disorders 29
cognitive function level 93
communication 60, 94
communication disorders 86
compensatory movements 59
compliance 38
comprehensive medical examinations 39
computed tomography 66
conductive 78
conductive deafness 26
congenital facial nerve palsy 82
congenital heart disease 38
congenital rubella syndrome 29
conscious intubation 93
considerate attitude 94
contact lenses with an iris pattern 83
contact transmission 44
Contergan 7, 8
Contergansprechstunde Hamburg 98
conventional outflow reconstruction surgery 83
COPD 44
corneal opacity 82
corneal pannus 83
coronary arteries 38
COX-2 selective inhibitors 56
CRBN modulator 16
creative uses of tools 58
crocodile tears 26, 82
crocodile tears syndrome 78, 79
crowding of the teeth 80
cuff 90
CVD 39

D

Dainippon Pharmaceutical 9
DATE 23
DDB1 16
defects 58
degenerative spondylosis 56
delirium 93
dental caries 80
dental plaque 81
depression 86
dermoid cysts 82
Diageo 23
diagnosing TE 26
diagnostic algorithm for thalidomide embryopathy 22
diagnostic criteria and severities 22
diagnostic criteria for thalidomide embryopathy by the Ministry of Health, Labour and Welfare 24
diagnostic imaging 66, 73
diagnostic procedures 22
differentiating TE from SALL4-related Disorders 28
difficult to insert the needle into 88
direct arterial blood pressure monitoring 92
disabilities in daily activities due 62
Distaval 8
Distillers 23
disuse syndrome 62
DM 34
DNA damage-binding protein 1 17
Doppler blood flow meter 38, 40
Doppler imaging 93
Dr. Becker Rhein-Sieg-Klinik 98
Dr. Kraus M. Peters 98
Dr. Lenz would have celebrated his 100th birthday 8
Dr. Mückter 9
droplet transmission 44
drug-induced tragedy 87
drug-related injury 86
drug therapy 56
dual-energy X-ray absorptiometry 66
duane-radial ray syndrome 26

Duane syndrome 22, 26, 78, 82
DXA 66
dyslipidemia 30, 31, 34

E

earwax 78, 94
eating nutritious 45
echocardiography 32, 38
elbow 38
electronic blood pressure meter 88
electric toothbrush 80
electrocardiography 38
embryopathy 8
endocrine and metabolic disorders 34
endoscopic pretreatment 48
endoscopic procedure 48
ENL 12
ensuring venous access 92
epidural anesthesia 93
epistaxis 48
ergonomic approach 62
ergonomic remedies 63
ergonomics 62
erythema nodosum leprosum 12
esophagogastroduodenoscopy 48
estimating upper-limb blood pressure 91
exercise 64

F

facial nerve 74
facial nerve palsy 22, 26, 78
falls 70
Fanconi anemia 27
FDA 11
feature upper limb domination 52
femoral neck 66
FG beads 16
fiber optic larynx/bronchoscope 93
field of view 71
filtration surgery 83
follow-up 78
food poisoning 45
forced expiratory volume in 1 second 44
front-tying gown 66
fruit 32
funeral announcement of Dr. Lenz 14
Fujimoto Pharmaceutical 12

G

gallbladder agenesis 30, 75
gastric cancer 48
gastrointestinal diseases 48
general anesthesia 93
General Health Questionnaire-28 86
Germany 22
gesticulating 79
glaucoma 83
glomerular filtration rate 38
Glutanon 9
gout 35
gown 67
grab 59
grasping and pinching 58
gripped electrodes 94
grip strength 63
Grünenthal 7, 8
Guidelines for sedation in gastrointestinal endoscopy 49
Guidelines for the Management of Hypertension 38
gum-elastic bougie 93

H

Hamburg 98
handicaps 87
hand washing 45
Hansen's disease 11
have left–right symmetry 52
healthcare professionals from various disciplines 94
health management 62
hearing aid 78
hearing aid specialist 78
heart disease 38
Helicobacter pylori infection 48
hemangioma of the upper lip 79
hemodialysis 38, 39
hepatic steatosis 30, 34
Holt–Oram syndrome 22, 26
HOMA-R 31
how best to give 66
humidity 45
hyperesthesia of the cervical enamel 80
hypertension 30, 34, 38
hyperuricemia 30, 31
hypoplasia of the left hip cup 28

I

image assessment 66
IMiDs 18
immunomodulatory 22
immunomodulatory imide drugs 18
impaired glucose tolerance 31, 34
implants 80
infectious gastroenteritis 45
influenza vaccination 45
influenza virus 44
inner ear malformation 78
insomnia 86
insulin sensitivity 31
insurance-covered drug 12
internal abnormalities 32
interviewing the patient 72
ischemic heart disease 38
Ishizue 11
Isomin 8

J

Jacob Sheskin 11
jaw 81

K

kidney/urinary tract malformation 38
Kiesselbach's area 50
Klinik Hamburg Eilbek 100

L

laptop 63
laryngeal mask airway 93
left–right asymmetry 63
left–right differential 38
left ventricular hypertrophy 32
lenalidomide 12
Lenz 7
Lenz's Warning 10
leprosy 11
lifestyle diseases 30, 34, 38
lifesyle habits 63
limited physical activity 34
lip-read 66
lips 80
living environment refinements 62
lobulation defect 75
local anesthesia 49
lower-limb blood pressure 38
lower-limb systolic blood pressure 90
lumbar pain 63
lumbar spine 66

M

magnetic resonance angiography 73
magnetic resonance imaging 66
maintaining body positioning during surgery 93
maintaining posture 94
malformations of the internal organs 26
malocclusion 80
mammography 66, 69
mask 45
McBride 29
measurements 91
meatoplasty 78
mechanism 16
mecobalamin 56
menopause 30
mental 86
metabolic syndrome 30, 31
microphthalmos 82
microtia 58
middle ear malformation 78
mirogabalin 56
misuse 52
mixed hearing loss 78
monitored 66
monitoring 67
mouse 63
mouthpiece 81
MRI 72
Mückter 8
multiple myeloma 12
muscle relaxant 93
muscle relaxation 92
musculoskeletal 52
musculoskeletal conditions 62
musculoskeletal disorder 52, 54
mutagen 29
myalgia 52
myopia 83

N

nasal pain 48
Nelufanan 9
new cases in Brazil 8
new claimer 22
new claimers in Japan 27

New Nifrol....9
New Night....9
New Zealand....23
nicotine dependence....44
nicotine patch....44
no limits....13
nonalcoholic fatty liver disease....31
non-narcotic opioids....56
nonspecific lumbar pain....56
nonspecific pain....62
nonsteroidal anti-inflammatory drugs....56
Nordrhein-Westfalen....98
norovirus....44, 45
North Rhine-Westphalia....11
numbers of babies born with thalidomide embryopathy in Japan....23
numbness....56
nursing....94

O

obesity....34
obstructive ventilatory defect....44
occupational health....64
occupational therapy....58
Okihiro syndrome....22, 26
operations....92
ophthalmologic dysfunction....82
optical isomers....18
optical purity....18
oral cleaning....80
oral mucosa....80
osteoarthritis....52, 54, 56
osteoarthritis of the shoulders and hips57
osteoporosis....34, 66
outer ear canal....73, 78
outer ear malformation....26, 78
Outpatient Center for Contergan Victims....98
overuse....52
overweight....35

P

p63....16
PAD....91
pain....56, 86
pain in the back and neck....52
pain when drinking cold water....80
palatine tonsils....79
patents were granted for drug manufacturing processes....9
patient with auditory hypoplasia....66
patient with upper-limb hypoplasia....66
pattern and severity classification of preaxial longitudinal hypoplasia in thalidomide embryopathy....25
percent vital capacity....44
peripheral venous route....95
periodontal tissues....81
periodontitis....80
perioperative management....92
peripheral artery disease....38, 90
peripheral neuropathy....52, 54, 56
photophobic....83
physical contact....50
physical manifestations of TE....24
pinch....59
polyneuropathy....9
pomalidomide....12
Pomalyst....12
poor renal function....31
Porbren....9
positioning....66, 70
postcard handwritten by Dr. Lenz....14
posterior tibial arteries....91
posture and motion....62
preaxial longitudinal hypoplasia....24
pregabalin....56
preoperative tests....92
preparation....72
preventing infections....45
Proban M....8
procedures for the proper control....12
properly interacting....58
properly open the mouth....81
pulmonary function tests....44

Q

Q&A on thalidomide-impaired people....66
QOL....68
quality of life....68, 86

R

radiculopathy....54
radiology technicians....66
reach....58
reacher....59
recall....11
reconstructive surgery of the lens....83
reducing the strain of daily activities 62
refining the patient's environment....62
regional anesthesia....93
regression formula....90
renal biopsy....38
requirements for a diagnosis of TE....23
result in a worn....80
Revlimid....12
RevMate....12
ribbon cutting ceremony at the launch of the outpatient center for thalidomide-damaged people....98
risk management system....12

S

SALL4 anomalies....29
Sanodolmin....9
sarcopenia....35
schedule of the outpatient center for Contergan victims....99
Schulte-Hillen....10
secondary disorders....62
secure a route....48
sedation....48
selection of endoscope insertion route....48
sensorineural....78
sensorineural deafness....26
sensorineural defects....93
serotonin-noradrenaline reuptake inhibitors....56
severe atrophy of the right kidney....28
severity classifications of upper-limb hypoplasia....25
shortened limbs....62
shunt....38
shunting....32
sign language....72
sign-language interpreter....66
signs....79
sitting posture....63
Sleeban....9
slip-on....95
slip-on gowns....67
smartphones....58, 62
smoking cessation....44
smoking index....44
sodium hyaluronate....56
sodium hypochlorite....44
soft palate palsy....81
somatic symptoms....86, 87
Spain....22
speech-to-text conversion application....96
spinal column....63
splint....81
spray....49
stage 4 or 5 CKD....73
stenosis....78
steroids....56
sticks....49
stiff shoulders....63
stretching....64
subarachnoid spinal block....93
substrate....16
substrate receptor....17

T

TAp63 α....19
tape-on electrodes....94
target protein....16
targets....16
tartar....81
teeth crowding....80
temporal bone computed tomography....78
temporomandibular joint disorders....80
tenosynovitis....52, 54
TERMS....12
text tracing applications....60
Thaled....12
thalidomide....8, 12, 16
Thalidomide Clinic Hamburg....100
thalidomide embryopathy....48, 82
thalidomide embryopathy diagnosis....22
Thalidomide Saga....10
thalidomide sales and the incidence of thalidomide malformations....11
the 12-Item Short Form Health Survey....86
therapeutic treatments....99
therapy provided to increase jaw mobility....81
thoroughly heating....46
thrombocytopenia-absent radius....27

thumb triphalangia 58
thyroid dysfunction 34
time management 62
toilet insert 94
Tokujiro Miyatake 11
tongue 80
tongue from becoming coated 81
tools 58
tooth alignment 80
tooth fracture 80
Townes–Brocks syndrome 26
transnasal approach 48
transnasal endoscopy 48
transoral endoscopy 48
triphalangeal thumbs of both hands .. 27
trismus 80
trunk CT 73
TSH 34
tympanoplasty 78

U

ubiquitin 16
UK 22
ultrasonography 92
undergone cleft palate repair 93
undescended testicle 38
Universitätsklinikum Hamburg-Eppendorf 12
University of Münster 12
upper-limb defect 38, 40, 44, 94
upper-limb hypoplasia 22
upper-limb systolic blood pressure estimate 38
urine container 94
use a computer 62
use of thalidomide drug products in Japan 12
utilizing new devices 58
uveal coloboma 82

V

vaccination 44
VACTERL syndrome 27
varenicline 44
vascular access 92
VATER 27
vertical gaze palsy 82
vestibular dysfunction 78
vestibular hypofunction or afunction 79
video laryngoscope 93
voice translation application 96

W

wear 80
wedge-shaped defect 80
WHO 23
Widukind Lenz 8, 10
Wiedemann 9
Wiedemann Syndrome 10
World Health Organization quality of life 86
wrist 63
written communication 68

X

xylocaine 49

Z

zebrafish 16, 17

2020 Guide for the Management of Thalidomide Embryopathy

Published on March 1, 2021

Editor: Fumihiko Hinoshita, Department of Nephrology,
Center Hospital of the National Center for Global Health and Medicine (NCGM)

Publisher: The Research Group on on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan
(Head: Fumihiko Hinoshita)
Grant-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare, Japan

c/o Department of Nephrology, Center Hospital of NCGM
1-21-1, Toyama, Shinjuku, Tokyo 162-8655, Japan

Copyright©2021 Printed in Tokyo, Japan

Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo

Date : July 14 & 15, 2019

Venue : Sola City Conference Center
Ochanomizu, Tokyo, Japan

Edited by

Fumihiko Hinoshita

Center Hospital of the National Center for Global Health and Medicine (NCGM)

Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo

Funded by Ministry of Health, Labour and Welfare

Date : July 14 & 15, 2019
Venue : Sola City Conference Center
Ochanomizu, Tokyo, Japan

Organizer and Editor: Fumihiko Hinoshita, Department of Nephrology, NCGM
Head, The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan
Grant-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare, Japan

Secretariat: Department of Nephrology
Center Hospital of the National Center for Global Health and Medicine (NCGM)
1-21-1, Toyama, Shinjuku, Tokyo 162-8655

Preface

Fumihiko Hinoshita, MD, Ph.D.

The 2nd International Symposium on Thalidomide Embryopathy (TE) was held in Tokyo on July 14 and 15, 2019. Four years had passed since we held the 1st International Symposium on TE in Tokyo. Research on TE and support for thalidomiders have greatly progressed worldwide during this period. Many research works on TE have been published, not only from European countries, but also from Japan, and a TE-associated law was amended in Germany. Moreover, some new programs to support thalidomiders have been tried in the UK and in some other countries as well. In Japan, we have also tried new approaches to treat and examine thalidomiders, including a nationwide survey regarding the actual life situations of thalidomiders (Birth Defects Res. 2019;111:1633-1642).

Based on these results, this symposium first focused on the clinical and social reports of TE in various fields, next incorporated the special lectures on mechanisms of thalidomide teratogenicity, hip joint surgery and a diagnostic aid to TE, valiDATE as well as on thalidomiders in Brazil, and finally closed with a joint discussion among the oral presenters and a few other moderators. In total, we had 9 special speakers from Germany, the UK, Sweden, Switzerland and Brazil, as well as 7 Japanese speakers and some moderators.

Basically, the babies with congenital deformities which were induced by thalidomide (Contergan) were born in the late 1950's and early 1960's in developed countries. Consequently, many of them survived the physical, medical, social or mental handicaps and hardship, and are now living in their 50's and 60's. The thalidomide disaster was one of the unprecedented human tragedies in medical history. Human society itself is to blame, as it is responsible for the thalidomide victims. Therefore, society should take care of them and treat them as long as they live, even as they would become older and older.

In years past, the anatomical malformations and problems in thalidomiders, particularly in the extremities, and hearing impairment, as well as facial problems, were thoroughly examined and treated. Most patients with TE have become accustomed to handling such physical hardship because they were born with these problems. However, now they face other problems such as persistent pain and more severely impaired ADL, in part due to age and in part due to overuse syndrome progression as well as lifestyle-related diseases which might not have been noticed in their youth. Therefore, researchers, clinicians and healthcare workers of TE are now discovering these problems and difficulties, which thalidomiders are suffering. I believe such an opportunity to hold an international symposium is one of the best chances to clarify, classify, and share those problems and themes. I hope that the experts of TE worldwide will make use of this good opportunity.

Recently, diagnostic aid or criteria are being determined in some countries. In the 1950's and 1960's, TE was diagnosed by some classic methods with physical findings, simple X-ray examinations for systemic bones, hearing tests and evidence of their mothers' taking thalidomide during pregnancy. However, a wealth of knowledge on TE has been accumulated, and image inspection methods have markedly progressed including MRI and CT as well as ultrasonography. Therefore, it might be necessary to newly determine a modern means of diagnosing TE using more sophisticated medical tools. Moreover, we must facilitate the next-generation of physicians to easily diagnose and understand TE, in part because we still find many new claimers for TE in various countries.

Most of the TE experts in clinical fields would mainly consider the clinical, physical, mental health and social problems. In realty, however, we should also think about the pharmacological mechanism which induces TE in embryos. There have been classic theories on the possible reason or mechanism for the congenital abnormalities of TE. Unfortunately, however, more specific or molecular mechanisms remain to be determined. Without the precise elucidation of this mechanism, we cannot truly be freed from this serious human tragedy, TE. Therefore, in this second symposium, we also included the opportunity to discuss the basic mechanism of thalidomide teratogenicity.

Now people throughout the world are facing another human disaster, COVID-19, which started in China from December 2019. I guess there may have been some countries that regarded COVID-19 as something unrelated to them at the beginning. Horribly, however, only a few COVID-19 infected people from abroad easily brought it back to their own countries and it promptly spread to many other countrymen resulting in a serious pandemic with an explosive surge of critically ill cases and deaths. This tragic fact reminds us that our world has become very small and we are living in a truly global society where people from different countries unavoidably connect with other people even though countries did close their border after the initial spread of COVID-19. Unfortunately, the openness, free travel and communication in the world has become a great disadvantage in the case of COVID-19, but it can serve as a good advantage in science and medicine. I think it is very meaningful to directly share the present problems of TE by many experts from different countries and to discuss them together.

We could publish this Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo as a culmination of many efforts. I hope this record of the 2nd Symposium will be read and shared by many clinicians and researchers working on TE. I believe the Proceedings will certainly contribute to the development of clinical practice and research on TE, as well as enhancing the social welfare for the thalidomiders; further, it should help to positively stimulate many researchers and clinicians as well as healthcare workers for thalidomiders.

Finally, it is noteworthy that this symposium was supported and funded by the Ministry of Health, Labour and Welfare (MHLW), Japan. I greatly thank Secretary Ms. Chikako Toyota for her assistance and Ms. Chiharu Matsuoka for contributing to the editing of the Proceedings. It was originally planned and managed by "The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan" which was organized by MHLW. In this Proceedings, you might notice awkward English and grammatical errors. There might be some inappropriately edited parts which are slightly different from what speakers really wanted to say. Therefore, I would like to ask you to overlook such small mistakes and to stress that the most important thing is not to find trivial mistakes but rather to understand the valuable contents each author would like to convey.

Note: This Guide was created under the FY2019 Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Health Labour Sciences Research Grants (under the title of "The research group on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan") from MHLW, Japan.

Program & Contents

Date: July 14, 2019

Welcome & Opening Remarks 6

Dr. Fumihiko Hinoshita *(National Center for Global Health and Medicine, Tokyo, Japan)*

Congratulatory address

Mr. Takeshi Annaka *(Ministry of Health Labour and Welfare, Tokyo, Japan)*

Dr. Tsugumichi Sato *(Public Interest Incorporated Foundation "Ishizue", Tokyo, Japan)*

Oral Presentation

Endocrine and Metabolic Disorders 8

Dr. Tetsuya Tagami *(National Hospital Organization Kyoto Medical Center, Kyoto, Japan)*

Medical Check-up of Otorhinolaryngology (ORL) for the Patients of Thalidomide Embryopathy (TE) 13

Dr. Nirou Tayama *(National Center for Global Health and Medicine, Tokyo, Japan)*

Two New Claimers in Japan 22

Dr. Ryoji Kayamori *(Teikyo Heisei University, Tokyo, Japan)*

Special Lecture

A Diagnostic Aid to Thalidomide Embryopathy 29

Dr. Emma Baple *(Royal Devon & Exeter NHS Foundation Trust, Exeter, UK)*

Mechanisms of Thalidomide Teratogenicity 42

Dr. Hiroshi Handa *(Tokyo Medical University, Tokyo, Japan)*

Date: July 15, 2019

Oral Presentation

Activities of the Japanese Research Group on TE and Nation-wide Survey of Actual Life Situation in Subjects with TE in Japan, 2018 55

Dr. Fumihiko Hinoshita *(National Center for Global Health and Medicine, Tokyo, Japan)*

Preserved Pulmonary Function in Thalidomide Embryopathy in Japan 65

Dr. Hiroyuki Nagase *(Teikyo University, Tokyo, Japan)*

Mortality in Thalidomiders in Germany Is Underdiagnosed Hypertension the Cause? 75

Dr. Jan Schulte-Hillen *(Notfallzentrun Klinik St. Anna, Luzern, Switzerland)*

Lessons from Thalidomide Embryopathy and Sharing Information with the Next Generation ~From Physiatrists' Points of View~ 82

Dr. Nobuhiko Haga *(The University of Tokyo, Tokyo, Japan)*

Thalidomide Embryopathy – Orthopaedic Aspects, Degenerative Changes and Quality of Life at Age 45 90
Dr. Shadi-Afarin Ghassemi *(Unversity of Gothenburg, Gothenburg, Sweden)*

Outpatient Center for Thalidomiders in Gemany: Treatment Strategies and First Results 98
Prof. Dr. Klaus M. Peters *(Dr. Becker Rhein-Sieg-Klinik, Nümbrecht,Germany)*

Growing Older with Thalidomide Embryopathy – Research and Support in the UK 104
Dr. Dee Morrison *(The Thalidomide Trust, St Neots, UK)*
Ms. Elizabeth Newbronner *(The University of York, York, UK)*

Ageing with Thalidomide Damage: Evaluation 2019 – Special Needs 113
Dr. Christina Ding-Greiner *(Institute of Gerontology, University of Heidelberg, Germany)*

Special Lecture

Total Hip Replacement in Thalidomide Enbryopathy? What Are We Worried About? 119
Prof. John Skinner *(Royal National Orthopaedic Hospital, Stanmore, UK)*

Thalidomide in Brazil: Recent Experience 137
Prof. Lavínia Schuler-Faccini
(Federal University of Rio Grande do Sul Genetics Department, Brazil)

Panel Discussion 148
Chairperson: **Dr. Fumihiko Hinoshita** *(National Center for Global Health and Medicine, Tokyo, Japan)*
Discussants: **Dr. Ryoji Kayamori** *(Teikyo Heisei University, Tokyo, Japan)*
Dr. Junko Fujitani *(National Center for Global Health and Medicine, Tokyo, Japan)*
Dr. Dee Morrison *(The Thalidomide Trust, St Neots, UK)*
Dr. Christina Ding-Greiner *(Institute of Gerontology, University of Heidelberg, Germany)*
Prof. Dr. Klaus M. Peters *(Dr. Becker Rhein-Sieg-Klinik, Nümbrecht,Germany)*
Dr. Shadi-Afarin Ghassemi *(Unversity of Gothenburg, Gothenburg, Sweden)*
Dr. Jan Schulte-Hillen *(Notfallzentrun Klinik St. Anna, Luzern, Switzerland)*
Prof. John Skinner *(Royal National Orthopaedic Hospital, Stanmore, UK)*
Prof. Lavínia Schuler-Faccini
(Federal University of Rio Grande do Sul Genetics Department, Brazil)
Dr. Emma Baple *(Royal Devon & Exeter NHS Foundation Trust, Exeter, UK)*
Ms. Elizabeth Newbronner *(The University of York, York, UK)*

Closing Remarks 160
Dr. Fumihiko Hinoshita *(National Center for Global Health and Medicine, Tokyo, Japan)*

Welcome & Opening Remarks

Staff: Ladies and gentlemen, thank you very much for waiting. Now, I would like to start the 2nd International Symposium on Thalidomide Embryopathy. We would like to ask Dr. Hinoshita to give the opening remarks.

Fumihiko Hinoshita

Good afternoon. First, I would like to thank everyone very much, especially the speakers from overseas, for coming all the way to Japan during this rainy weather. I also heard it took 2 whole days to arrive from Brazil. I believe that you, Prof. Faccini, are busy and very tired, but fortunately, all of the guest speakers here today look good to me, so I am very glad that you arrived here in Tokyo without too many serious problems.

Moving on, this is the 2nd International Symposium on Thalidomide Embryopathy. Four years have passed since we held the 1st International Symposium in 2015. During these 4 years, I believe that the researchers and specialists in Japan and overseas have conducted a number of new studies. Therefore, more up-to-date information is currently available. We would like to have this information to be shared among everyone so that we can make use of it for the treatment of and further research on thalidomide embryopathy.

We have a lovely audience in this room and wonderful speakers from Brazil, Sweden, Germany, the UK, Switzerland, and Japan. As this is such a great opportunity, we would like to encourage you to have very active discussions and a valuable exchange of opinions.

Now, I would like to begin with opening remarks from our distinguished guests. The first speaker is Mr. Takeshi Annaka, the Director of the Office of Drug-induced Damages of Ministry of Health, Labour and Welfare of Japan.

Takeshi Annaka

Good afternoon everyone. My name is Takeshi Annaka from the Office of Drug-induced Damages of Ministry of Health, Labour and Welfare. Welcome to the 2nd International Symposium on Thalidomide Embryopathy, and thank you very much for coming, especially the speakers from overseas.

I would also like to express my appreciation for the day-to-day efforts made by Dr. Hinoshita of National Center for Global Health and Medicine (NCGM) and all the members of the Thalidomide Embryopathy Study Group.

Thalidomide was approved in Japan in 1957. After that, a teratogenic problem became apparent. From mid-1962, the recall of thalidomide products began, and many thalidomide embryopathy victims were born. In 1963 and after, lawsuits started being filed, and ultimately, 309 victims were officially certified.

The government of Japan paid compensation that provided pension and additional support for these victims, as well as funding for research.

It has been 50 years since the onset of thalidomide embryopathy (TE). Many victims started to experience body pain because of postural problems, subsequently suffering additionally from lifestyle-related diseases with aging.

Dr. Hinoshita and other specialists in the study group have tried to understand the current situation in Japanese thalidomiders by providing medical checkups and conducting questionnaire surveys. As the number of physicians who know TE well is decreasing, the study group provided a guide for the management of TE. We can now share their research on TE with many experts overseas.

Recently, we have also started to see claims from potential new victims of TE. However, for the past 30 years, we have not certified any new victims of TE, so currently, we need to think about how we can deal with newly emerging patients — so-called new claimers. Therefore, we believe that much more experience has been accumulated overseas, and we would like to hear some presentations and comments in regard to this from overseas speakers.

After these opening remarks, we look forward to listening to presentations from prominent specialists and having very active discussions, so that research on TE will progress and be further developed, not only in Japan, but also overseas. With this, I would like to close my opening remarks. Thank you very much.

Fumihiko Hinoshita (Moderator): Mr. Annaka, thank you very much. Next, Dr. Tsugumichi Sato, the Director of the Ishizue Foundation, the Public Interest Incorporated Foundation of Thalidomide Victims in Japan, will give his opening remarks.

Tsugumichi Sato

My name is Tsugumichi Sato from the Ishizue Foundation, the Public Interest Incorporated Foundation of Thalidomide Victims. Thank you very much for your invitation. The Ishizue Foundation is an incorporated foundation under the terms of the settlement of the thalidomide lawsuit for compensation that provides support to thalidomide victims. This organization was established as a welfare center.

When this organization was established, it was operated by the parents of the thalidomiders; however, for about the past 20 years, the organization has been operating in accordance with the initiatives of the victims. Therefore, the victims are now the operators.

I also gave opening remarks in the first symposium, and at that time, I mentioned that historically, holding this symposium for thalidomide embryopathy in Japan is quite epoch-making. And it's been 4 years since then.

I believe that this is another historical epoch-making symposium, and that's great news for me. For many years in various countries around the world, specialists have gotten involved in medical care for the victims of thalidomide embryopathy, and I am really looking forward to listening to their lectures.

Today, not only I but also the thalidomiders currently operating the Ishizue Foundation, have joined this symposium. Nine board members are in attendance, in addition to social workers who provide consultations. We, the thalidomiders, are currently facing various problems, and 'health', one of the themes of the symposium, is quite an important issue for us.

In Japan, many TE victims have died each year, especially the last couple of years. Last year, three victims passed away, so we really have deep concerns about our health. Fortunately, centered around Dr. Hinoshita, we have a MHLW-initiated research group, and this group is very active in terms of research and investigations. We would like to show our appreciation for their efforts. I believe that the efforts of the group will be of great help in maintaining our health.

I am currently 56 years old. Most European victims are probably 1 or 2 years older than me. Anyhow, we are rapidly approaching 60 years of age. Therefore, we have started thinking about our remaining life, and especially if we can receive appropriate care as we age in the future.

Japan provides long-term health care insurance and ensures public support to all residents. However, in our case, we have complications associated with aging and thalidomide-related symptoms, so I wonder if we can receive comprehensive support.

For this as well, we really count on measures guided by research by specialists that can identify the best type of support for older thalidomiders. As Mr. Annaka mentioned, we have recently started to see new claimers for potential TE.

Dr. Kayamori is going to introduce us two new claimer cases, followed by another. This person has a hearing problem. For a long while after the thalidomide disaster, the victims were not registered as thalidomiders, probably because of certain reasons of the parents. But now that they have reached a certain age and began having problems, they have started to make new claims. Therefore, we have to recognize them as new thalidomiders and think about how we can deal with them.

At the same time, there is probably a grey zone or borderline patients, so how we can deal with them is currently under consideration by authorities and specialists. Also regarding this point, appropriate recognition as thalidomiders should be given as early as possible if legitimate.

Again, I am thankful for this very valuable opportunity to listen to presentations by specialists and very much looking forward to it. Thank you very much.

Endocrine and Metabolic Disorders

Tetsuya Tagami

The Medical Checkup Center, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

Fumihiko Hinoshita (Moderator)

Good afternoon. Now let me introduce the first presenter or speaker of this symposium. I introduce Dr. Tagami, the Director of the Medical Checkup Center at National Hospital Organization (NHO) Kyoto Medical Center. He will be giving a presentation on endocrine and metabolic disorders in thalidomiders. Dr. Tagami, please.

Thank you very much, Dr. Hinoshita, for your very kind introduction. Good afternoon to everyone. I am Tetsuya Tagami of NHO Kyoto Medical Center. We've been investigating thalidomiders with a focus on endocrine and metabolic disorders. (Fig. 1)

I will talk about endocrine and metabolic disorders in patients with thalidomide embryopathy (TE) from our hospital in Kyoto. We have examined 46 TE patients, including 15 men and 31 women, at NHO Kyoto Medical Center. Among these 46 patients, 11 (4 men and 7 women) were examined twice at our center in 9 years over a cumulative total of 57 visits (19 for men and 38 for women). Their mean age was 53 years. (Fig. 2)

First of all, some patients are already under treatment with lifestyle-related diseases. Six patients (2 men and 4 women) with hypertension, 3 with diabetes mellitus, 8 with dyslipidemia, 2 women with osteoporosis, and 2 men with gout were under treatment already. Three of these patients who were examined twice were started on medication for a lifestyle-related disease by the second visit. Two patients were treated during this period. There is a possibility the results of the first examination initiated medication. Three patients (1 man and 2 women) were under treatment with more than two different diseases simultaneously from among hypertension, diabetes, and dyslipidemia. Accumulating risk factors, which lead to atherosclerosis, should be addressed through diet and exercise therapy.(Fig. 3)

The second topic is overweight. Ten patients had obesity; 9 of whom were women. The BMI of 1 woman was 34. Another woman had a decreased body weight from 60 kg at the first visit to 53 kg at the second, with a BMI decreasing from 26 to 23. Patients with TE are prone to becoming overweight



Fig. 1

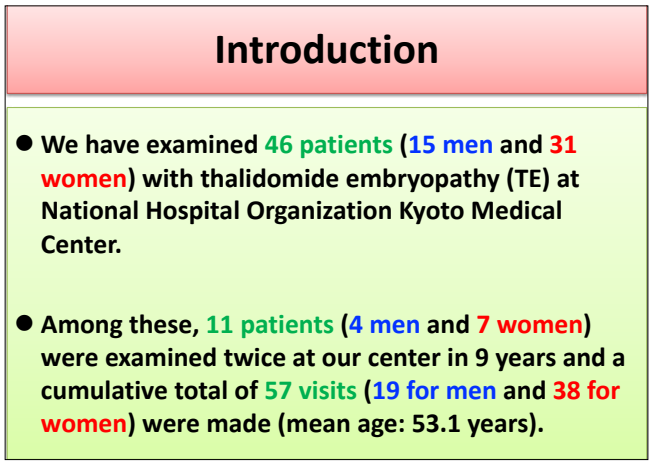


Fig. 2

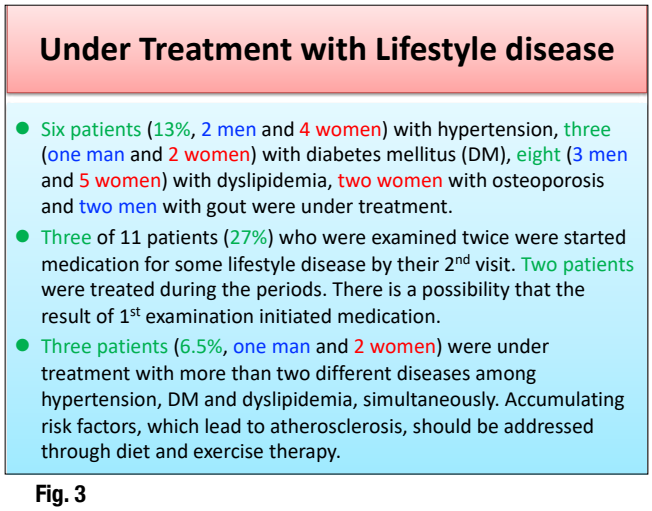


Fig. 3

because of not only developmental limb disorders, but also of finding going outside to be a hassle. As these patients age, they are at increased risk of reduced muscle mass in their healthy limbs, which is called sarcopenia, as well as weight gain, because this reduction lowers their basal metabolism, leading to sarcopenic obesity. Ways must be found to maintain muscle mass in these patients. (Fig. 4)

Hepatic steatosis. Regarding liver function, seven patients had high ALT levels. The ALT of one man improved at his second visit. The ALT of one woman was as high as 53 IU. High ALT levels were not only liver-related. Ultrasonography revealed a finding of hepatic steatosis. High hepato-renal echo contrast was seen in 21 patients (46%). At-risk patients would benefit from a better diet. (Fig. 5)

Dyslipidemia. More than half of the patients had hyper-LDL cholesterolemia. LDL cholesterolemia had improved in two women at their second visit. Blood LDL cholesterol levels were more than 150 in some patients, more than 170 in two women, and over 200 in two women. One man had hypo-HDL cholesterolemia. Thirty patients had hypertriglyceridemia. Blood triglyceride levels were more than 200 in some patients and more than 300 in one man and two women. Persisting lipid disorders exacerbate atherosclerosis. At-risk patients would benefit from proper eating habits and appropriate pharmacotherapy. (Fig. 6)

Abnormal glucose metabolism. A high level of HBA1c was observed in five patients (2 men and 3 women). The HBA1c level was 7.0 to 8.0 in one person and 6 to 7 in four. Because the HBA1c level increased in almost all of the patients who were examined twice, we have to follow up their health carefully. (Fig. 7)

Hyperuricemia. Ten patients had hyperuricemia, and one male had a blood uric acid level on the order of 8 mg/dL. Hyperuricemia not only causes gout flare-ups, but also is considered a risk factor for atherosclerosis. Pharmacotherapy would be recommended in such a patient if urinary calculus, renal disorders, hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome or other such comorbidities were present.(Fig. 8)

Chronic kidney disease (CKD) was seen in three patients. A female patient with an eGFR of 17 showed findings of polycystic kidney in an ultrasound examination. Solitary kidney and other deformations are reported in patients with TE. Caution in the form of regular examinations is needed,

Overweight

- Ten patients (22%, one man [6.7%] and 9 women [29%]) had obesity (i.e., body mass index [BMI] > 25 kg/m^2). The BMI of one woman was 34.4 kg/m^2. Another woman decreased her body weight from 60kg at 1st visit to 53kg at 2nd visit (from 26 to 23 in BMI).
- Patients with TE are prone to becoming overweight not only because of developmental limb disorders, but also because many find going outside a hassle.
- As these patients age, they will be at increased risk of reduced muscle mass in their healthy limbs (sarcopenia) and weight gain as this reduction lowers their basal metabolism (sarcopenic obesity). Ways must be found to maintain muscle mass in these patients.

Fig. 4

Hepatic Steatosis

- Seven patients (15%, three men [20%] and four women [13%]) had high alanine aminotransferase (ALT) levels（>30 IU/L）. The ALT of one man improved at his 2nd visit. The ALT of one woman was as high as 53 IU/L.
- High ALT levels were not the only liver-related concern. Ultrasonography revealed findings of hepatic steatosis (high hepato-renal echo contrast) in 21 patients (46%, nine men [60%] and twelve women [39%]).
- At-risk patients would benefit from a better diet.

Fig. 5

Dyslipidemia

- More than a half of the patients (27 of 46 [59%], 8 men [53%] and 19 women [61%]) had hyper-low density lipoprotein (LDL) cholesterolemia (>120 mg/dL). LDL cholesterolemia had improved in two women at their 2nd visit. Blood LDL cholesterol levels were 150–159 mg/dL in three men and two women, 170–179 mg/dL in two women, and over 200 mg/dL in two women.
- One man (6.7%) had hypo-high density lipoprotein (HDL) cholesterolemia (<40mg/dL).
- 13 patients (28%, six men [40%] and seven women [23%]) had hypertriglyceridemia (>150 mg/dL). Blood triglyceride levels were 200–299 mg/dL in two man and three women, and 300–399 mg/dL in one man and two women.
- Persisting lipid disorders exacerbate arteriosclerosis. At-risk patients would benefit from proper eating habits and appropriate pharmacotherapy.

Fig. 6

Abnormal Glucose Metabolism

- The high level of hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program) level (>6.2%) was observed in five patients (11%, two men [13%] and three women [10%]).
- The level of HbA1c was 7.0-7.9% in one person (under treatment with diabetes mellitus [DM]) and 6.0-6.9% in four persons (one was under treatment with DM and another was within normal range at 1st visit).
- Because the HbA1c level increased in almost all the people who were examined twice, we have to follow up carefully with their health.

Fig. 7

even where no clear evidence of deformation is present, because such patients may experience age-related diseases associated with renal function more quickly than healthy people. (Fig. 9)

Osteoporosis. Bone mineral density analysis revealed lumbar spine density of less than 70% of the young adult mean in three patients and 70% to 80% in nine patients. Femoral neck density was less than 70 in eight patients and 70 to 80 in 16 patients. Consequently, 10 patients (2 men and 8 women) had confirmed osteoporosis, and 18 had confirmed osteopenia. Endogenous risk factors for osteoporosis include: 1) being a post-menopausal women at least 55 years of age; 2) being underweight; 3) being on corticosteroids; 4) having diabetes mellitus or thyroid disease; and 5) having a family member with osteoporosis. Lifestyle-related factors include: 6) being a smoker; 7) being a heavy drinker; and 8) not exercising or not getting sunlight, which is a particular concern in patients with TE. (Fig. 10)

Finally, endocrine and metabolic abnormalities. Among the 29 patients who underwent measurement, abnormal blood thyroid-stimulating hormone levels were observed in three (slightly high in 2 patients and slightly low in 1). Although we did not perform any diagnostic tests focusing on endocrine function, the adverse reaction to thalidomide listed below suggests that embryonic exposure could possibly affect the development of endocrine tissues. These are secondary effects of thalidomide and the thalidomide derivative, lenalidomide, on endocrine and metabolic function. First, increased insulin resistance; second hypothyroidism; third, thyrotoxicosis; fourth, hypoadrenalism; and fifth hypogonadism.(Fig. 11)

Now, I will summarize the key points. Obesity, which includes sarcopenic obesity, may be the result of limited physical activity. Hepatic dysfunction is often caused by hepatic steatosis. Patients often have dyslipidemia. Some patients have impaired glucose tolerance or chronic kidney disease. Osteoporosis may affect men as well as women. Thalidomide and its derivatives cause thyroid dysfunction and endocrine and metabolic abnormalities. (Fig. 12)

Thank you for your attention.

Hyperuricemia

- Ten patients (22%, seven men [47%] and three women [10%]) had hyperuricemia (>7.0 mg/dL). One male patient had a blood uric acid level on the order of 8 mg/dL.
- Hyperuricemia not only causes gout flare-ups but is now also considered a risk factor for arteriosclerosis. Pharmacotherapy would be recommendable in such a patient if urinary calculus, renal disorders, hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome, or another such comorbidity were present.

Fig. 8

Chronic Kidney Disease (CKD)

- CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) was seen in three patients (6.5%, one man [6.7%, eGFR = 55] and two women [6.5%, eGFR = 17, 59]). A female patient with an eGFR of 17 mL/min/1.73 m^2 showed findings of polycystic kidneys in an ultrasound examination.
- Solitary kidney and other deformations are reported in patients with TE. Caution in the form of regular examinations is needed, even when no clear evidence of deformation is present, because these patients may experience age-related decreases in renal function more quickly than healthy people.

Fig. 9

Osteoporosis

- BMD analysis revealed a lumbar spine density of less than 70% of the young adult mean (YAM) in three patients (one man and two women) and 70% to 80% of YAM in nine patients (three men and six women).
  Femoral neck density was less than 70% of YAM in eight patients (one man and seven women) and 70% to 80% of YAM in 16 patients (five men and eleven women).
- Ten patients (22%, two men [13%] and eight women [26%]) had confirmed osteoporosis, and 18 patients (39%, four men (27%) and 14 women (45%) had confirmed osteopenia.
- Endogenous risk factors for osteoporosis include (1) being a postmenopausal woman at least 55 years of age, (2) being underweight, (3) being on a corticosteroid, (4) having diabetes mellitus or a thyroid disease, and (5) having a family member with osteoporosis, and lifestyle factors include (6) being a smoker, (7) being a heavy drinker, and (8) not exercising or getting sunlight. Risk factor #8 is a particular concern in patients with TE.

Fig. 10

Endocrine and Metabolic Abnormalities

- Among the 29 patients who underwent measurements, blood thyroid stimulating hormone levels were observed in three patients (10%); slightly high in two patients (6.9%, one man [12.5%] and one woman [4.8%]) and slightly low in another woman (3.4%, 4.8%).
- Although we did not perform any diagnostic tests focusing on endocrine function, the adverse reactions to thalidomide listed below suggest that embryonic exposure could possibly affect the development of endocrine tissues.
- Secondary effects of thalidomide and the thalidomide derivative lenalidomide on endocrine and metabolic function:
  (1) Increased insulin resistance
  (2) Hypothyroidism: Incidence of 0.9% (per package insert),
  (4) Thyrotoxicosis (thyroiditis)
  (5) Hypoadrenalism
  (6) Hypogonadism

Fig. 11

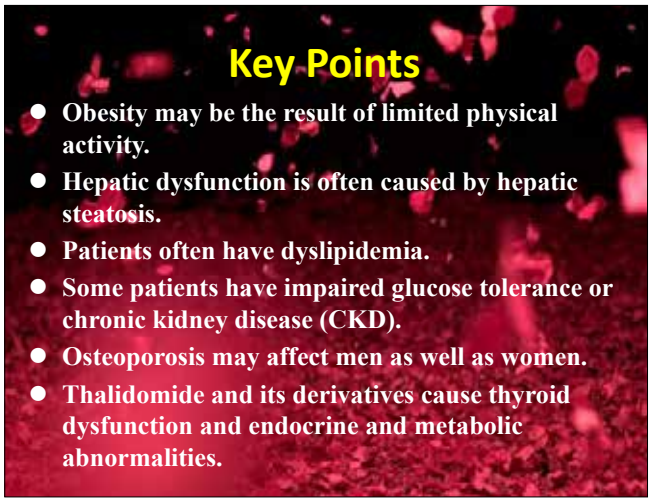


Fig. 12

Q&A

Fumihiko Hinoshita: Thank you very much, Dr. Tagami. Do you have any questions from the floor? Hi, please.

Jan Schulte-Hillen: I would like to know the pathologies you found in the endocrinologic functions of the thalidomiders, are they augmented with respect to the normal Japanese population? For example, as I remember, you found elevated HBA1c in 11% of the patients from Germany. I know that in this age group, the percentage of people who have elevated HBA1c is already something between 5% and 20%. Those numbers seemed very high and I would like to know how the data of thalidomiders compares with that of the normal Japanese non-thalidomide population. Thank you very much.

Tetsuya Tagami: Thank you for your question. We have not directly compared thalidomiders with the normal population in terms of prevalence. But there is, I think, the possibility that thalidomiders engage in less exercise, maybe, which causes obesity, so the prevalence may be higher than that in the normal population, but I don't have any direct comparison data now.

Fumihiko Hinoshita: Next, please.

Christina Ding-Greiner: We have a similar situation in Germany, too. We have a lot of thalidomiders with these kinds of diseases, which are bad for atherosclerosis. I have the impression that they are thinking mainly of thalidomide damage, and that they don't think they may have something as trivial as a high glucose or higher cholesterol and so on. I have the impression that they are not very well informed of what they can actually do for their own health.

If I speak to them and I tell them about prevention, they are astonished and they say, "Well, then, I will proceed like that. I will do that."

So, I think it's very important to think of that and inform people that they have an opportunity to do something against these additional lifestyle-related illnesses as they are growing older. The problem is, they don't think of it. Thank you.

Tetsuya Tagami: Thank you very much. I think our job is to find such diseases, lifestyle-related diseases, and then, we can start a statin or some glucose-lowering medicine. So, that is, I think, very important. Thank you.

Fumihiko Hinoshita: Okay, I can give some additional comments for you. You know, in Japan, there is such a good system to carry out general medical checkups. His hospital also has such a system, you know, the general medical checkup. So we, the Japanese research group, have carried out medical checkups at three medical hospitals or centers on 24 thalidomiders per year.

Then, those patients receiving medical checkups are lucky in the respect that abnormalities such as high glucose levels, dyslipidemia, obesity, and fatty liver will be found; thus, they will be informed early about such abnormalities, which promotes prompt measures or treatment. So, maybe they are lucky. Do you understand, Dr. Greiner?

So, those thalidomiders with lifestyle-related diseases would be treated early because they were examined in general medical checkups and basically, any abnormalities would soon be known by recipients with TE. But it is also practiced in the general population, too. That is, the Japanese medical checkup system.

Christina Ding-Greiner: We do have free checkups in Germany, but for thalidomiders, it's difficult because it's often hard to take blood samples and measure blood pressure. They are not bound to go for a checkup, they are free not to go. Maybe they are not thinking of the hazards. They think more of the difficulty in taking blood and so on, and they say, "Well, I don't want any checkup". That's a great issue, too.

Fumihiko Hinoshita: Oh, I understand. You mean there are some differences in the severity of TE between Germany and Japan. You know, we have only a few thalidomiders with both serious upper and lower limb problems, only two or three.

Basically, they might have short arms and deformities so that we can't take blood from some vessels on the arms in a limited number of cases with TE. So, it is very rare not to

take any blood samples or measure blood pressure. But in your country, you know, there are some thalidomiders with no or very short limbs. Dr. Morrison, do you have any comment?

Dee Morrison: Yes. Two questions. I may need both of you to answer. We have seen some with TE with sleep apnea in the UK, and we know this contributes to cardiovascular disease. Increased risks are obesity, etc., but also jaw problems and abnormalities of the nasal passages. I wonder if you have looked at sleep apnea—we haven't actually done any formal research yet—and whether you have any knowledge of this?

My second question is on CKD. You mentioned that even though they had normal renal function, they might be more at risk as they age. Is there any evidence for this or is it a supposition?

Tetsuya Tagami: I will answer the second question first. I think the obvious abnormality is not present, maybe, but some microscopic abnormalities may be present, but I have no evidence, sorry. Regarding the first question on CVD, I haven't experienced it before. Do you have any experience with this, Dr. Hinoshita?

Fumihiko Hinoshita: Okay, I might roughly understand almost all of the data—clinical data taken at those medical checkups. But so far, I have not found any marked association of high or significant risks for cardiovascular diseases in thalidomiders in Japan. Namely, no marked association so far for cardiovascular diseases. In general, in Japan, there are fewer people who would suffer from coronary problems compared with Western countries.

Next, I should partly answer your question about sleep apnea syndrome. You might have mentioned sleep apnea syndrome, SAS, in short, too. Sorry, I know that in your country you are trying to disclose problems associated with SAS in thalidomiders, right? But in Japan we have not done it.

As for as jaw problems, at least at my National Center for Global Health and Medicine, we have been checking abnormalities of the jaw in subjects who were receiving general medical checkups. I'm sorry to say, however, that today, the chief of the dental and oral surgery department at our center could not attend, but he said Japanese thalidomiders do not significantly have any serious unexpected jaw problems. That's all.

Tetsuya Tagami: As Mr. Sato mentioned before, I heard that some patients have already died. Then, do you know the cause of this?

Fumihiko Hinoshita: Maybe, someone is now raising his hand.

Tsugumichi Sato: Well, we don't know all the causes of death for everybody who has passed away, but many of them experienced sudden death. So, sudden death is a mainstay these days. To respond to the question of Dr. Schulte-Hillen, in my memory, Japanese thalidomiders have diabetes, hyperlipidemia, and hypertension at nearly twice the rate of the general population for similar age groups.

And these are the data from a national survey for Japanese thalidomiders.

Fumihiko Hinoshita: You are talking about the second national survey last year?

Tsugumichi Sato: Yes, yes.

Fumihiko Hinoshita: But, as for hypertension, almost the same frequency.

Tsugumichi Sato: Sorry, I mean diabetes and hyperlipidemia.

Fumihiko Hinoshita: I should correct his comment because I myself performed it. Then according to the recent national survey about the present situation and current diseases in thalidomiders in Japan, I don't know why, but the frequency of hypertension in the thalidomiders is almost the same as that in the age-matched general population.

Fumihiko Hinoshita: Are there any other comments or questions? OK. Dr. Schulte-Hillen.

Jan Schulte-Hillen: Yes, I would like to answer whoever asked the question regarding if the cause of death was known. I would like to say that 2 years ago in Germany, 32 thalidomiders died, and there are no scientific data for the cause of death. It is absolutely not known. But, if you ask peer groups, if you ask friends, they say that they passed away without any warning, so we are talking about something like sudden death, like stroke or myocardial infarction, I think.

Fumihiko Hinoshita: Some stroke or cardiovascular events have been reported in your country. But in Japan, maybe no marked causes have been found in most cases with TE, as Mr. Sato said. Okay, anyway, our time is up, so now, let's move on to the next presentation. Thank you very much, Dr. Tagami.

Medical Check-up of Otorhinolaryngology (ORL) for the Patients of Thalidomide Embryopathy (TE)

Nirou Tayama

Department of Otorhinolaryngology, National Center for Global Health and Medicine, Tokyo, Japan

Tetsuya Tagami (Moderator)

The next speaker is Dr. Nirou Tayama, from National Center for Global Health and Medicine, Tokyo, Japan. The title of the talk is "Medical Checkups Regarding Otorhinolaryngology (ORL) for Patients with Thalidomide Embryopathy (TE)". Now, Dr. Tayama, please.

Thank you very much. I would like to talk about ENT medical checkups for ORL (otorhinolaryngology), what kind of results are gained, and what we should do. So, ENT and hearing disorders, as well as malformations, have been studied. CT images are also used to study the situation and with that, we came up with problems likely faced by thalidomiders in the future and what kind of countermeasures or treatments we should provide. This is something we are thinking about.(Fig. 1, 2)

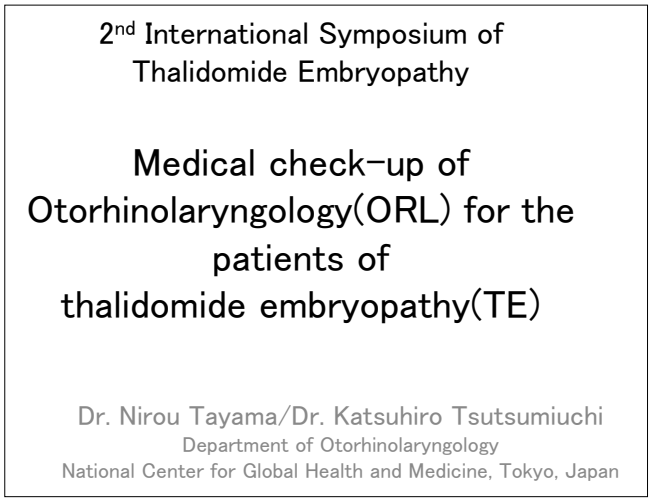


Fig. 1



Fig. 2

In ENT, when it comes to malformations, Dr. Tanaka of Teikyo University has presented a list and a report. As his study progressed, he observed the temporal bone malformation, the outer, inner, and also middle ear malformation and abnormalities within them that make hearing difficult, and he came to find the impact of the site malformation. So, if there is an inner ear problem, nerve deafness would occur, and if there is an outer ear problem, then conductive deafness would occur. And if both, in that case, combined deafness would develop.(Fig. 3)

So, in the nose and oral cavity, abnormalities or malformations have been pointed out. But we haven't really recognized these clearly as symptoms according to our study. So, for about 3 years, the total number is 28 (19 males, 9 females). (Fig. 4)

According to a report by Dr. Tanaka, the number is limited; however, we conducted CT scans on all the patients for comparisons, that's the great approach. So, malformations of

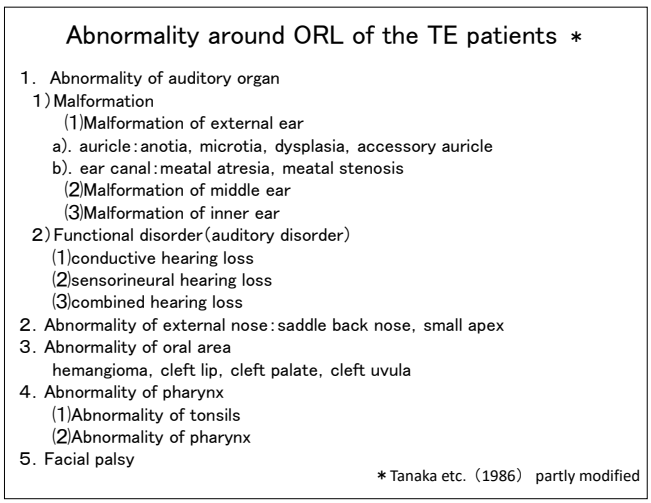


Fig. 3

the inner, outer, or middle ear are quite conspicuous as ORL problems, hearing loss, equilibrium disturbance, facial palsy, and others.(Fig. 5)

Now, the problem is that hearing loss is one problem, but other ear malformations, especially outer ear malformations, lead to other problems, like being unable to wear masks or glasses. Also, if the external ear canal has a malformation, it's very difficult to wear a hearing aid.

These problems increase with age, I believe. So currently, these thalidomiders, their age is right around 60 years, and with aging, they are going to have more and more hearing problems. There might be more such patients exceeding 65 years of age. In that case, how hearing aids can be appropriately used and worn will be a problem that we may encounter more frequently.

So, in the future, we have to of course think about countermeasures for that. This is quite a busy slide, but this is a list that we came up with. Hearing problems, CT findings, and limb disabilities, and how they are distributed, were also studied in a total of 28 cases.(Fig. 6, 7)

Medical Check-up of ORL

Duration : 14, Nov, 2015 – 15, Jan, 2019

Numbers : 28 (M 19, F 9)

Age : 52y.o. – 57y.o.

Evaluation items :

- Malformations in ORL
- Hearing disorder

Fig. 4

Problems in ORL

- Caused by abnormality in ORL organs
  - Hearing loss :
    - Malformations of external/middle/inner ear
  - Equilibrium disturbance :
    - Malformations of inner ear
  - Facial palsy :
    - Malformations of inner ear
  - Unable to wear mask/glasses :
    - Malformations of external ear
  - Unable to wear common HA :
    - Malformations of external ear
- Caused by other abnormalities (mainly disorder of upper limbs)
  - Unable to blow nose
  - Unable to clean ear canal

Fig. 5

In 1986, Dr. Tanaka had already studied many cases with TE. And in the study the hearing test was the main focus. The malformation of the inner, middle, and also outer ear hasn't been really studied by CT. (Fig. 8)

According to the 28 cases we studied, malformations of the inner, external, and middle ear are just like this. And

Full List of our Cases

No.	sex	age	External ear Mal.	middle ear Mal.	Inner ear Mal.	Hearing level	CT	notes	Eye movement	Upper limbs
1	M	52	なし	△	なし	右：15dB、15dB 左：15dB、10dB	両側きめた骨低形成の可能性	軽度の中耳奇形あるが聴力正常	なし	○
2	M	54	なし	なし	なし	右：10dB、25dB 左：15dB、35dB	なし	異常なし	なし	拇指要害
3	M	57	○ 耳介形態異常（術後） 外耳道閉鎖	○	なし	右：90dB、110dB 左：90dB、85dB	外耳道膜様閉鎖 両側つち骨、きぬた骨形成不全	外耳・中耳奇形	なし	なし
4	M	53	なし	なし	なし	右：10dB、20dB 左：10dB、25dB	なし	異常なし	なし	○
5	F	52	なし	なし	なし	右：10dB、10dB 左：10dB、30dB	なし	異常なし	なし	○
6	M	54	なし	なし	なし	右：20dB、55dB 左：20dB、50dB	なし	聴力低下は加齢変化？	なし	○
7	M	52	なし	右真珠腫性中耳炎	○	右：110dB、scale out 左：50dB、scale out	両側外側半規管低形成 右慢性中耳炎	真珠腫性中耳炎 内耳形態異常	なし	○
8	F	57	なし	なし	なし	右：25dB、20dB 左：25dB、35dB	なし	異常なし 軽度聴力低下は加齢変化	なし	○
9	M	52	外耳道狭小？	なし	なし	右：50dB、80dB 左：20dB、45dB	なし		なし	○
10	M	56	なし	なし	なし	右：15dB、10dB 左：15dB、25dB	なし	異常なし	なし	○
11	F	54	なし	なし	なし	右：5dB、5dB 左：10dB、5dB	なし	異常なし	なし	○
12	F	56	なし	なし	なし	右：5dB、10dB 左：5dB、10dB	なし	異常なし	○	○
13	F	54	耳介正常、外耳道狭窄	左真珠腫性中耳炎	○	右：35dB、25dB 左：40dB、20dB	右外側半規管低形成 両側慢性中耳炎 左真珠腫性中耳炎		なし	○
14	F	54	なし	なし	なし	右：10dB、10dB 左：10dB、20dB	なし	異常なし	なし	○
15	M	54	耳介軽度？ 外耳道狭窄＋	なし	○	右：105dB、95dB 左：40dB、40dB	右蝸牛半規管低形成 左外側半規管形成異常 左真菌管無形性		なし	○
16	M	54	なし	なし	なし	右：10dB、10dB 左：10dB、10dB	なし	異常なし	なし	○
17	M	54	○ 耳介奇形（右＞左） 右外耳道狭窄、左閉鎖	○	○	高度難聴	右側頭骨異常 外耳道形態異常 中耳奇形（耳小骨すべて） 内耳形態異常 左側頭骨異常 外耳道無形性 中耳奇形（耳小骨すべて） 内耳形態異常	外耳・中耳・内耳奇形 左下顎頭扁平化	外転障害	なし

Fig. 6

No.	sex	age	External ear Mal.	middle ear Mal.	Inner ear Mal.	Hearing level	CT	notes	Eye movement	Upper limbs
18	M	55	なし	なし	なし	右：10dB、15dB 左：5dB、10dB	正常	異常なし	なし	上肢
19	M	56	右：耳介奇形、外耳道狭窄で耳垢＋ 左：耳介正常、外耳道狭窄、鼓膜異常	○	○	高度難聴	両側内耳低形成 （みぎ蝸牛・半規管低形成、ひだり蝸牛・半規管低形成） 両側中耳奇形 （ツチ骨・キヌタ骨低形成、アブミ骨無形成） 両側外耳道狭窄	外耳、中耳、内耳	外転神経麻痺	重複
20	M	54	右：耳介正常、外耳道狭窄 左：耳介正常、外耳道狭窄で耳垢＋	○	○	高度難聴	両側内耳低形成 （みぎ蝸牛・半規管低形成、ひだり単洞化） 両側中耳奇形 （耳小骨はつとも あり、主にキヌタ骨低形成） 両側外耳道狭窄（軽度）	知的障害	眼球運動障害	聴覚
21	M	55	なし	なし	なし	右：10dB、5dB 左：10dB、10dB	正常	異常なし	なし	上肢
22	F	55	なし	なし	なし	右：10dB、10dB 左：10dB、5dB	正常	異常なし	なし	上肢
23	M	56	右：耳介低形成、外耳道狭窄 左：耳介やや低形成、外耳道狭窄で細く確認できず		高度難聴		両側内耳無形成（内耳道含め） 両側中耳奇形 （ツチ骨・キヌタ骨低形成、アブミ骨無形成） 両側外耳道狭窄	外耳＜中耳＜内耳	眼球運動障害	聴覚
24	M	55	なし	なし	なし	右：15dB、10dB 左：40dB、75(30)dB	外耳・内耳に明らかな奇形は認めない 両側キヌタ骨やや低形成	左鼓膜石灰化	なし	上肢
25	M	58	右：耳介形成術後、外耳道狭窄、耳垢 左：耳介形成術後、外耳道閉鎖	○	○	高度難聴（混合性）	両側内耳奇形なし（ひだりやや低形成？） みぎ中耳奇形なし ひだり耳小骨無形成 みぎ外耳道高度狭窄、ひだり外耳道閉鎖		左顔面神経麻痺	聴覚
26	F	57	右：耳介形低形成、外耳道閉鎖 左：耳介形低形成、中耳術後	○	○	高度難聴	両側内耳奇形 （みぎ＞ひだりで半規管・蝸牛低形成） 両側中耳奇形 （みぎツチ骨・キヌタ骨低形成、アブミ骨無形成） ひだり耳小骨無形成 みぎ外耳道閉鎖、ひだり外耳道閉鎖術後		顔面神経麻痺 外転障害	聴覚
27	F	55	なし（右に耳垢）	なし	△	右：15dB、10dB 左：15dB、10dB	両側外側半規管やや低形成		なし	上肢
28	M	58	なし	なし	なし	右：20dB、20dB 左：20dB、20dB	正常		なし	上肢

Fig. 7

Abnormality of ear

	Our cases	Tanaka(1986)
External ear		
Malformation of auricle	7/28(25%)	43/137(31%)
Malformation of ear canal	10/28(35.7%)	39/137(28%)
Middle ear	8/28(28.6%)	
Inner ear	8/28(28.6%)	
Hearing loss	*12/28(46.9%)	83/137(61%)

(*contains age-related and other diseases)

Fig. 8

when it comes to findings regarding hearing problems, most of the cases have malformations in their ears.

And here, while the number is a bit distant, about 70% of the patients with a malformation had hearing loss.

In some cases, the surgery was already done, the ossicle chain was generated, a hearing aid was worn, or an external ear canal was established. But in such cases, earwax tends to be accumulated, so this has to be well taken care of. (Fig. 9)

So now, this one is the microtia, and also there is atresia for the outer ear canal, and you hardly see anything at all. Then, there are various inner ear abnormalities. The malformation takes place in the case of the inner ear.(Fig. 10, 11)

This is case #3, which involved very severe hearing difficulties. This part of the auditory ossicle is malformed on the right and left, causing a malformation of the inner ear. (Fig. 12, 13)

This is case #7. Towards the right, there is the otitis media and cholesteatoma. We have seen other similar cases.(Fig. 14, 15, 16)

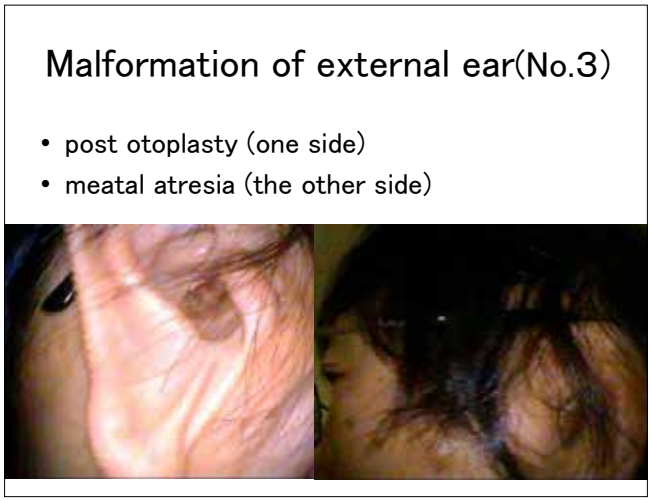


Fig. 9



Fig. 10



Fig. 11

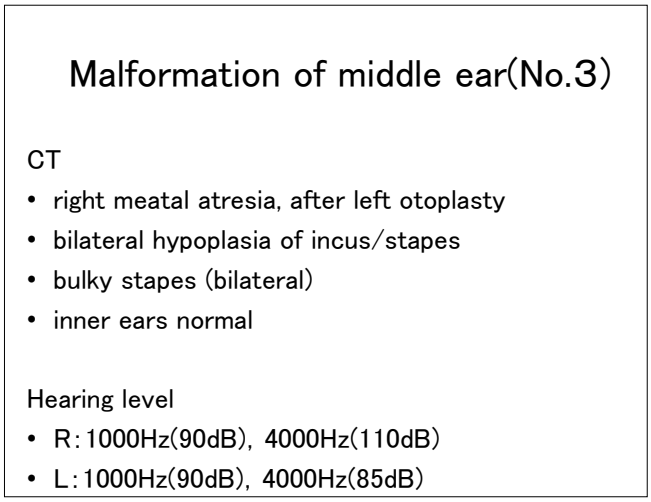


Fig. 12



Fig. 13

And in this case, the semicircular canal has a malformation. So, to what extent is this temporal bone malformation and otitis media cholesteatoma correlated? The number of cases is limited, so we don't know the relation between those two. Here is the auditory ossicle and here you can find the lesion.

Case #17. Malformation of inner ear. Here you can see various abnormalities, and the auditory ossicle is also malformed. In this case, a very severe hearing difficulty developed, so hearing capability was almost lost. Then, other known otological disorders. Well, these are limited. Five cases of ocular motility disorder and facial palsy due to malformation of the temporal bone. Nose, larynx, pharynx, no abnormalities. And the malformation of limbs and ORL abnormalities are correlated based on Dr. Tanaka's study. (Fig. 17, 18)

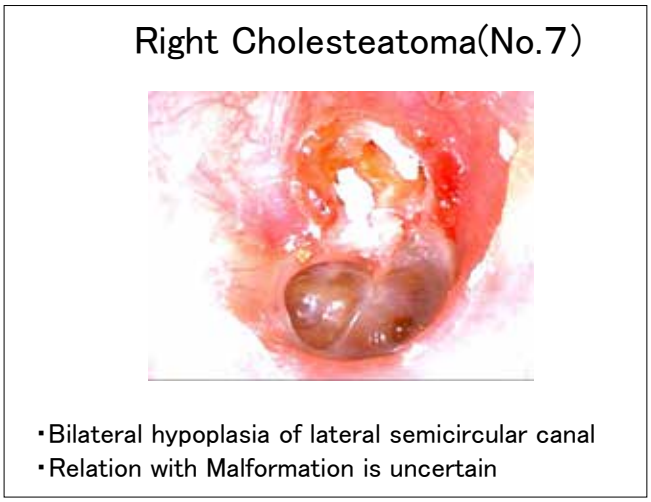


Fig. 14



Fig. 15

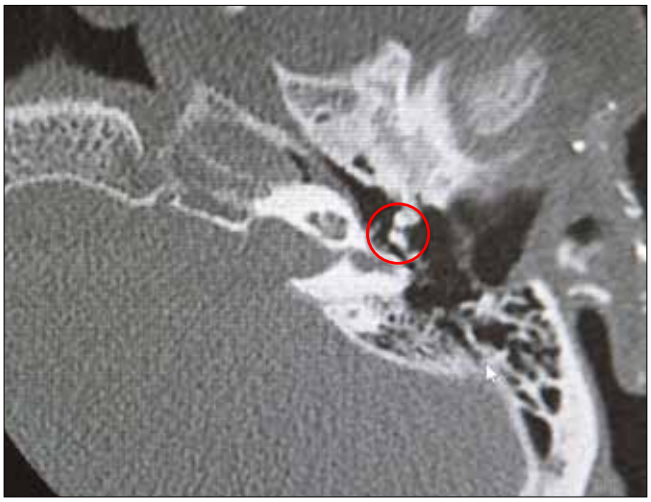


Fig. 16

The malformation of limbs and ORL abnormalities were concomitantly found in seven cases, and 15 cases had malformation of limbs only and no ORL abnormality. Hence, six cases had ORL abnormalities without any limb abnormalities. (Fig. 19, 20)

The hearing and CT results regarding the malformation of the inner ear are not always in concordance, and there are some differences. Even though there is mild hearing impairment, and in some of them, no anatomical abnormalities are clearly shown by CT. Therefore, it cannot be clearly identified what actually causes hearing loss in such cases. (Fig. 21)

Well, so what are the main problems in relation to ORL?

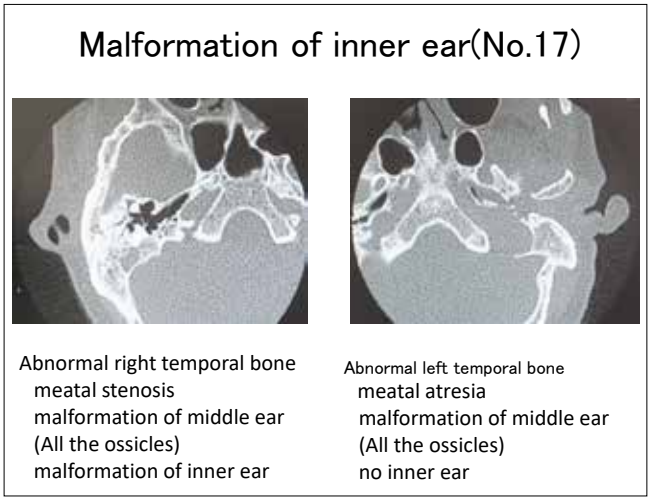


Fig. 17

Relation between malformation of limbs and ORL abnormality

Tanaka etc.(1986)

Malformation of limbs	ORL abnormality		total
	yes	no	
yes	50(7)	46(15)	105(22)
no	32(6)	0(0)	32(6)
	91(13)	46(15)	137(28)

( )shows our cases

Fig. 18

Mostly, some patients need regular ear treatment, like those who have stenosis in the ear—external ear canal stenosis. In such cases, it's very difficult to clean up the ear canal to remove the earwax. Also, some had ear surgery in the past. Then, due to the deformity, the ear canal becomes very complicated in terms of shape. In order to treat such a complicated structure, we need a doctor who is quite used to that kind of treatment, otherwise, it would be very risky. If they have otitis media, this should also be treated.(Fig. 22)

In addition, as for deformities in the external or internal ear, patients have difficulty in self-care of the ear canal because of upper limb deformities. Regarding the future, TE victims will have hearing problems due to aging, so they will need to wear a hearing aid. However, they also have some deformities in the ear, so it will be very difficult for them to wear a hearing aid. And also, hearing aids require adjustment. However, if they have an upper limb deformity, they will have difficulty adjusting their hearing aid. Therefore, even though they are not so old, in 10 or 20 years, the hearing loss due to aging will be a huge problem for TE victims.

This is also the case of patients with upper limb disorders, who have an accumulation of earwax and cannot clean it on their own because of limb disorders. Of course, sometimes there are people who have difficulty cleaning their ears even without a limb disorder. Thalidomiders, however, certainly have limb disorders, so it would be even more difficult for them. (Fig. 23)

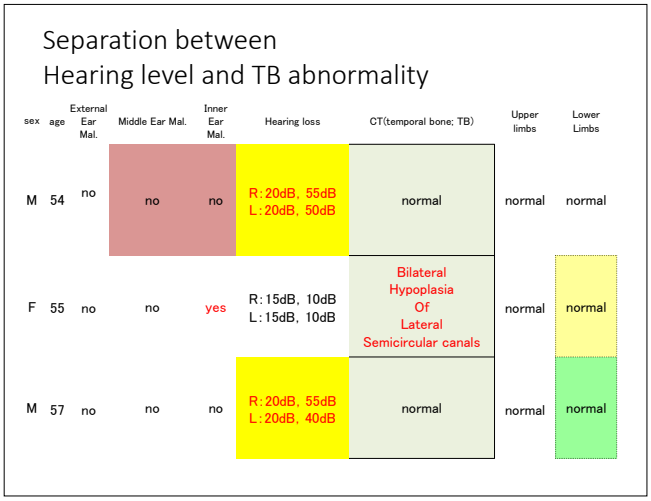


Fig. 21

Non ontological disorders

- Ocular motility disorder : 5 cases
- Abnormality in nose : 0
- Abnormality in larynx/pharynx : 0
- Facial palsy : 2cases

Fig. 19

Malformation of limbs	Hearing disorder		total
	yes	no	
yes	7	15	2
no	5	1	6
total	12	16	28

Malformation of limbs	abnormal temporal bone		total
	yes	no	
yes	6	15	21
no	7	0	7
total	13	15	28

Fig. 20

Problems

- Need regular treatment of ear
  - Meatal stenosis
  - Post ear surgery
  - Otitis media
  - Disorder of upper limbs
- Age-related hearing loss → HA
  - Problems the same as above

Fig. 22

The case of upper limb disorder



Ear wax

Fig. 23

This is a person who had surgery and whose ear canal is quite complicated in terms of shape because of the surgical procedure. Here is the earwax. Actually, it took me more than once to clean it. It's very difficult, even for experienced doctors.(Fig.24) Again, here is an accumulation of earwax. The earwax has become very hard and difficult to remove. In my general impression, we see this in many such thalidomiders. (Fig. 25)

This patient has otitis media. I recommended this person to be treated by a nearby ENT doctor.(Fig. 26)

Again, we find an accumulation of earwax that gets very hard. Removal requires some extra treatment.(Fig. 27)

This is the ear post-surgery. A very wide area of the external ear canal is seen after the otitis media surgery. In this cavity, we found lots of accumulated earwax that took more than 1 day to remove.(Fig. 28)

Moreover, the entry is very small. However, there is a huge cavernous area or cavity. I am quite used to cleaning earwax, but this actually took me more than once; therefore, I requested the patient to go to the nearby ENT doctor for cleaning, but there are not many ENT doctors who treat TE victims on a day-to-day basis. Therefore, we made a special petition to the Oto-Rhino-Laryngological Society of Japan. I was actually a member of the Welfare and Medical Committee of this society. (Fig. 29)



Fig. 24



Fig. 25

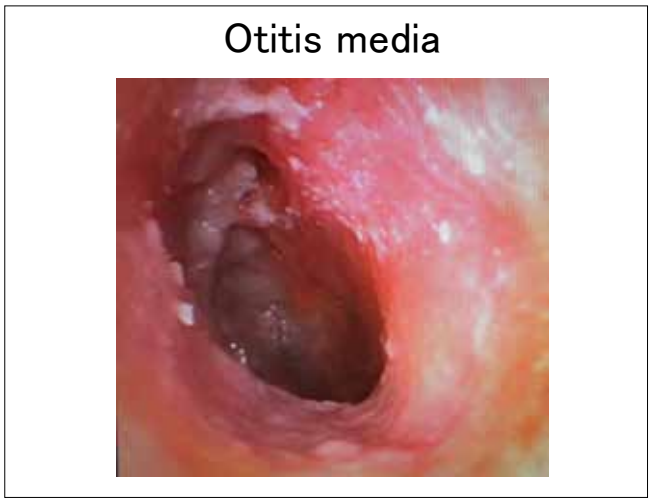


Fig. 26



Fig. 27



Fig. 28

Advanced skills are required in the future to treat these people; therefore, we have requested the society to take special measures and considerations. We have specialists who are consultants for hearing aids, and there are many designated consultant doctors all over Japan.

Thus, we petitioned the society so that those consultant doctors would also be ready to examine TE victims. I am sorry, this slide is shown in Japanese, but it explains more about the hearing aid consultant doctors. They are of course doctors who have a good understanding of hearing aids and hearing impairments. (Fig. 30)

And here we have a list of consultant doctors in each locality. We have requested and made a special petition through the society to take special care of thalidomiders. (Fig. 31, 32)

We have also explained to otolaryngologists that thalidomiders have limb problems and complicated hearing problems, and that this will increase further in the future with aging. TE victims can also contact our research group directly or through the Ishizue Foundation. (Fig. 33)

Then, in the course of the discussion, we can introduce them to key persons for hearing aids who are consultant doctors located near the patient's residence. We can thus recommend that they visit such consultant doctors. (Fig. 34, 35)



Fig. 31

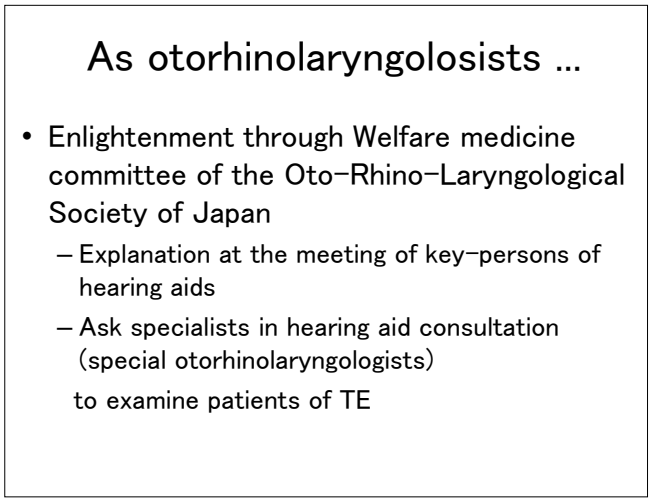


Fig. 29

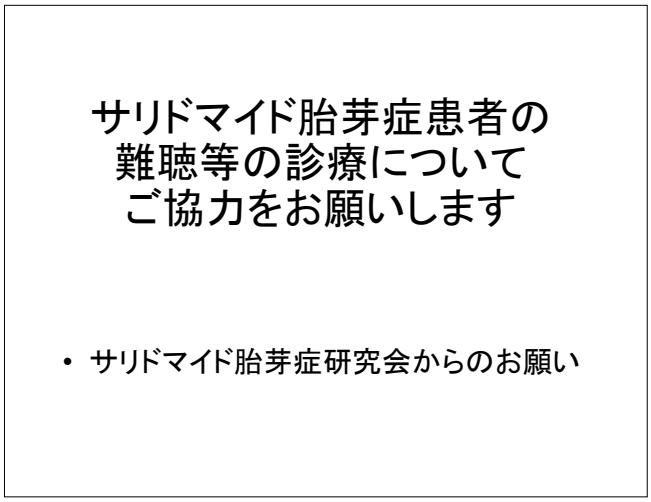


Fig. 32

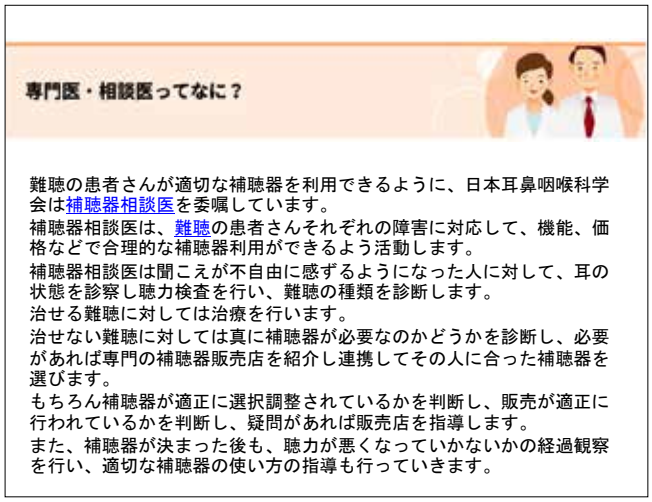


Fig. 30

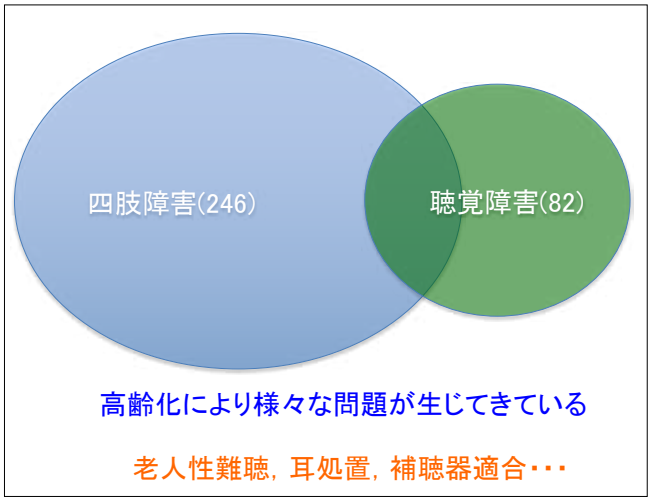


Fig. 33

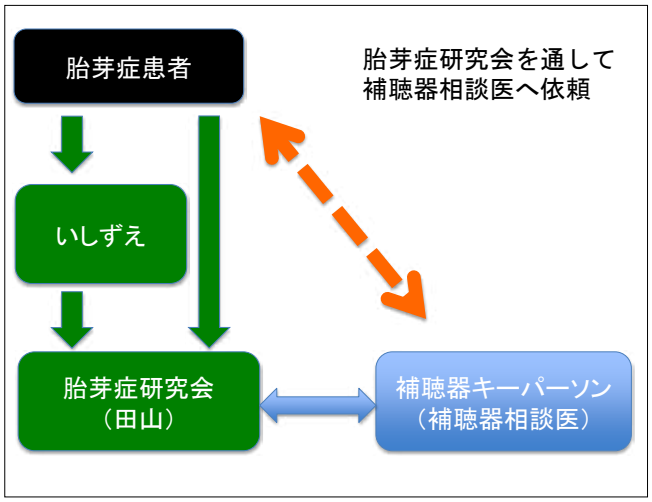


Fig. 34



Fig. 35

When TE victims visit a general ENT doctor, the doctors sometimes don't know how to treat them, so they just decline. Thus, in order to avoid such situations, we recommend TE victims to come to the Ishizue Foundation or to our research group so that we can make appropriate recommendations for and introductions to hearing aid specialists. We would like to aid the treatment of TE victims in the future from the standpoint of ENT doctors. Thank you very much for your attention. (Fig. 36)

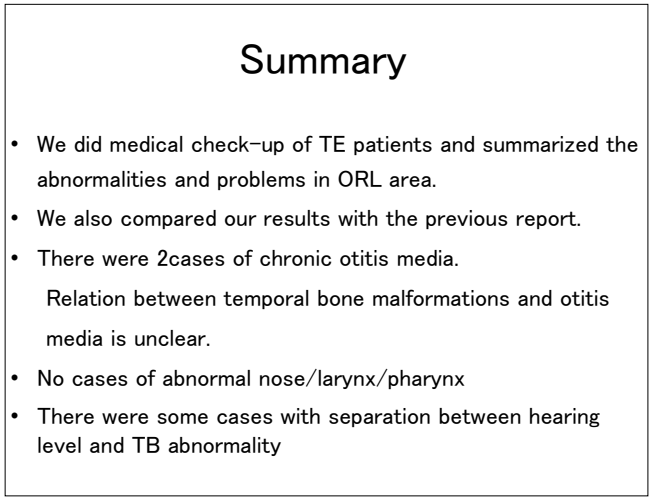


Fig. 36

Q&A

Tetusuya Tagami: Thank you, Dr. Tayama. Now, we would like to have the Q&A session. Any questions or comments?

Fumihiko Hinoshita: Thank you, Dr. Tayama. Very interestingly, we heard about your examination results in the otorhinolaryngological area. I was surprised to find that there were so many thalidomiders, even those with upper limb deformities, who have hearing impairments mainly caused by serious earwax or some other reason.

Nirou Tayama: Well, the overlapping (mixed) type is the main cause of the hearing difficulties because of upper limb malformations. Generally, there are a lot of patients without malformations, but with an accumulation of earwax. However, the number of patients who have hearing difficulties because of earwax is not so large. As you know, hearing difficulties occur because of age, that is, physiological symptoms. Therefore, I think we will see more and more such problems in the future.
So, if they receive treatment or periodical consultations with ORL specialists, then most of the cases with hearing difficulties can be prevented or delayed. Hearing loss cannot be prevented if it's the result of aging, especially in thalidomiders 65 years of age and older, and then, hearing problems will progress. Among those aged over 80 years, 80% have hearing problems or hearing difficulties. Hearing problems due to aging could increase, and are very difficult to stop. Thus, otitis media should be avoided to preserve hearing function. Or, if it occurs, it should be well treated.
So, those are the countermeasures for such a disease, but when the cause is aging, it's difficult to handle. Thank you.

Christina Ding-Greiner: In our first survey, we had the impression that one thing is hearing loss and another thing is deafness. We had in our sample, which was about 900 persons, 47 who were deaf, and only about 50% had malformations of the limbs; the other 50% had normal limbs, normal long arms and legs. Among people with hearing loss, we have many with damage to the upper and lower limbs, and they have the same orthopedic problems as the general sample. So, we had the impression that it is a different thing to be deaf and to have hearing loss. Deafness is an early type of fetal damage, which includes eye damage, too.

Nirou Tayama: Well, absolutely, the deaf tend to have a very strong malformation from birth. And such people actually don't acquire language at all. But in the cases in Japan, and with my own survey, of course it's limited, but I usually don't find such severe people in Japan; therefore, they are moderately impaired. And in the case of inner ear malformations, they have some conductive hearing problems; therefore, we can give them a hearing aid.
Those without any hearing loss may have a problem in the future; therefore, we might be able to classify them into three groups: those with very highly marked hearing loss, those with hearing loss due to age, and those with good hearing who may have hearing loss in the future. Those with moderate hearing loss may have severe hearing loss in the future.

Tetsuya Tagami: According to Dr. Tanaka's survey, you didn't find anybody who was completely deaf?

Nirou Tayama: There were, yes, there were some of them, but they were very small in number.

Tetsuya Tagami: Any other questions or comments? No questions? Thank you very much. So now we would like to close this session. Thank you very much.

Two New Claimers in Japan

Ryoji Kayamori

Department of Physicotherapeutics, Teikyo Heisei University, Tokyo, Japan

Junko Fujitani (Moderator)

Hello, my name is Junko Fujitani. I am a rehabilitation doctor at National Center for Global Health and Medicine (NCGM), and I am very honored to introduce Dr. Kayamori, a Professor at Teikyo Heisei University. He is one of the legends among thalidomide embryopathy (TE) doctors. He has been involved in the treatment of thalidomide patients for many years. He was a good clinical doctor for thalidomide victims in childhood, and he is still a very active clinical doctor and researcher. Today, his presentation is about new claimers in Japan. Please start.

Thank you, Dr. Fujitani. Ladies and gentlemen, good afternoon. I am so glad to have you here, even on this rainy day. I am going to introduce new claimers in Japan. These two cases of thalidomide victims were referred from the Ishizue Foundation. The first case is a 54-year-old man born in 1962, and the second is a 46-year-old woman born in 1971. They wanted to know whether their malformations were due to thalidomide. However, they were too modest to ask their mother that question. They could not ask their mothers whether their mothers had taken thalidomide during pregnancy before their mothers expired or became senile. (Fig. 1)

This is the number of new claimers in the United Kingdom from 2013 to 2018. Overall, 276 people applied for new claims. Four cases were accepted, six cases are in trial, and the others were rejected. This is the number of new claimers in Germany from 2009 to 2017. Overall, 105 people applied for new claims, 10 were accepted, 43 were rejected, and 49 remain unsettled. (Fig. 2, 3)

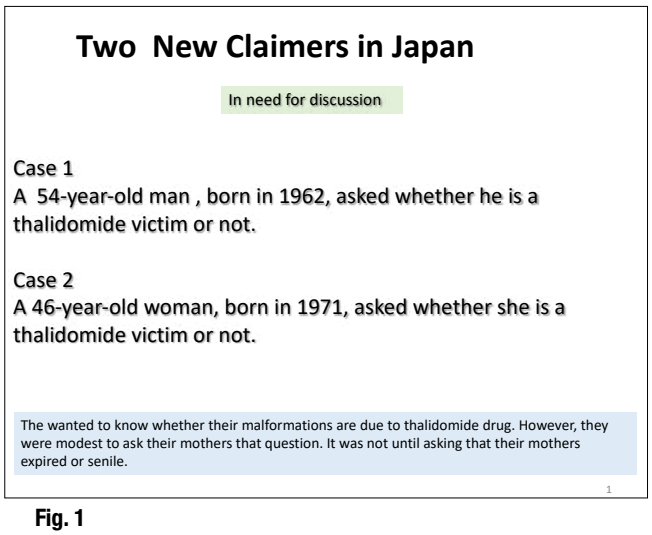


Fig. 1

So, this is the first case, a 56-year-old man born in Osaka in 1962. You can see a bilateral triphalangeal thumb with hypoplasia of the thenar muscles. Triphalangeal thumb can be seen on X-ray. Compared with the normal control, these thumbs have three phalanges, which is considered not a real thumb, but rather, a form of pre-axial polydactyly. There is

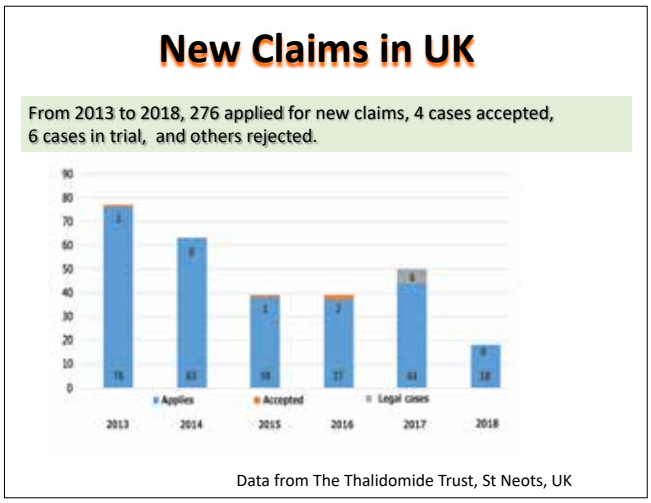


Fig. 2

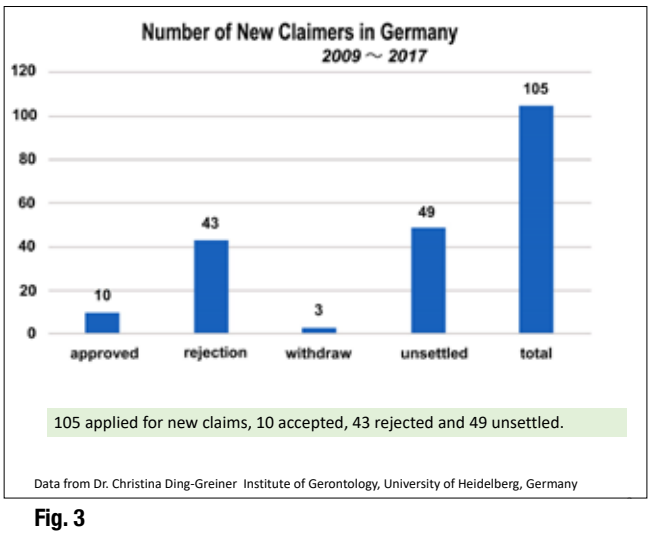


Fig. 3

also hypoplasia of the trapezium and scaphoid bone, in addition to minimal hypoplasia of the radial styloid process. (Fig. 4, 5)

Again, I make sure that triphalangeal thumb is considered a form of preaxial polydactyly. (Fig. 6)

It means a lack of a thumb and polydactyly affecting five fingers on both sides. The pisiform bone is really prominent. (Fig. 7)

One of the basic principles in TE is preaxial longitudinal ray hypoplasia including the thumb, radius, and humerus in the upper limb. (Fig. 8)



Fig. 4

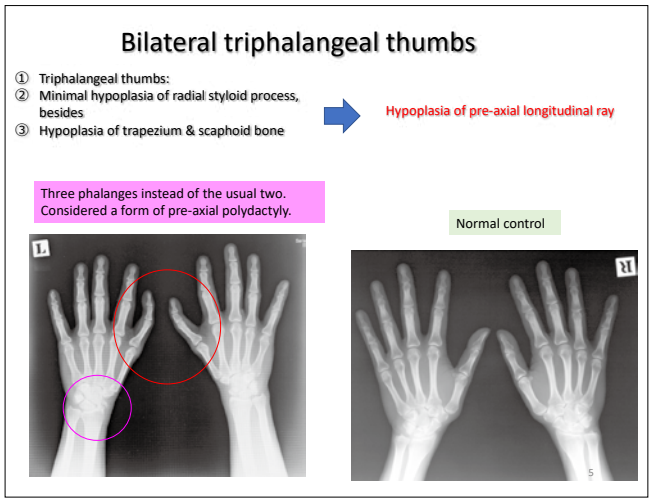


Fig. 5

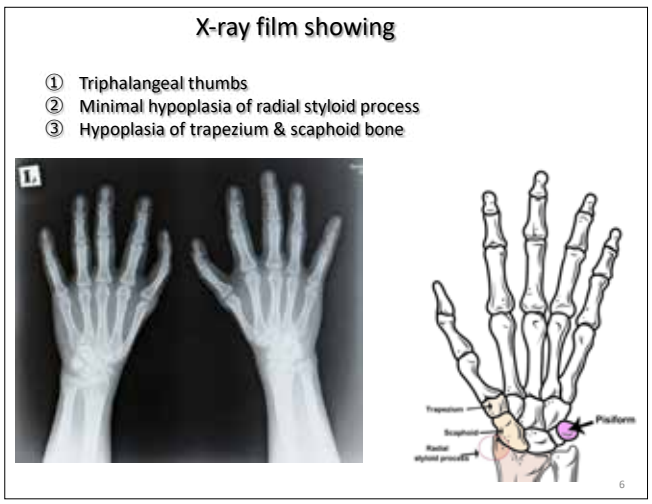


Fig. 6

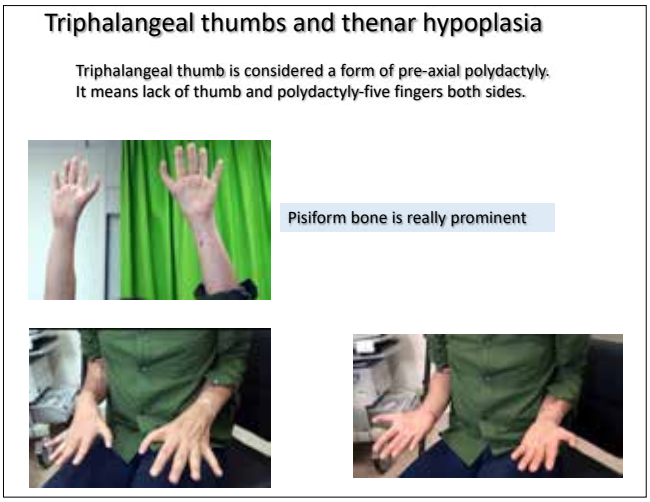


Fig. 7

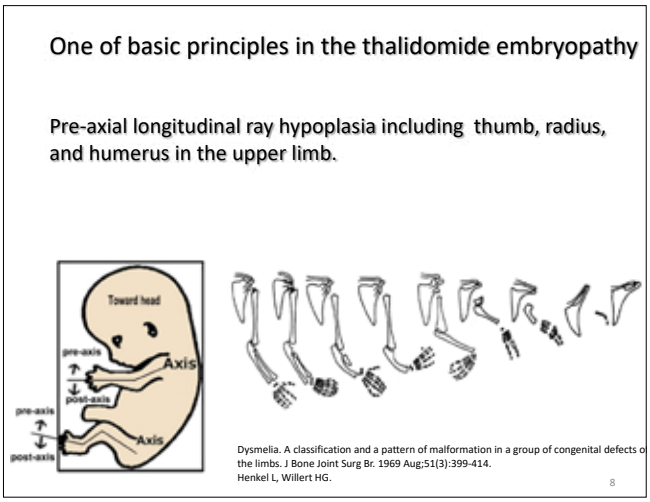


Fig. 8

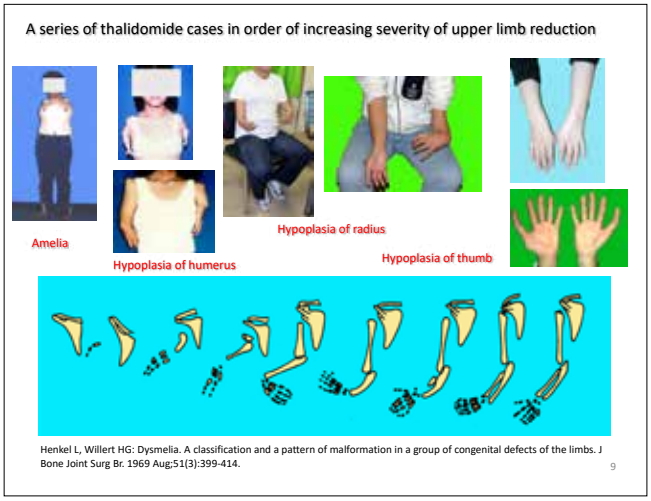


Fig. 9

Here are a series of thalidomide cases with upper limb reduction in the order of severity. Amelia and hypoplasia of the humerus, radius, and thumb are arranged in the order of severity in the upper limb from left to right in the slide. The last picture shows bilateral triphalangeal thumbs. (Fig. 9)

Congenital malformations are classified into hereditary and embryopathy in etiology. There are lots of similarities in morphological malfunction between the two to make a diagnosis of TE, and no family is indispensable, although they share preaxial longitudinal ray hypoplasia, for instance, triphalangeal thumb or Duane syndrome, in common. Malformations are inherited in cases of hereditary or familiar etiology, but cases with embryopathy are not inherited. (Fig. 10)

This is a picture of an old case. Dr. McBride in Australia, one of the heroes of the thalidomide scandal, published a paper reporting that TE could be inherited, and reduced the anxiety of many thalidomide victims. Around 1990, without genetic analysis, it was difficult to differentiate between hereditary and embryopathy with almost the same malformations. (Fig. 11)

Regarding triphalangeal thumb, there are many hereditary syndromes presenting as trigeminal thumb. They show autosomal dominant genetic transmission. The differential diagnosis is shown below. Duane radial syndrome, so-called Okihiro syndrome or Holt-Oram syndrome are so famous. In embryopathy, there are a couple of syndromes showing triphalangeal thumb. (Fig. 12)

Again, let's return to the first case. His disabilities consisted of grip and pinch without the thumb. The grip is not between the thumb and finger, but between the fingers and pisiform bone. The pinch is not between the thumb and index finger, but between the index and middle fingers.

Whenever he grips, he has to use the pisiform bone instead of the thumb, which is the reason why that bone has become prominent. (Fig. 13)

I will show you an abdominal CT. He does not have a gallbladder and the right kidney is markedly atrophied. (Fig. 14)

This is an MRI. I will show you the right kidney, which is severely atrophied with benign cystic lesion or vascular anomaly. This area shows a cystic neoplasm or vascular

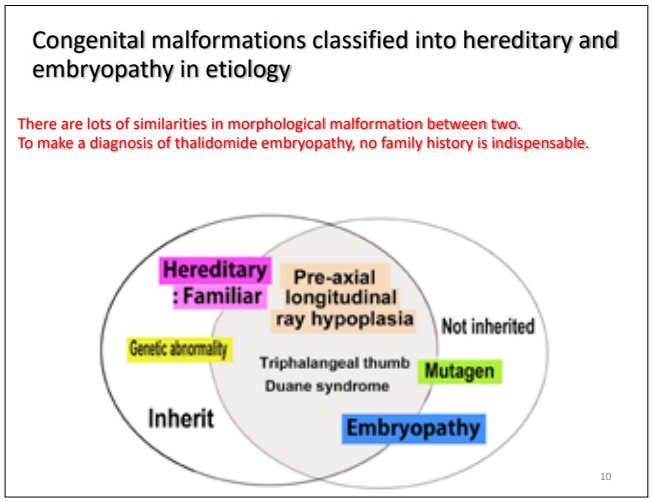


Fig. 10

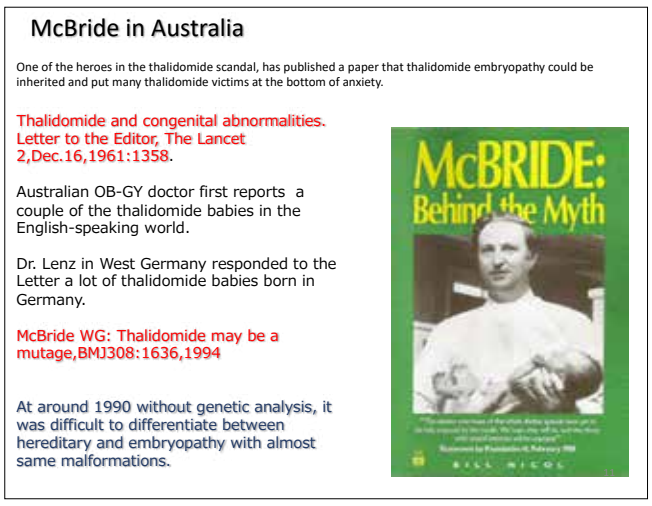


Fig. 11

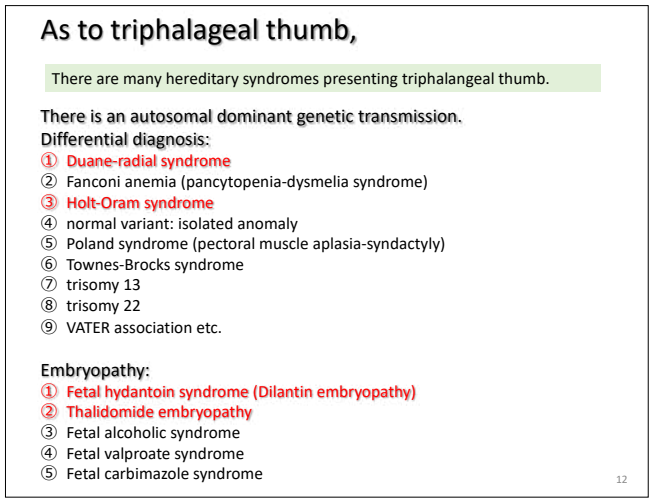


Fig. 12

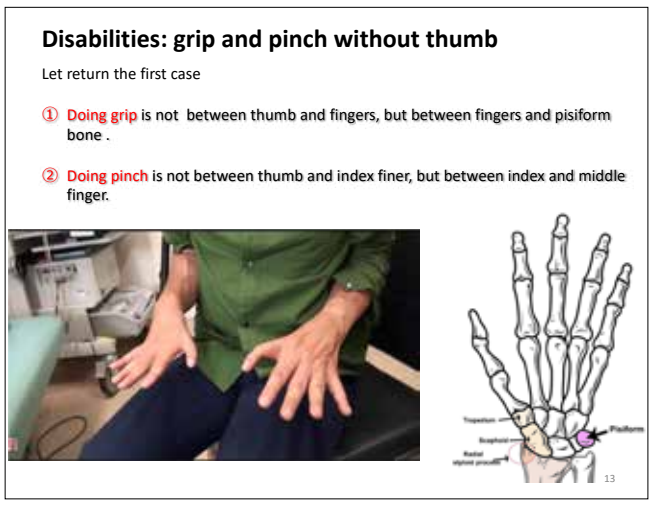


Fig. 13

anomaly, but I don't have any knowledge about this. The right kidney is severely atrophied, but no agenesis is seen. (Fig. 15)

This is the second case, a 46-year-old woman born in Kagoshima, the southern part of Japan, in 1971. (Fig. 16)

She has a short club hand with a rudimentary thumb on the left. On the right, her thenar muscle is hypoplastic. (Fig. 17)

On X-ray, she has hypoplasia of the radius and thumb. The carpal bones are not clearly separated on the left. Unfortunately, the hypoplasia of the thumb and carpal bones is not clear on X-ray because of technical problems on the right. (Fig. 18)

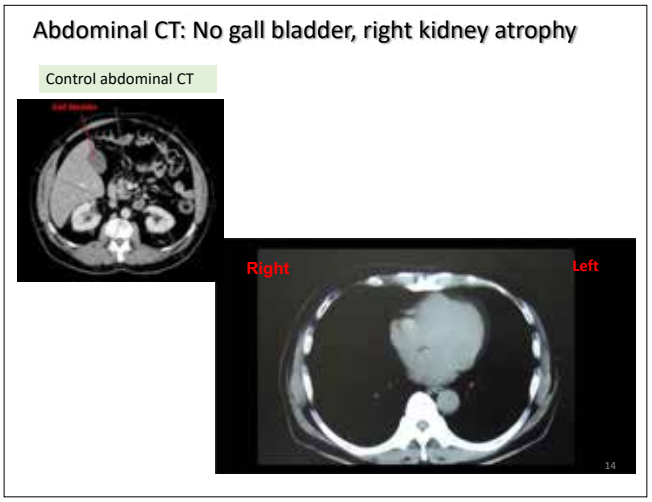


Fig. 14

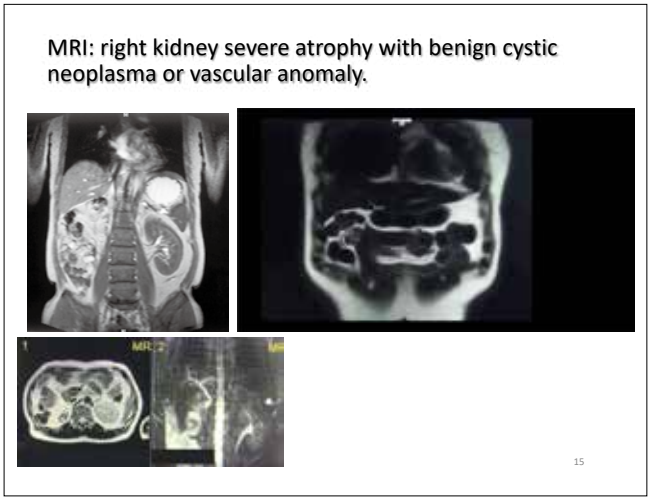


Fig. 15

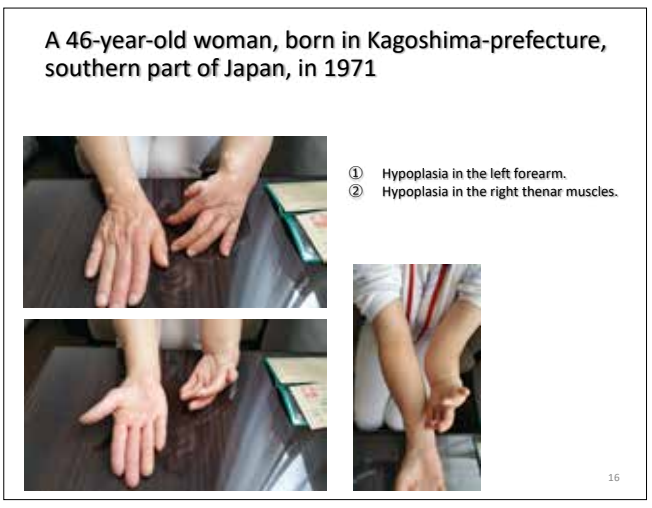


Fig. 16

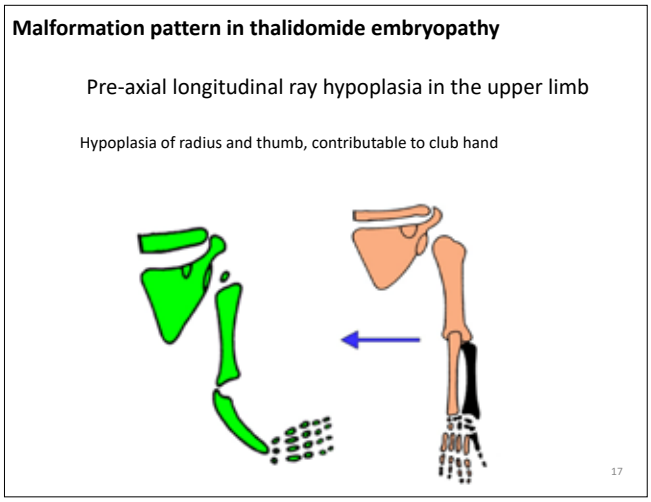


Fig. 17



Fig. 18

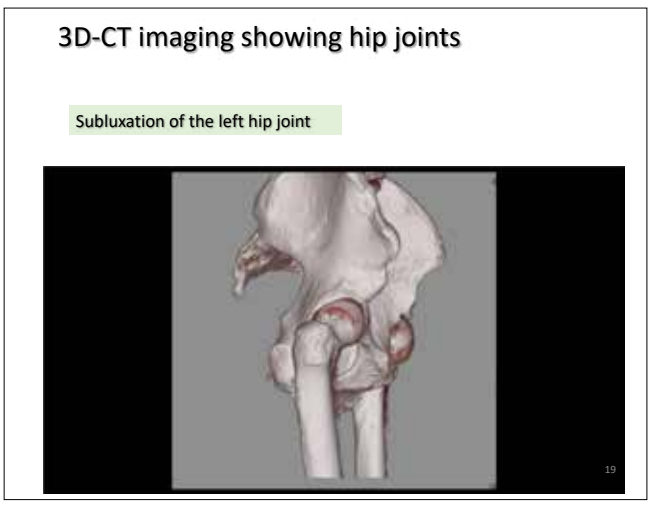


Fig. 19

This is a 3D-CT image showing the hip joint. Her left acetabulum is small and shallow, resulting in subluxation or osteoarthritis deformans in the left hip. (Fig. 19)

This is a coronal section of the abdominal cavity on CT that shows prominent scoliosis and agenesis of the right kidney, in addition to subluxation of the left hip joint. (Fig. 20, 21)



Fig. 20

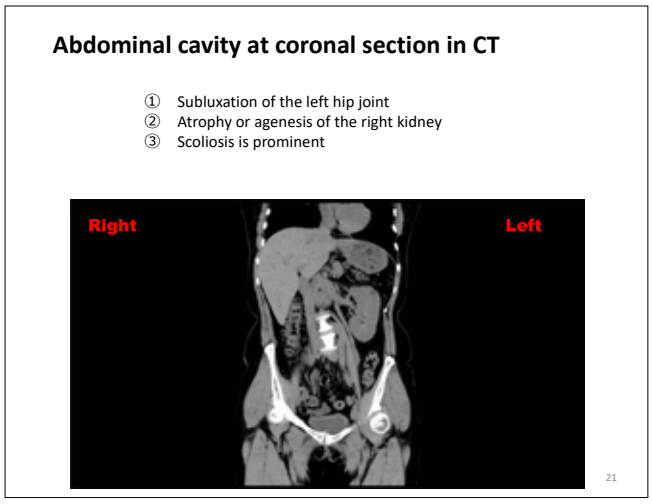


Fig. 21

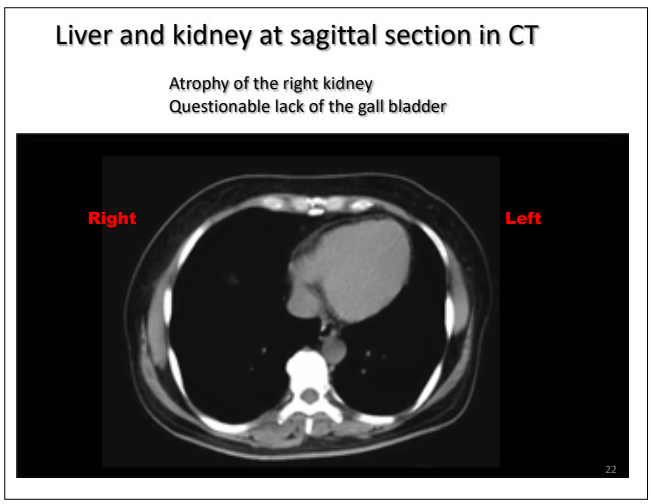


Fig. 22

As to the kidney anomalies in TE, intravenous pyelography is showing a crossed non-fused renal ectopia on the right in the other thalidomide victim. The ureter is located on the left side of the bladder in contrast to the kidney on the right. It might be likely to migrate to the right. Thus, it is indispensable to survey abdominal malformations using abdominal CT and/or MRI in thalidomiders. (Fig. 22, 23)

Now, we have the discussion. Both cases are almost the same in morphological malformations with preaxial longitudinal ray hypoplasia in the upper limb and atrophy or agenesis of right kidney. The only difference is the birth date. The first case is 1962 and the case is 1971. The difference seems to be crucial.

The first case may be a thalidomider, but not the second, judging from the perspective of the diagnostic algorithm for so-called DATE. (Fig. 24)

Most thalidomiders in Japan were born between 1959 and 1964. The recall of thalidomide began in September 1962 in Japan. On the other hand, it started in November 1961 in Europe after Dr. Lenz's warning. Dr. Lenz is known as the

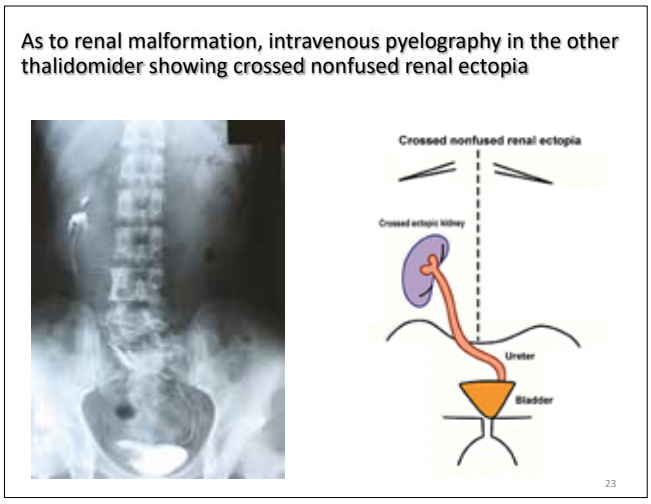


Fig. 23

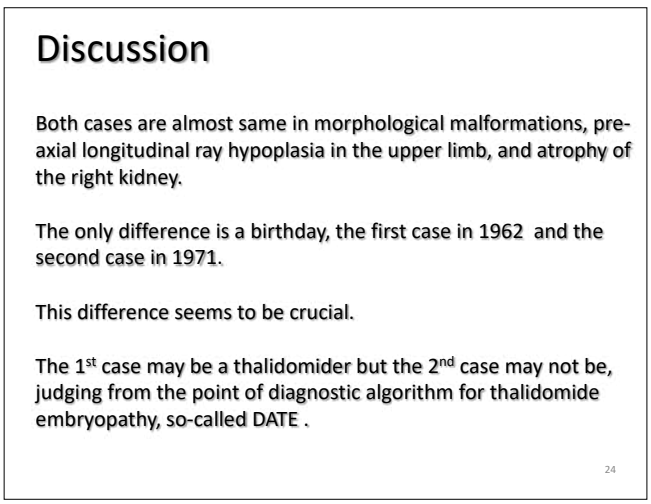


Fig. 24

father of thalidomiders in Japan. (Fig. 25)

This is one victim who was born in 1969 in Okinawa, where the United States ruled at that time. The notification of thalidomide recall from the Japanese government might not have reached the family of this victim. (Fig. 26)

This patient was born in 1969 in Okinawa. This is a rare exceptional case. The prohibited sale of thalidomide was not fully communicated, and that's the reason why he was born 7 years after the ban. We are happy that Okinawa returned to Japanese rule in 1972. (Fig. 27)

Epidemiology in the thalidomide scandal taught us a lot, and this was the starting point of academic epidemiology, so no more thalidomide victims would be born after the banning of thalidomide sales. This illustration shows the relationship between thalidomide sales and the incidence of TE. Thalidomide victims began to diminish 8 months after recall. (Fig. 28)

This is the diagnostic algorithm for TE (DATE) by Dr. Mansour, Dr. Baple, and Dr. Hall from St. George's University of London. We are looking forward to hearing the lecture on DATE by Dr. Baple. Thank you very much for your attention. (Fig. 29)

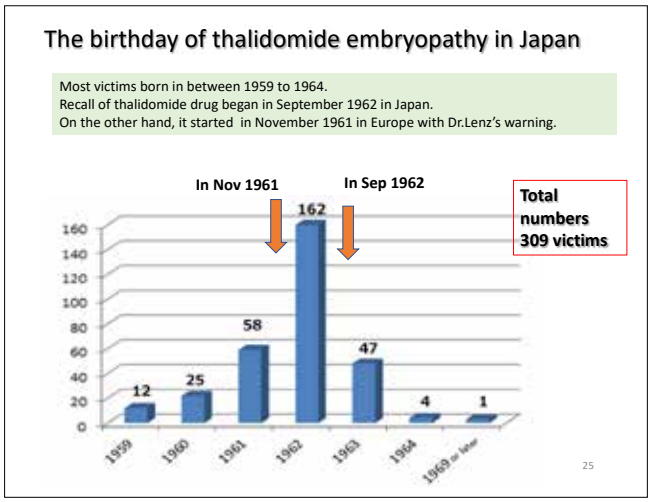


Fig. 25



Fig. 26

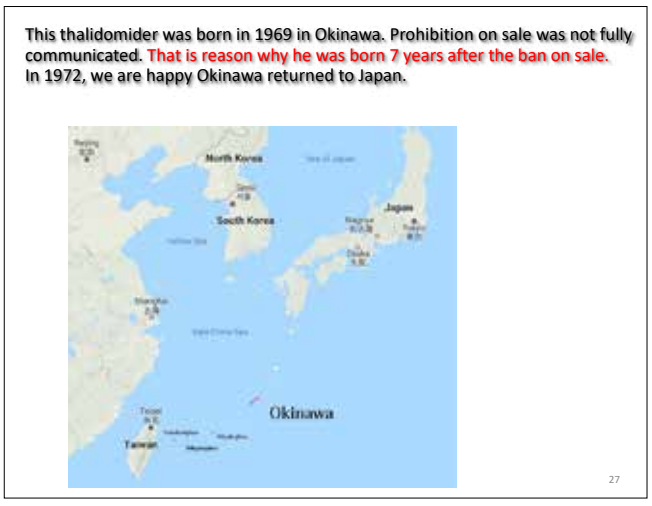


Fig. 27

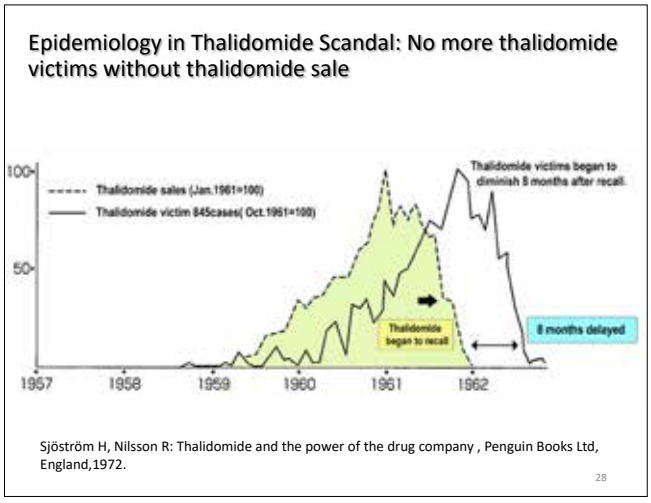


Fig. 28

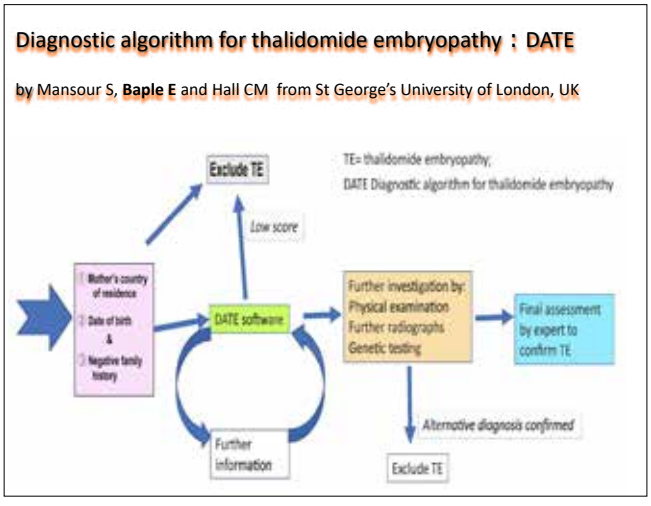


Fig. 29

Q&A

Junko Fujitani: Thank you, Dr. Kayamori. Do you have any questions or comments?

Lavinia Schuler-Faccini: Okay. Thank you for your beautiful presentation. And, as I am from Brazil, I'm going to talk tomorrow, but in Brazil, thalidomide never went off the market. It was not really commercialized, but it was provided by the government. So, we are facing lots of questions from people. And it's very difficult sometimes, as you have shown, to reach a diagnosis based on the clinical presentation. I think one of the saddest parts is that lawyers have discovered a way to make money from people, so they sell the history of the mother who took a drug that she didn't know about, and thus, it's really difficult to help these people. Thank you so much.

Ryoji Kayamori: We are looking forward to hearing your lecture tomorrow.

Junko Fujitani: Any other comments?

Jan Schulte-Hillen: Thank you very much. I would just like to say that a late birth of somebody with typical birth defects should not be used to rule out a thalidomide condition automatically. When I was working as a physician in Munich, the last time I saw thalidomide in one of the medical cupboards of a patient at their home was only 7 years ago. So old people don't throw drugs away, and perhaps the drug was still working when taken.

Ryoji Kayamori: Thank you, Jan.

Female Participant (Unknown Speaker): Thank you very much for your very nice presentation. I just have a question about the two new cases. Do you know, I mean, if there was any kind of malformation like those in other members of the family, it's my first question. And if you ask the parents, I mean, obviously, it may not be the case in Brazil, but they might actually have a history. Have you asked about this, because it's so late, I mean, 1971 is quite late. Thank you.

Ryoji Kayamori: Yeah, it is one of the most important things. But I have not heard from the Ishizue Foundation, a welfare foundation for thalidomide victims, that there is any family history so far. But I didn't examine this in detail. Family history is very, very important.

Junko Fujitani: Any other questions or comments? Okay, so thank you very much, Dr. Kayamori.

Ryoji Kayamori: Thank you very much.

A Diagnostic Aid to Thalidomide Embryopathy

Emma Baple

Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

Ryoji Kayamori (Moderator)

The next speaker is Dr. Emma Baple. She earned her MD from St. Bartholomew's and the Royal London School of Medicine and Dentistry in 2002. She earned her PhD at the University of Exeter Medical School in 2014. Her specialty is Clinical Genetics. Her current position is Clinical Senior Lecturer specializing in Genomic Medicine at the University of Exeter. She has won numerous prizes, awards, and research grants, and has many publications. It's difficult to detail everything. We are very looking forward to hearing her lecture especially on DATE. Could you start?

Thank you. Thank you very much for the kind invitation. I want to tell you today about what we have now actually renamed ValiDATE, which is a diagnostic aid for thalidomide embryopathy (TE) that I have worked on with a team from St. George's Hospital, where I undertook some of my Clinical Genetics training. This work is done by myself, Professor Sahar Mansour, who is a professor of Clinical Genetics and a Clinical Geneticist at St. George's Hospital, and Professor Christine Hall, who is an internationally renowned radiologist who previously worked at Great Ormond Street Hospital. Even though she is retired, she is still often asked to help with difficult cases and has led a lot of the work that we've done on this.

So, I'm only going to talk to you very briefly about the background of this work because everybody in this room already knows a lot about thalidomide and TE, but a brief overview helps to put the work we have done in context. (Fig. 1)

In summary, I am going to talk to you about our diagnostic algorithm, how it came to be, describe DATE or ValiDATE as we are calling it now, the WHO Conference which helped to inform its development, and how we hope it might be useful. (Fig. 2)

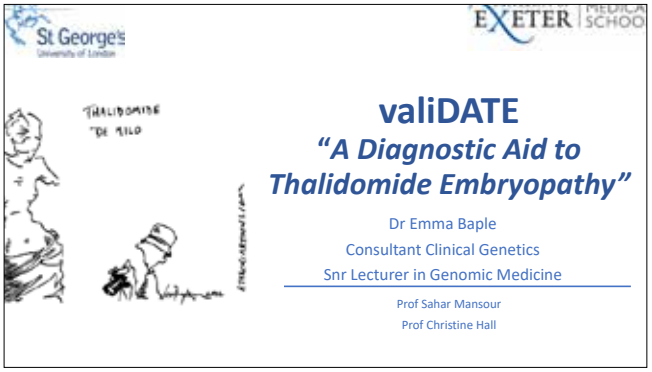


Fig. 1

So, first, a little background. When we were initially doing this work, we were looking at thalidomide from the UK perspective. As people know, thalidomide was available in the UK between April 1958 and November 1961. The majority of births affected by TE happened between 1959 and 1962, so that was where the majority of cases and clinical information that we have been able to collect date from. (Fig. 3)

So, TE is a diagnostic dilemma as many people in this room already know, and the two cases previously presented today make this apparent. Part of the reason for this is the lack of evidence of exposure. And I recall, when we initially went to speak with The Thalidomide Trust, Dr. Claus New-

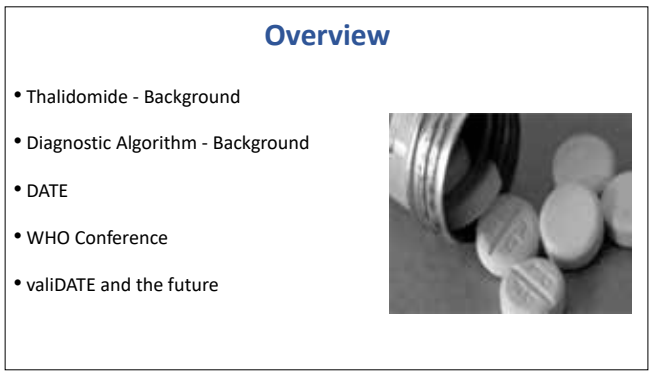


Fig. 2

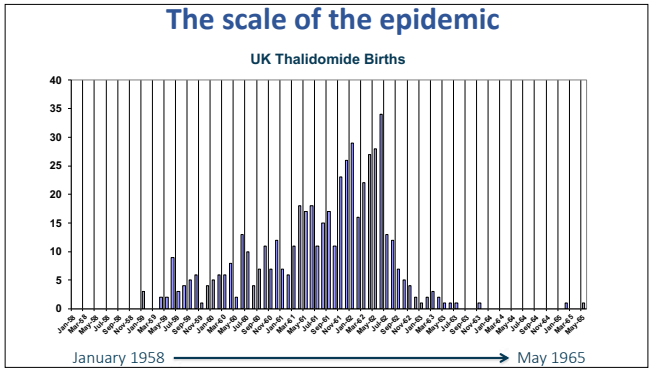


Fig. 3

man, who has worked with the Trust for a number of years, told us that there's only probably about 50% of individuals whose mothers actually recall even taking thalidomide, and those are TE claimants who were certainly affected by TE. (Fig. 4)

Part of the problem is that particularly in Germany, but also elsewhere, thalidomide was included in some medications but not listed. So it wasn't always obvious what people had taken and when.

Birth defect records were nonexistent or incomplete back in those days, and only very severe limb defects and other severe physical defects were recognized because they had previously been rare. And as we know, as all the clinicians here would know, patients' memories are very unreliable, so recalling exactly what happened is difficult.

So, in 1964, the Ministry of Health in the UK produced the document shown here about the deformities caused by thalidomide. And they said what I think is a very pertinent quote. "It's impossible to say with any certainty what constitutes a thalidomide deformity. There seems to be little evidence of a typical thalidomide deformity." So that's really the question that we were trying to address with ValiDATE.

The timeline shown here has been extremely useful. And Lenz, whose picture I show here, was one of the pioneers that really helped us to understand the deformities associated with thalidomide and its relation with the time of exposure during pregnancy. Lenz did this work with Knapp. They investigated the records for 86 women looking at the time, at the precise time, at which they took thalidomide, and the dose that they took.

Their work showed that it was the time of exposure and not the dose that was important. They showed that around half of TE-affected babies were born with upper limb defects only, one-quarter had upper and lower limb defects, and one-sixth had anotia or microtia, so an absent or small ear. Their work defined this timeline, which actually still stands today, so this is a very important piece of work. (Fig. 5)

The additional text on the timeline, which is in italics, comes from the excellent work that was done in Sweden looking at the facial and ocular abnormalities seen with TE.

So, thalidomide as we all know is a teratogen, and all of the birth defects shown on this slide will be familiar to people in this room. It was also suggested in the 1990s that thalidomide might be a mutagen; in other words, that defects could be passed from one generation to another. What we now know is that those cases have subsequently been shown to be a genetic disorder, a genetic variant that was passed down through the generations that caused a genetic syndrome that mimicked TE, or what we call a phenocopy of thalidomide. (Fig. 6)

There has been very robust work done demonstrating that thalidomide is not a mutagen.

I'm not going to dwell on this now though, because I am sure that this will be covered by Lavinia Schuler-Faccini

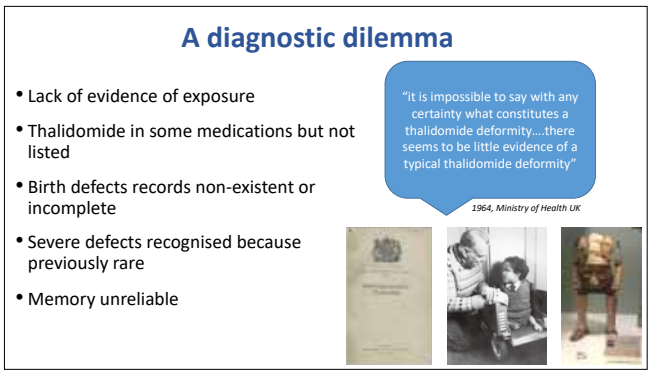


Fig. 4

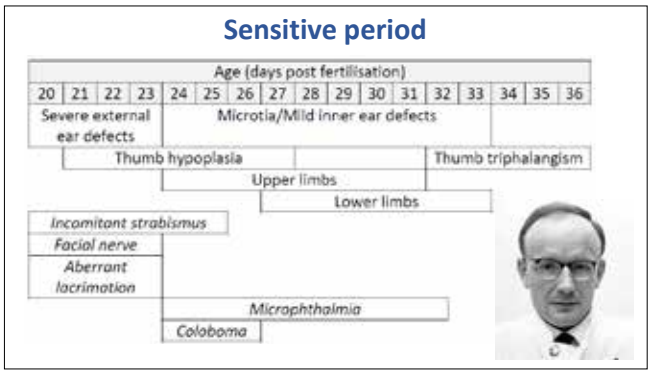


Fig. 5

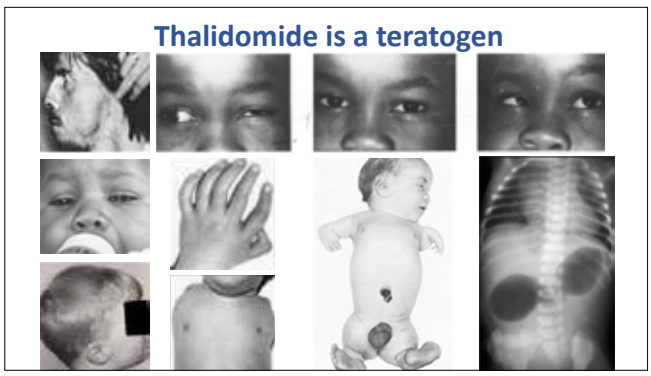


Fig. 6

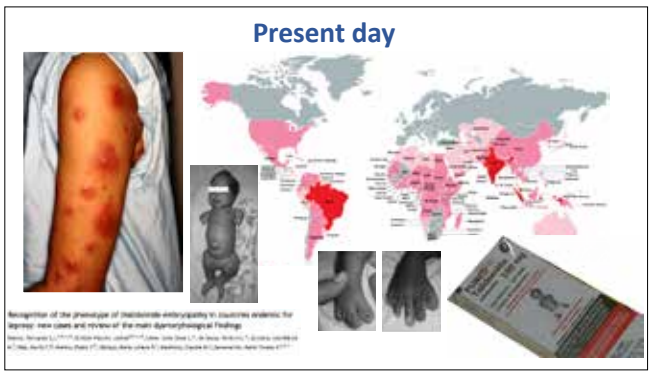


Fig. 7

tomorrow. Thalidomide was reintroduced in 1965 in the UK as a treatment for multiple myeloma in individuals over the age of 65. But it is also still used to treat the cutaneous manifestations of erythema nodosum leprosum. (Fig. 7)

The current use of this drug in countries like Brazil has led to a large number of individuals being born with TE. (Fig. 8)

So, this is just to remind us all of the scale of the TE problem globally, which is actually still growing in certain parts of the world like Brazil. So, many people, when you tell them you work on or are interested in thalidomide, say well, all those individuals must be getting older now and the problem must be decreasing. But actually, all those older individuals still have problems that resulted from this drug, as we'll hear more about tomorrow. In addition, there are still more individuals being born today. (Fig. 9)

So that really was where we started from in terms of the background when we were thinking about this diagnostic algorithm.

So, how did it really come to be? Well, we were invited by The Thalidomide Trust in the UK to write an independent review of TE, and this work has been done intermittently by St. George's University over the years. The brief was to cover the historical facts and the proposed teratogenic mechanisms and to look at whether there was any new knowledge that might help inform the diagnosis, the characterization of the phenotype, and the differential diagnosis and genetic tests that might help. There were no financial links to the trust in any of the work that we'd done other than the production of the software, which I'll come to. (Fig. 10)

When we first started this work, we were trying to think how we might best try to solve this diagnostic dilemma. If you look at the pictures of these children here so I am a clinical geneticist, and any clinical geneticist would recognize the facial features of these children as indicating that they had a condition called Kabuki syndrome. And this excellent paper here, which looked at only a very small number of individuals with Kabuki syndrome, identified mutations in the coding region of gene MLL2 as the cause of the disorder. (Fig. 11)

What that work teaches us is that if you diagnose a condition accurately, it enables you to characterize that phenotype even more clearly as time goes on and to identify the underlying cause and mechanism of the disorder. Once you understand the underlying cause, you can really get at what's

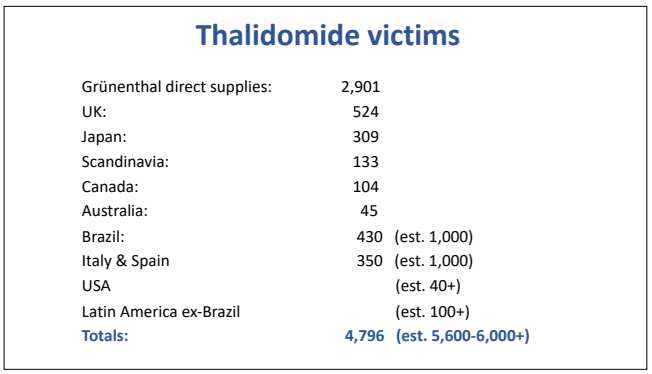


Fig. 8



Fig. 9

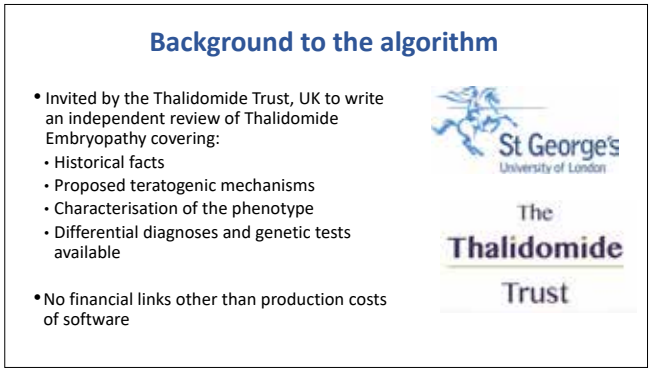


Fig. 10



Fig. 11

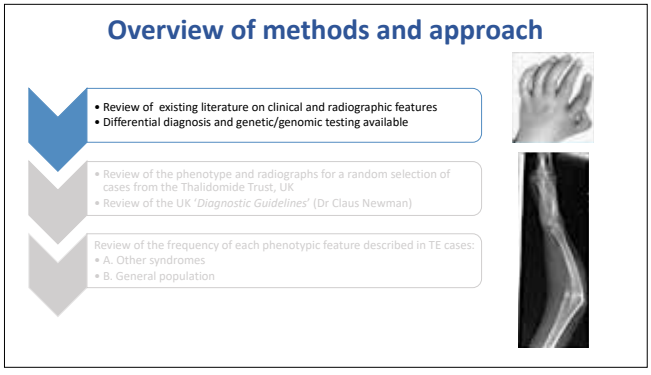


Fig. 12

going on in the body. So, this was our goal. (Fig. 12)

So, what did we do to tackle this issue? Well, we reviewed the existing literature on the clinical and radiographic features, and there is quite extensive literature available on this. We then looked at the potential differential diagnoses for TE and the genetic and genomic testing that was available. So, this was all back in around 2012–2013 when we started doing this. (Fig. 13)

So, since TE was initially a problem we have recognized a huge number of genetic syndromes over that time, and that list grows daily. So, there's an extensive list of differential diagnoses for TE, one of the most important being Okihiro syndrome, which is caused by mutations in a gene called SALL4 and is one of those phenocopies I mentioned earlier that can be passed down through generations. We looked at all of the potential TE phenocopies and any condition with phenotypic overlap with TE. We looked at the aspects of the condition that were absolutely indistinguishable from TE and those that were more variable.

So, individuals with Okihiro syndrome can have something like a Duane anomaly and radial ray malformations. They can have those features in isolation, and those are both features seen in TE. (Fig. 14)

Other abnormalities seen in Okihiro syndrome that overlap with TE but are perhaps less common in one or the other condition include anal stenosis or imperforate anus, renal anomalies, other ocular abnormalities, external ear anomalies, and abnormalities of the lower limbs, although these are much, much rarer in Okihiro syndrome than in TE.

And so then, we looked at the differentiating features. (Fig. 15)

So, you never see phocomelia or amelia in Okihiro syndrome. The lower limb defects that you do see on occasion are tibial hemimelia and syndactyly of the toes. The external ear anomalies are also very different. So, we did this work for all of the disorders we felt were phenotypically overlapping with TE.

What did we do next? We reviewed the phenotype and the radiographs for a random selection of cases from The Thalidomide Trust, and we also reviewed the UK diagnostic guidelines that the trust was using at that time, which were written by Dr. Claus Newman. (Fig. 16)

When we looked at these cases, we wanted to look at the radiology again. Christine Hall did this work. So you'll have to excuse the fact that I am not a radiologist. I will point out those things that she has taught me.

So, amelia, we would all recognize as an absence of a limb, and phocomelia, which is a term we've used in medicine, but is not actually always that well defined. So, phocomelia is absence of the intermediate part of a limb with the presence of some fingers. There are individuals in the medical literature said to have phocomelia where they really don't match that description, so it's important to get this right. (Fig. 17)

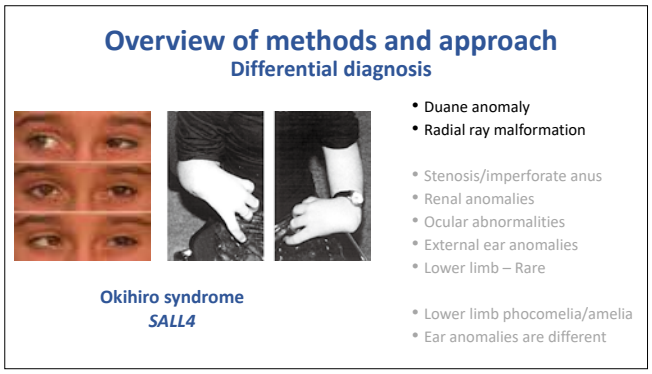


Fig. 13

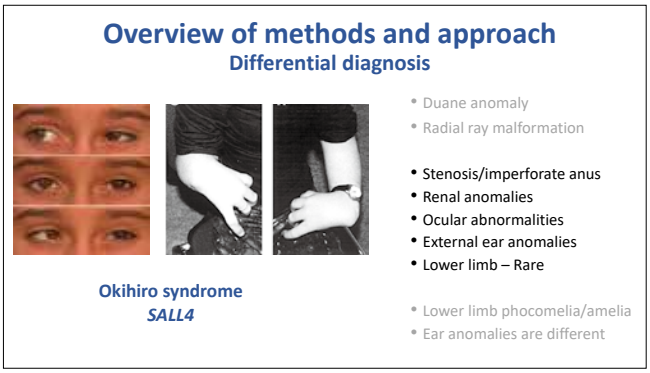


Fig. 14

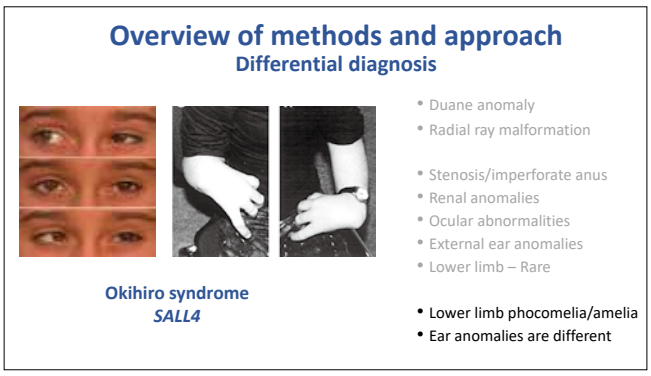


Fig. 15

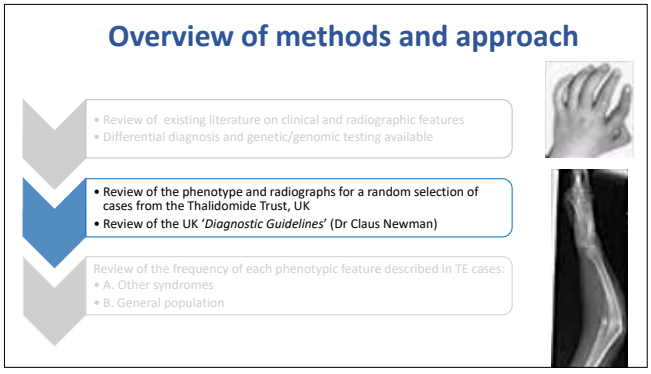


Fig. 16

And actually, before I go any further, I guess that's the one lesson I've learned from this what's written in the literature and what you actually see when you examine or really look at radiology can be very different, and it's important when you are trying to recognize the features of something that you are absolutely accurate.

So, this is a little boy with TE who is now grown up. He gave me this picture of him on the beach when he was little. And what this picture happens to show is a very characteristic feature of TE. This is pointed shoulder. This pointed shoulder is really unusual. We don't really see this in any other disorder. It is characteristic of TE and is due to this abnormality, which you can see on the X-rays here. (Fig. 18)

So, you get this very long clavicle and acromion process – which is indicated by these arrows. And this is what gives you this pointing of the shoulder shown here. You also see this hypoplastic or absent glenoid fossa, which is indicated by these arrows on the X-rays, and it's that combination that's creating this pointed shoulder. (Fig. 19)

So, we think again about the other disorders that overlap with TE. Children affected by these disorders may have been diagnosed with TE because they would have still been born with this during the time thalidomide was around. If you look at pictures of these children's shoulders, you will see that they look different. For example, in Holt-Oram syndrome, the shoulders never have that point. In fact, they are actually very characteristic in appearance. They slope downwards. And if we look at Roberts syndrome, which can be an almost exact phenocopy of TE, you don't see those pointed shoulders, so that's really important. (Fig. 20)

There are other abnormalities that you see in TE affecting the upper limbs that are also unusual. This is proximal hypoplasia of the humerus. You see this unusual appearance at the top of the humerus and often very bizarre shapes to the bones, which you don't typically see in other forms of skeletal dysplasia. You can see a very short humerus and a subluxed shoulder joint. (Fig. 21)

These fusions around the elbow joint are also unusual, particularly the longitudinal fusion that's seen here, this humero-ulnar fusion that's seen here. This is very unusual, but is sometimes seen in TE. You can see fusion around the elbow in TE: humero-radial, humero-ulnar, or radio-ulnar fusion. So here you've got this very nice illustration of humero-ulnar fusion, and then there is oligodactyly.

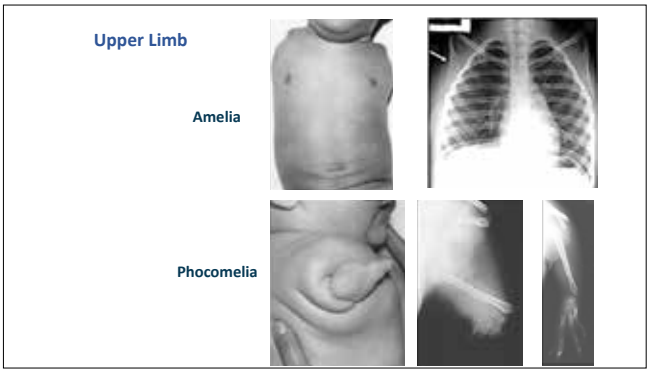


Fig. 17

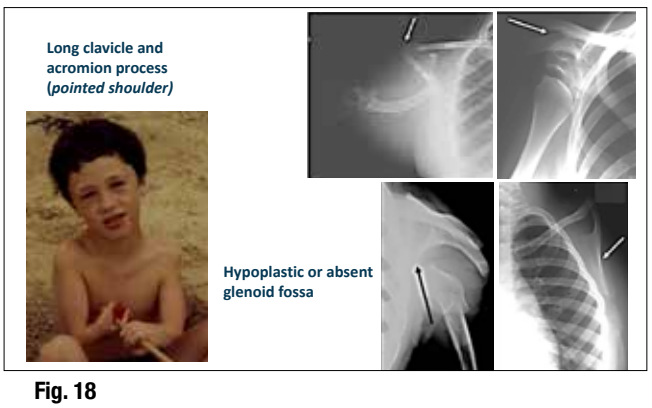


Fig. 18

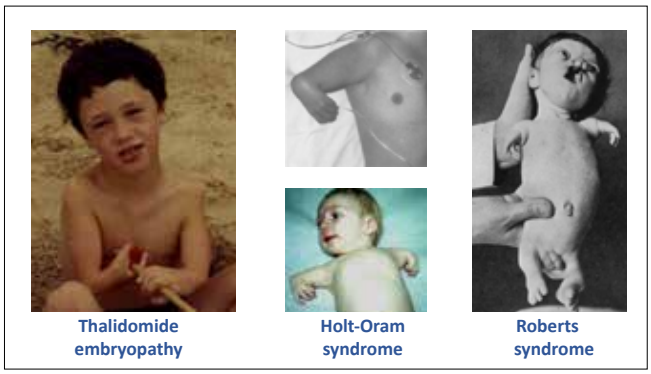


Fig. 19

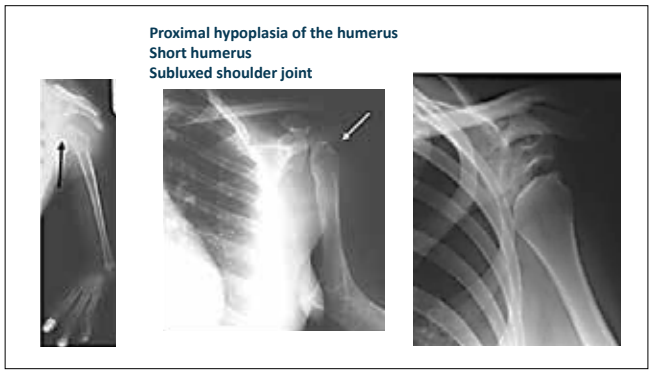


Fig. 20

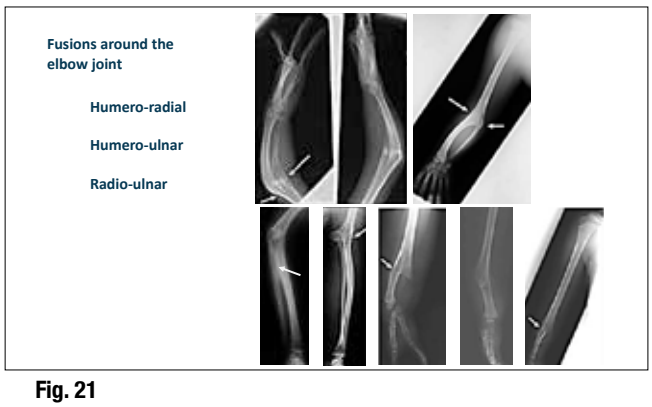


Fig. 21

So, other abnormalities that we see moving down the upper limbs are hypoplastic and absent radii. So, you'll notice as I'm going down, these pre-axial defects that I am highlighting. Here we can see that you've got an absent radius or hypoplastic radius, and the thumb coming off of it is unusual or absent. (Fig. 22)

The ulnar, and I want to emphasize this, is abnormal in these radiographs. It doesn't look normal, but the ulnar abnormalities that you are seeing are occurring as a secondary consequence of the radial abnormality. So, there's a lot in the literature about TE around the possibility of ulnar abnormalities being part of the condition. Yes, this is true, but only in association with radial abnormalities, not on their own. So, here, essentially, the ulnar is being pulled around by the absent or hypoplastic radius and is thickened you can see the stress lines in the ulnar. So these are secondary abnormalities. (Fig. 23)

Carpal bone abnormalities. Again, carpal bone abnormalities are frequently described in TE. We know that they occur. What's important though is the type of carpal abnormality that is seen. So, you can see these transverse fusions, these fusions across the rows of the carpals. You can see them here and here, both proximal or distal. You often see absence of or abnormally shaped bones on the radial side, the pre-axial side again, for example, the scaphoid is missing here. The scaphoid and trapezium are missing here.

This is what I want to draw your attention to though.

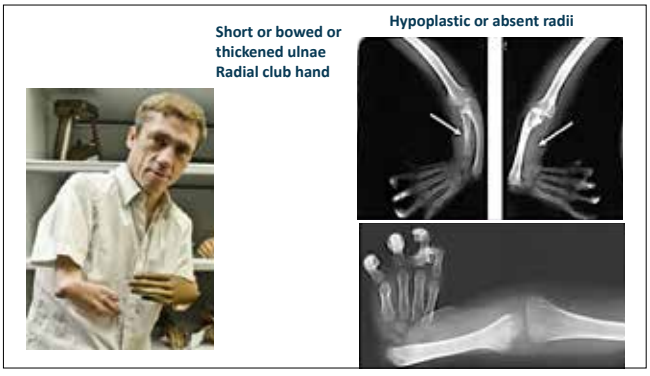


Fig. 22

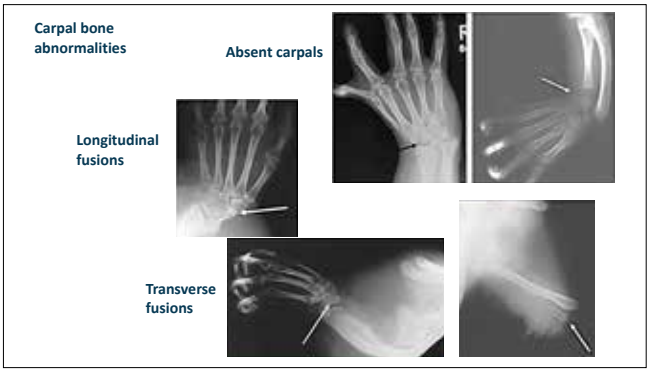


Fig. 23

This longitudinal fusion, this fusion between the scaphoid and the trapezium, this is basically not seen outside of TE. It's really unusual. So, if you see that, that is a characteristic feature seen in TE.

Thumb abnormalities. So, thumb abnormalities can include a triphalangeal thumb, a hypoplastic or absent thumbs, and pre-axial polydactyly. (Fig. 24)

Lower limb abnormalities are analogous to upper limb abnormalities with the exception of the foot. So, you can see the absence of the limb or phocomelia. (Fig. 25)

Moving down the limb, you often see proximal femoral deficiencies. So again, similar to what we've seen with the humerus, you see these unusual looking femora, and the bone itself can often look very unusual, and you can see the proximal deficiency here. You get very shallow acetabula of the hip, and the femora can be short. (Fig. 26)

Again, emphasizing the preaxial abnormalities that are

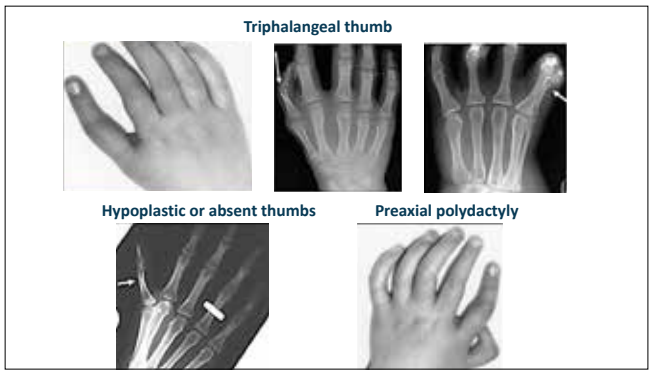


Fig. 24

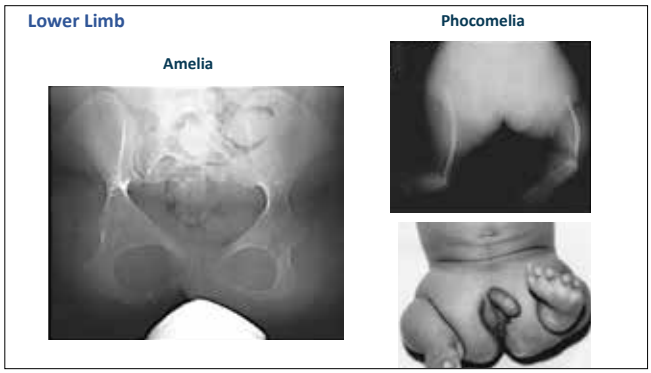


Fig. 25

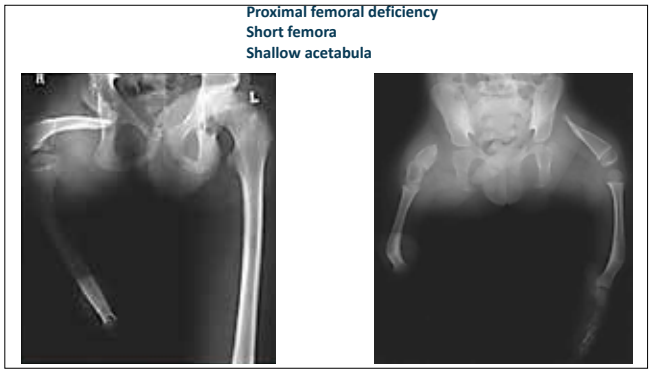


Fig. 26

seen in TE. You see absent or hypoplastic tibiae. The fibula is relatively unscathed in this abnormality. It's relatively preserved. It can be abnormal, but its abnormality again we believe is secondary to that of the tibia. So, it can be dislocated, it can be a bit shorter. In the feet, we tend to see pre-axial polydactyly, so a little different from what you are seeing in the hands with extra digits. (Fig. 27)

You can see fusions in the knee joints. I couldn't find any X-rays that clearly demonstrated that. But fusions in the knee joints are seen, they are just less common. (Fig. 28)

So, what did we do after that? Well, we next reviewed the frequency of each phenotypic feature described in the TE cases, in other syndromes, and then in the general population because we wanted to define what was really characteristic of TE, what were the cardinal features of TE, and what do we not see as part of TE? (Fig. 29)

This is the London Dysmorphology Database, a tool that clinical geneticists have used for many, many years. (Fig. 30)

If you look up TE, you find that there are huge numbers of defects listed. Its fifth in the database for the number of defects associated with it, and there are a lot of genetic syndromes and teratogens in that database.

So, what were the limitations to our approach? We did a literature review and a review of the UK cases initially, but much of the detailed and original clinical information wasn't available. There were no full skeletal surveys. An accurate interpretation of the radiology is crucial, so although there was some great literature out there, we couldn't get ahold of the original old radiographs that the clinical descriptions had been based on. Many of them had been destroyed, so we are relying on what people said that they saw. And when we looked at the radiographs with contemporary eyes, what people had written and what we saw were sometimes quite different. So, accurate and contemporary interpretation is crucial. (Fig. 31)

For a small number of cases that were included, we could clearly recognize an alternate diagnosis, from either their radiology or their photographs. It's very rare to have evidence of thalidomide intake during pregnancy, so it is often presumed, and that's clearly an issue.

So, the conclusion we came to was that we needed an international consensus on the diagnostic criteria for TE. (Fig. 32,33)

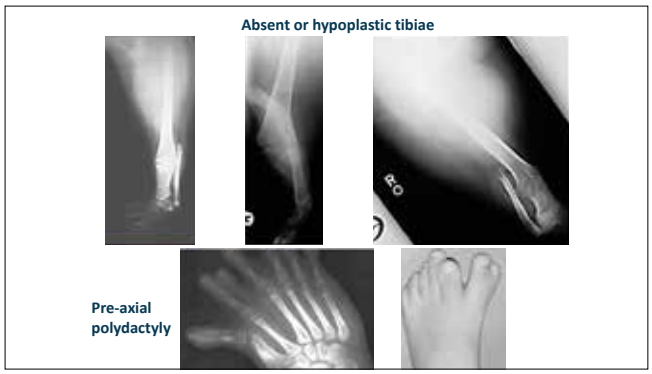


Fig. 27

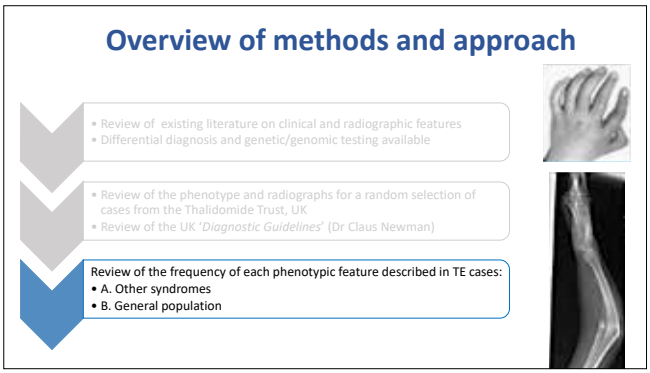


Fig. 28

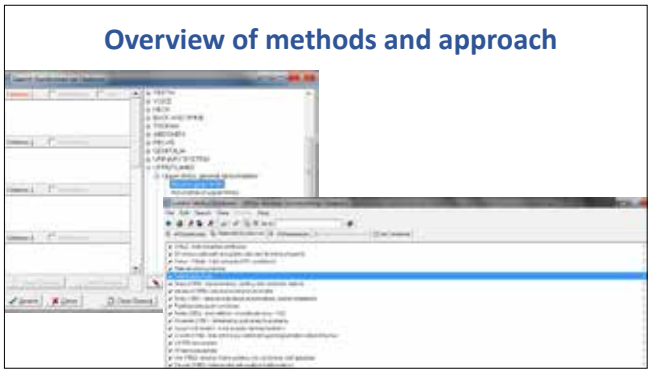


Fig. 29

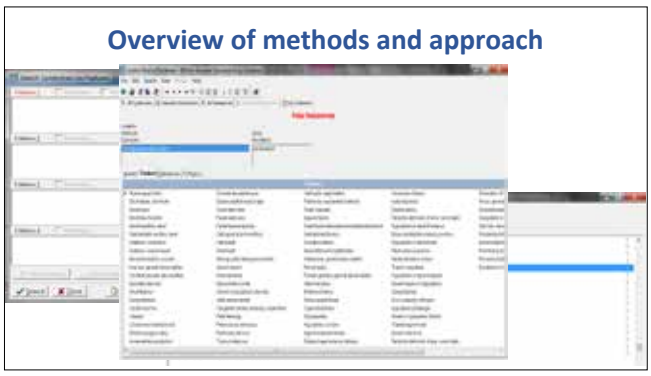


Fig. 30

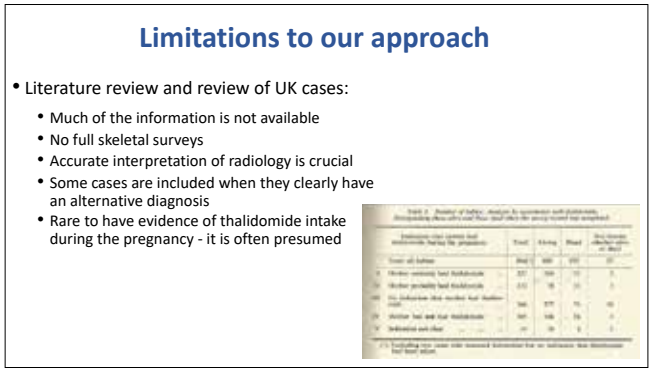


Fig. 31

And, to inform that, we were going to put together a diagnostic algorithm that would help, and that could be refined as part of that international criteria, and we were going to call that diagnostic algorithm DATE. (Fig. 34)

What we basically did was look to create a score that would indicate the likelihood that an individual's abnormalities were due to TE. Those scores were going to be weighted depending on whether the features were classical of TE, so, typical and highly suggestive of TE, otherwise rare, and occurring rarely outside of it. Those unusual fusions that I was talking about, amelia and phocomelia, we would include those, as well as clinical features that are often seen in TE, but rarely outside, rarely in other genetic syndromes.

Nonspecific features of TE that occur both in TE and in other conditions would include things like triphalangeal thumb. We know we see these outside of TE, so, they are not as specific.

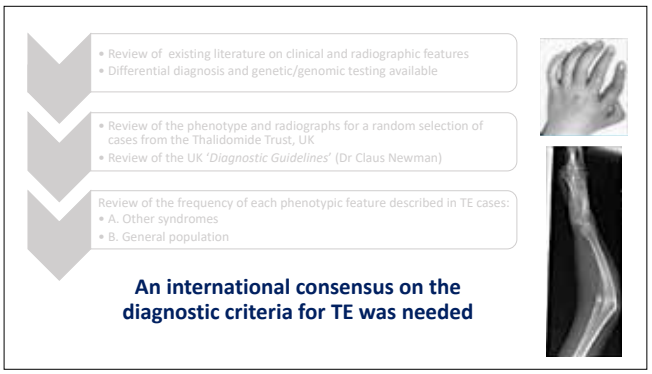


Fig. 32



Fig. 33

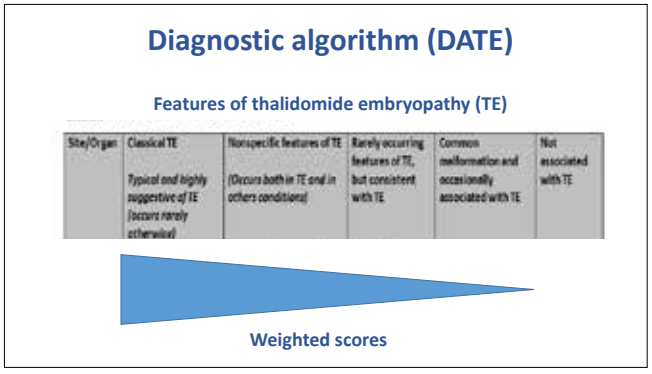


Fig. 34

Common malformations that are occasionally associated with TE would include dislocated hips, for example. Then, also importantly, some presentations are not associated with TE, where we would say we don't need to go any further with our investigations. These would include transverse limb defects, ectrodactyly, isolated unilateral limb defects, and isolated post-axial limb defects. So we gave each feature a weighted score. For some features, we know that one feature always occurs with another feature or more commonly with another feature. For example, facial palsy and Duane abnormality, these would get a combined score that was basically synergistic. In other words, the score was enhanced by that combination occurring together. (Fig. 35)

So, this is what the algorithm looked like. And in fact, it was my husband that originally designed the prototype software for this algorithm, so I'm going to thank him for it. So, this is what it looked like. It was effectively a piece of software, and the user would answer questions with bilateral, unilateral, none, or unclear. They would have a definition and would have radiographs as examples and pictures to help to inform their choice. And at the end, the user would get a score for the case. (Fig. 36)

We also wanted to give an indication of the differential diagnosis. So depending on what features the person put in, the software would pull out the features that were found in that individual, and also in the genetic syndrome, and give you a list of differential diagnoses. Then you could click on that diagnosis and it would give you information, telling

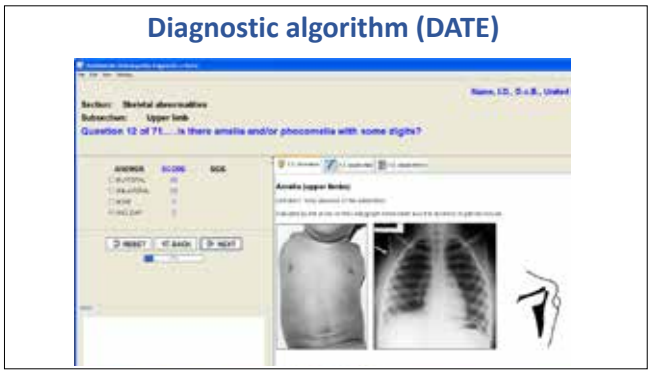


Fig. 35

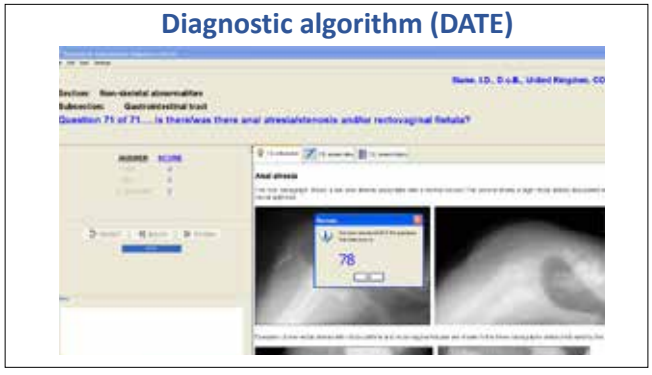


Fig. 36

you about the disorder, the genetic test that was available, and the features that were characteristic of that disorder not found in TE that you might want to look for. (Fig. 37, 38)

And so, we took DATE to a conference organized at the World Health Organization (WHO). We had approached the WHO and explained that TE was still a big problem worldwide and that there was a lack of consensus on the diagnostic criteria. The WHO wanted to invite international experts, many of whom are sitting in this room, to a meeting to use this piece of software and to help us refine this piece of software. The experts were asked to bring cases and to help us to define three score cutoffs: probable TE, possible TE, and unlikely to be TE. (Fig. 39)

So, that conference was over a long time ago now, in 2014, and it was described as an expert workshop to establish the diagnostic criteria for TE. Experts from the UK, Germany, Sweden, Australia, Brazil, America, and EUROCAT came to help us and to be involved in this work.

The goal set out by the WHO was to define the minimum diagnostic criteria required for a diagnosis of TE. The aim of this was to target help and support for victims of TE and to develop a better understanding of the underlying mechanisms.

So, this is a case that Lavinia Schuler-Faccini brought to the meeting: a little boy with TE. This little boy has features, including bilateral upper limb phocomelia, that you can see here. Importantly, you can see his very pointed shoulders. He had bilateral lower limb phocomelia, facial hemangioma, bilateral narrow auditory canals, bilateral hearing loss, and bilateral cryptorchidism, as you can see here. (Fig. 40)

His score was 73, and in terms of the score that we had as a cutoff as probable TE at that time, he very much exceeded that. (Fig. 41)

If you were to put his features into DATE, you would find that the differential diagnosis was Roberts syndrome. But I think you can differentiate his case from Roberts syndrome, genetic testing or not. (Fig. 42)

So, after that conference, we had some spirited debate and discussion about what were really characteristic features of TE, and probably most debate around what were not features of TE. We wanted to take that forward and develop DATE. (Fig. 43)

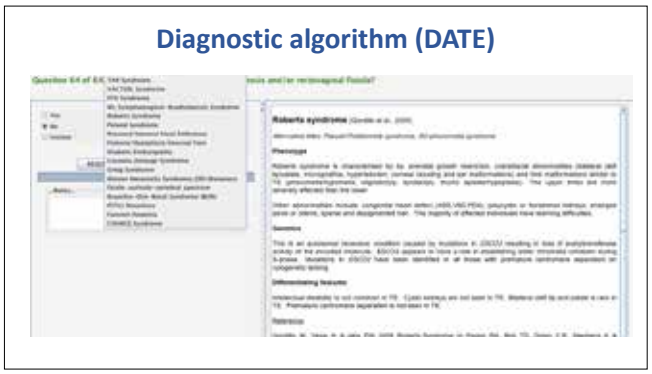


Fig. 37



Fig. 38



Fig. 39

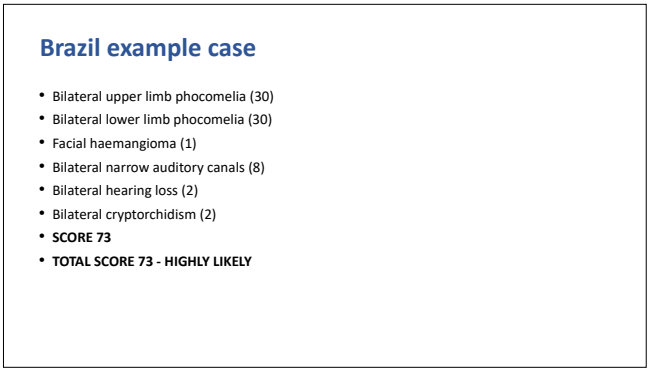


Fig. 40

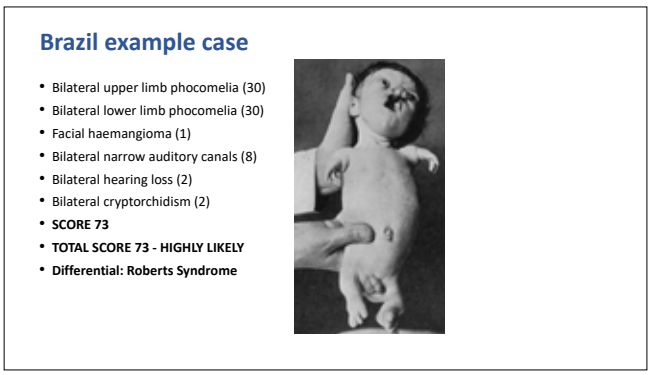


Fig. 41

So, we needed to do some more work, really. We'd had good input at the meeting, but we really needed to validate DATE. And how did we do that? Well, we took these three German papers that were translated and included very extensive information about TE cases. There were 142 cases across these three papers, and really, these three papers contained extremely good information on a case-by-case basis, and that's what we were looking for. We used DATE to assess those cases.

And what we found, which was interesting, was that 87% of cases had upper limb abnormalities, almost all bilateral, a very high proportion of which had amelia and phocomelia. Only two individuals who had lower limb abnormalities did not have upper limb abnormalities.

Anotia and microtia were found in one-fifth of the cases; 26% of individuals with facial hemangioma also had anotia and microtia. Anotia and microtia were found in all of the individuals with facial palsy.

However, although we had really good information in those papers, we couldn't go back and look at individual radiology. Contemporary cases like those from Brazil are therefore really important for us in terms of trying to fully establish the radiological features of TE. You could say we could go back and get repeat radiology for all of the individuals from The Thalidomide Trust. I would debate the ethics of doing that now, but more than that, it wouldn't be a huge amount of use to us because of the damage that would've been done to those joints over the years.

So, the cases that would be most useful going forward for really helping to refine this are cases from countries like Brazil, where we know that we have got contemporary radiology that we can look at. We put all of this work together, refined DATE, and published a clinical review, "An Introduction to the Algorithm", which came out earlier this year.

You've seen this already today. It is a bit of a busy slide, but this was the pathway for assessment of TE that was in our manuscript. I have changed the name to ValiDATE here, so there is one difference. What we had originally included in DATE, and people will possibly remember, that we brought to Geneva in 2014, was that we had questions about the mother's country of residence, date of birth, and negative family history. We've removed that from the software for reasons that you've heard about already today. This is helpful information for us to collect, but it shouldn't be a reason to not go forward with the algorithm. So, we've removed this now, and that was really through direct feedback from the meeting in Geneva. (Fig. 44)

We would suggest that ValiDATE be used only by individuals assessing patients and those being very careful about how you use that sort of information if you are going to use it to exclude TE.

So, the software starts after that point. If you get a low score, then TE is excluded. If your patient has some of those features that I talked about earlier, like a transverse limb defect, you won't go any further and will exclude TE you will get a zero score and it will not let you progress any further. Once you are in ValiDATE, it may be that you find you need further information about the patient. It might be that you cannot answer the questions that are asked because you don't have that information about the case.

If ValiDATE gives you a score that's probable or possible TE, and I'll come down to this in a minute, then further investigations that might be warranted could include a physical examination, further radiographs, and/or genetic testing.



Fig. 42

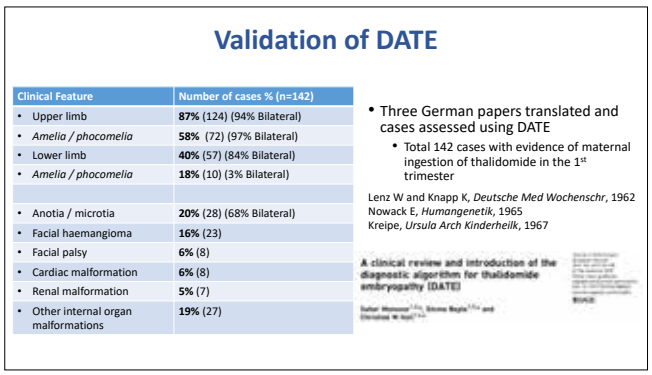


Fig. 43

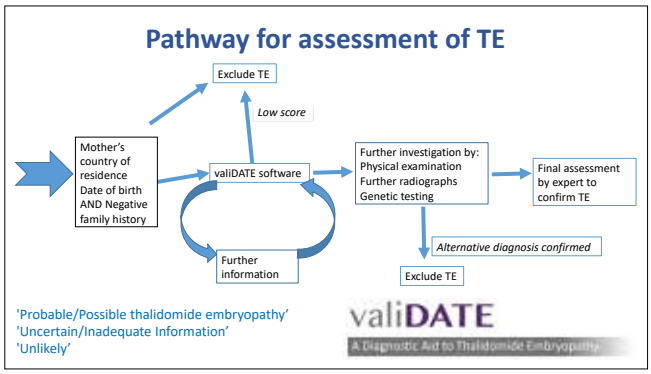


Fig. 44

So ValiDATE, instead of being called a diagnostic algorithm now, is termed a diagnostic aid to TE. It's not a standalone tool that you should use to say yes or no. This is important. It's an aid that's giving you a score of the likelihood an individual suffers from TE.

If after this, an alternative diagnosis is confirmed, then you've excluded TE; if not, then we suggest a final assessment by an expert in TE to confirm or refute the diagnosis.

So, we have also refined our categories I told you about earlier. When we went to the WHO, we had three: probable, possible, or unlikely. Probable and possible have now been merged.

I should touch "Uncertain", inadequate information and unlikely.

So, what have I told you about TE that you did not already know? Not a lot really. It still presents a diagnostic dilemma. The work that we've done has helped to characterize some of the clinical and radiological features. I talked a lot about radiology, but in DATE, we included all of the excellent work that was done by the Swedish teams and others looking at the non-radiological features of TE. Accurate phenotyping will lead us, we hope, to a better understanding of the underlying mechanism. But, most importantly, accurate phenotyping of contemporary cases will help us to really refine the features of TE. (Fig. 45)

So, what's the future? Well, ValiDATE is currently being refined. We have adjusted the scores and criteria in response to the Geneva Conference and some additional work we have done subsequently on cases and with others. We are refining and establishing the final scores within the algorithm, and the software is being beta-tested to assist us all in providing an accurate diagnosis, and to allow us to consider alternative genetic or teratogenic diagnoses for TE. (Fig. 46)

It will be available to everyone soon via an online interface. So any clinician only for clinicians I would point out, reviewing potential TE patients will be able to use this as an aid to the work that they are doing.

The Thalidomide Trust set up the ValiDATE Trust to make sure that this algorithm doesn't just stand still and does not evolve. It will be maintained and refined as new knowledge comes about. We want to continue to review and refine the algorithm, and we would welcome input from others who are experts in this area. (Fig. 47)

This is a picture of the St. George's team that went to Geneva back in 2014. I want to thank you all for listening to me today, and I would also like to say that The Thalidomide Trust would welcome any questions that you have about ValiDATE. This is the e-mail to use if you have any questions. (Fig. 48)

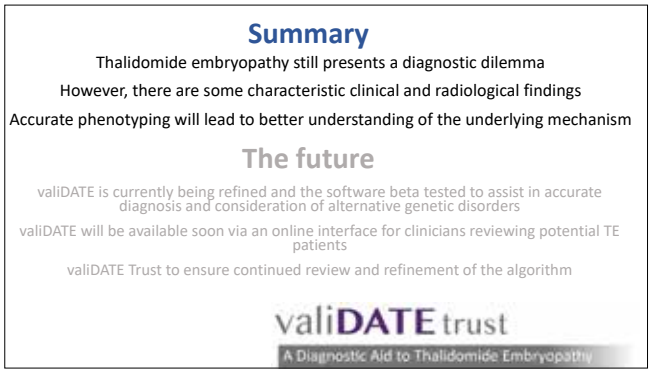


Fig. 45

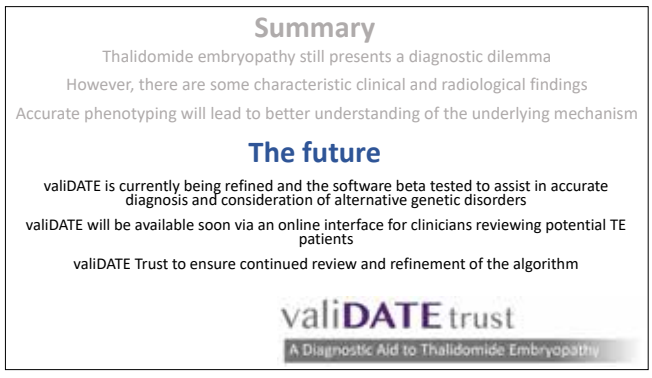


Fig. 46

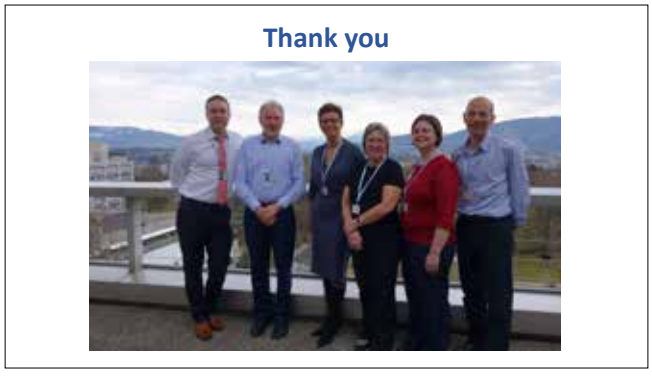


Fig. 47



Fig. 48

Q&A

Ryoji Kayamori: Thank you, Dr. Baple. We are now open to questions or comments.

Nobuhiko Haga: Thank you for your lecture. My name is Nobuhiko Haga from the University of Tokyo. I want to ask about pointed shoulder.

Emma Baple: Yes.

Nobuhiko Haga: You told me that the length of the clavicle is relatively long, so this leads to pointed shoulder. But I wonder if it comes from the true overgrowth of the clavicle or from the hyperplasia of the glenoid fossa or something like that.

Emma Baple: I think it's possibly a combination of both of those things. I think in the Brazilian case, you could really see that point that I am talking about.

Ryoji Kayamori: Any other questions?

Nobuhiko Haga: In the last slide, you told us that the ValiDATE system will be available for all clinicians. So does this mean that it is available also in Japan as long as we clinicians?

Emma Baple: Yes. It's not quite available yet. The software company we are working with is a company called Certus Technology. We need to make sure that the algorithm works the way it did in our software by putting in test cases again and again to make sure there are no glitches in the code. But it will be available online, and there will be a way that you can apply for a password to use it, put in the information, and get back a report for your patients that you are assessing. And that should be this year.

Nobuhiko Haga: Thank you very much.

Ryoji Kayamori: Any other questions or comments?

Klaus M. Peters: I think DATE is a very helpful tool to prove if a victim has a TE. But you say the next step is that one of the experts says it is TE or it isn't. That is still a problem we have to deal with in Germany at the moment. We have a lot of cases in Germany that could be TE. And one group of experts says "it is TE" and the other says "no, it's not", and then the problem is that the cases stay unclear.

Emma Baple: So, what, so, in terms of your question, how do you want to see that addressed? Because I believe that ValiDATE will help to address that.

Klaus M. Peters: Yes. To make the last step a bit easier because we have the Commission in Germany, and the Commission comes to a result and the result is not explained. It's said that it's unlikely and then it's finished.

We haven't used DATE up to now. But I think it will be helpful for us. But the last step will remain a problem because the German Commission normally says no to all new cases.

Emma Baple: Oh, I see. Okay. I can't help with that. But I hope by actually collecting these cases and using this algorithm, we will be able to show them that that position is not correct. So maybe it can help in that way.

Klaus M. Peters: Okay. Maybe I can help with cases.

Emma Baple: Absolutely, we would love that.

Ryoji Kayamori: Okay, next one.

Lavinia Schuler-Faccini: Thank you Emma for your brilliant conference, and this algorithm is going to be very helpful in Brazil. I think that most clinicians using the application are going to be from Brazil. However, my question is, do you have or are you planning to have a genetic panel, and do you use exome sequencing for the differential diagnosis?

Emma Baple: So, the answer to that is, I have together with Dr. Mansour and Professor Hall, put together a list of genetic tests that could be used. And we've done that for, other parts of the world have asked us to do that. I personally think that doing the different, looking at the differential diagnosis for the patient and testing them appropriately for those differential diagnoses is a better way forward. I say that because of the limitations of genetic technologies and the interpretation of the results that come out of genetic technologies.
We could do genome sequencing on all of these individuals, but we will, and I know from having done this for some patients with TE, find variants of uncertain significance in genes. And then you are stuck with, clinically, I do not feel the patient has this disorder, but they now have a variant of uncertain significance in a disorder that's said to have phenotypic overlap with TE, and you are in a worse position than you were to start with because you won't have relatives to test in order to help you to increase your certainty.

So I am in less in favor of that approach and more in favor of the approach we would typically take, which is clinical genetics, which is testing for the disorders that you think the patient may have. And that is really what I guess I feel we should be doing, and if we don't find that they have one of

those, then actually, we have to err on the side of this being TE, particularly in patients who have these characteristic abnormalities that are not found or very rarely found outside of TE.

Lavinia Schuler-Faccini: Thank you very much. I totally agree.

Emma Baple: That's good. That's really good.

Ryoji Kayamori: Next, please.

Christina Ding-Greiner: Thank you for your presentation. It was very interesting. What do you think about asymmetries? I saw in your pictures that the children you showed us were not typically symmetric. And in all the old papers, a certain amount of asymmetry is described. But our foundation states that if a person is asymmetric, there is no possibility of being thalidomide-affected. I can't believe that because if you look at non-thalidomide-affected people, we all are asymmetric.

Emma Baple: I am sorry, I didn't emphasize that in my talk. You do see some asymmetry in TE. What I do not believe you see is isolated unilateral abnormalities. I think that, having reviewed quite a lot of radiology now, what we think is that people misinterpreted the findings, and you do see abnormalities on the other side. They may be less extreme, but you do see some asymmetry.

Christina Ding-Greiner: Okay. Thank you.

Female Participant (Unknown Speaker): Thank you very much. It was really interesting to hear about what you have been doing. About asymmetry, is it anything—can you say if it's asymmetrical malformations on the upper limbs and lower limbs? Because you were saying that the most cases you found had upper limb malformations, which was, if I understood you correctly, a little bit, I mean when, I mean me and my supervisors looked at the all thalidomiders, and in 31, we actually found just five proximal femoral deficiencies, and some of the cases were unilateral.
I mean, we found some other malformations on the other side, but it wasn't PFFD (proximal femoral focal deficiency). However, for the upper extremity, it was more symmetrical, although it wasn't exactly the same. So what, I mean I am getting a little bit confused about what we've been looking at in those 31.

Emma Baple: So I think if you looked, if I've understood, I want to make sure I've understood your question correctly, but if I've understood your question correctly, you will see when I showed that table, I don't know if I can go back to it, can I? I don't know if I can. You will see when you look at the lower limb, I showed you the phocomelia and amelia, we were sure we saw that there was more asymmetry in the lower limbs, exactly as you've said. That was from the German papers.
Sorry, I can't – I haven't got the numbers at hand. What was very interesting about the review of all of the cases that we did was the temporal relationship between the abnormalities. So, I think that's what you are asking, isn't it?

Female Participant (Unknown Speaker): Yes.

Emma Baple: Yes, yes, good.

Ryoji Kayamori: Thank you, Emma. So, we have 1 minute to go. Symmetry or asymmetry, that has been a long-debated point. So, being symmetry with certain variations, that is suspected TE. In Germany, what is the most contentious is symmetric. So, one side, normal or healthy, the other side abnormal, that is not acceptable. That has been extensively debated in Germany. This is a question I would like to ask Dr. Baple. Scores. So 73 is a high score, that is why the diagnosis is TE. And that particular part we are not sure. Probable, possible, unlikely—unfortunately, we do not have enough time to understand the criteria. So diagnostic aid or algorithm, features about a diagnostic aid or algorithm, which is better? Your article title is "Diagnostic Algorithm for TE", but this time you mentioned this as being a diagnostic aid for thalidomide. Which is better?

Emma Baple: Well, I suppose what we were trying to get at with aid as opposed to algorithm was to say that it's an aid. It doesn't mean that you shouldn't use your brain or clinical acumen.

Ryoji Kayamori: Okay, thank you. Thank you very much.

Mechanisms of Thalidomide Teratogenicity

Hiroshi Handa

Department of Nanoparticle Translational Research, Tokyo Medical University, Tokyo, Japan

Nobuhiko Haga (Moderator)

Now, I would like to proceed to the last lecture of the first day of this symposium. The presenter is Professor Hiroshi Handa. He is now working in the Department of Nanoparticle Translational Research at the Tokyo Medical University. He graduated from Keio University, Faculty of Medicine, in 1972, and he obtained his PhD 4 years later. Then, he worked at The Tokyo University Institute of Medical Sciences, and then went to the States to study at the National Institute of Health and Massachusetts Institute of Technology. And then, he came back to Japan and worked at The University of Tokyo, Tokyo Institute of Technology, and the National Institute of Genetics.
So, the title of this paper is "Mechanisms of Thalidomide Teratogenicity". So, please start your lecture.

Thank you, Professor Haga, for your kind introduction. I am happy to have this opportunity to share our interdisciplinary research with you. I would like to talk to you about our work on the mechanisms of thalidomide embryopathy (TE). (Fig. 1)

Here is the content on my talk today. I'll talk about the five topics shown here. (Fig. 2)

So first, I will give you a little background of thalidomide, which is the same as Emma, the former presenter. Thalidomide, its structure shown here, was developed and commercialized as a sedative in the late 1950s. However, thalidomide was completely withdrawn from the market in the early 1960s, shortly after its negative effects on newborns became clear. About 10,000 affected children were born worldwide. On the other hand, thalidomide was later found to be an effective treatment for leprosy and multiple myeloma, and was returned to the market in less than a half century. Thalidomide is now approved for use in patients with multiple myeloma. However, little was still known about its mechanisms of action regarding both its beneficial effects and side effects. (Fig. 3)

Here, I show a timetable of the period in which embryos are sensitive to thalidomide. When pregnant mothers take thalidomide during the days after fertilization, it causes multiple developmental anomalies in their children, such as a shortening or complete lack of the limbs, as well as malformation of the ears and eyes. This indicated that TE develops in time- and site-specific manners, implying multiple actions. (Fig. 4)

This table shows the rate of site-specific anomalies caused by thalidomide. Thalidomide most frequently caused developmental defects of the limbs and ears among a wide range

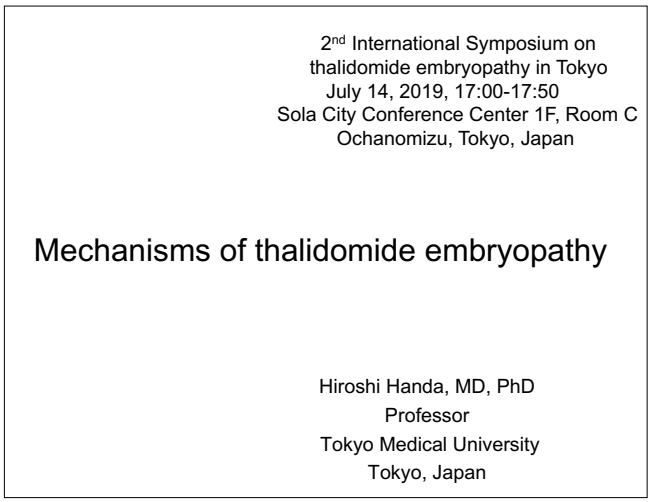


Fig. 1

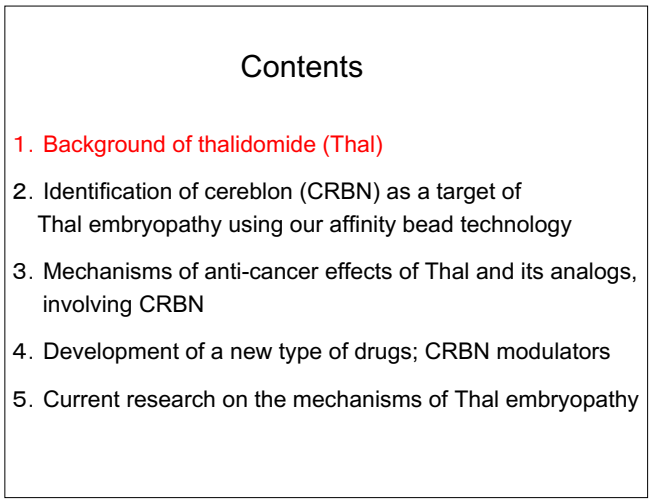


Fig. 2

of anomalies. (Fig. 5)

However, the pathogenic mechanism remained unknown, although various hypotheses, shown here, have been proposed. Disruption of angiogenesis was most commonly supported. But even this hypothesis was not firmly established because the target of thalidomide responsible for embryopathy remained unidentified. (Fig. 6)

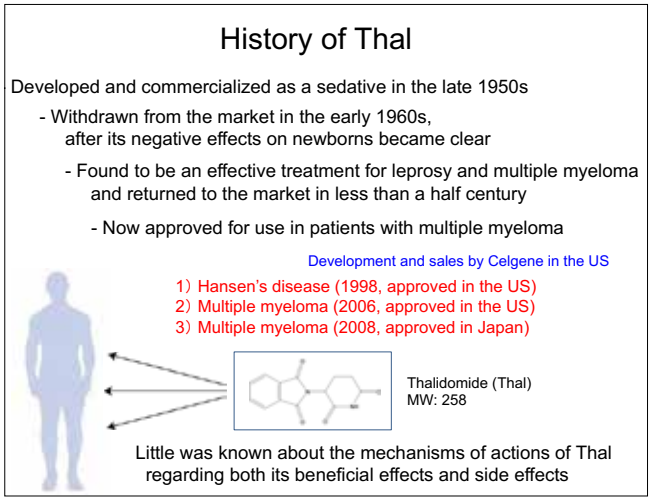


Fig. 3

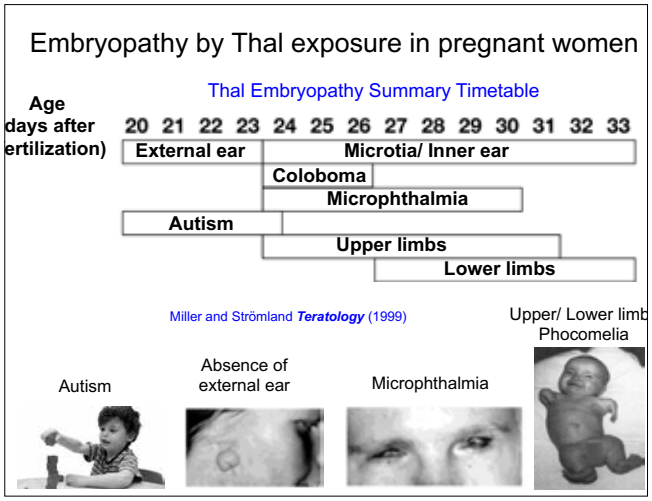


Fig. 4

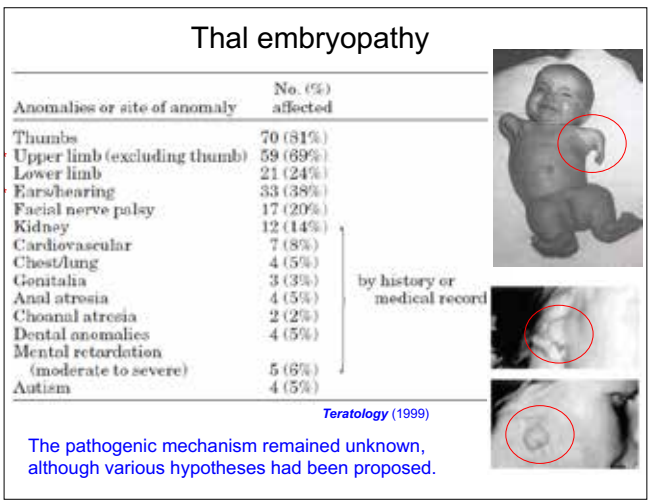


Fig. 5

The target in this case is expected to be a protein that directly and specifically binds to thalidomide with the highest level of binding affinity, resulting in TE.

And now, I'll talk about the identification of cereblon, or CRBN, as a target of TE using our affinity bead technology. (Fig. 7)

To isolate drug-binding proteins directly from protein libraries, we previously developed two types of nano-sized beads as novel matrices for affinity chromatography. (Fig. 8)

First, we developed double-layered latex beads called SG beads, which are composed of styrene-GMA copolymers at the core and poly-GMA at the surface. Then, to enable the automatic isolation of drug-binding proteins, we developed magnetic beads called FG beads, which have magnetite nanocrystals in the core of the SG beads. These beads, now often called Handa beads, have several advantages, including having large numbers of reactive groups, high dispersibility, extremely low nonspecific protein-binding, and resistance to organic solvents. These characteristics greatly increase the recovery rate and purity of the isolated drug-binding proteins.

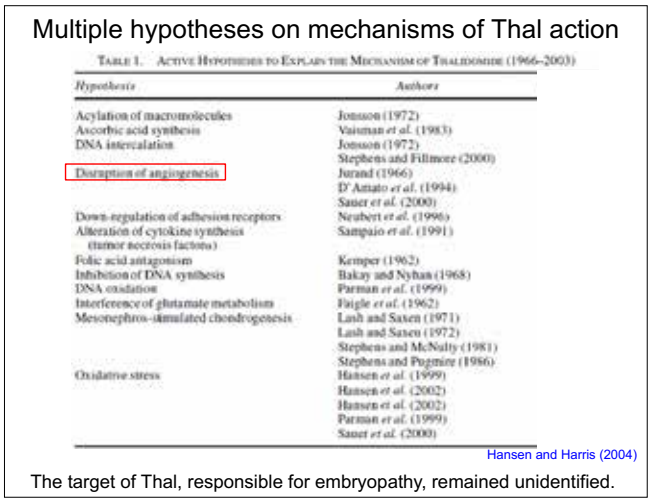


Fig. 6

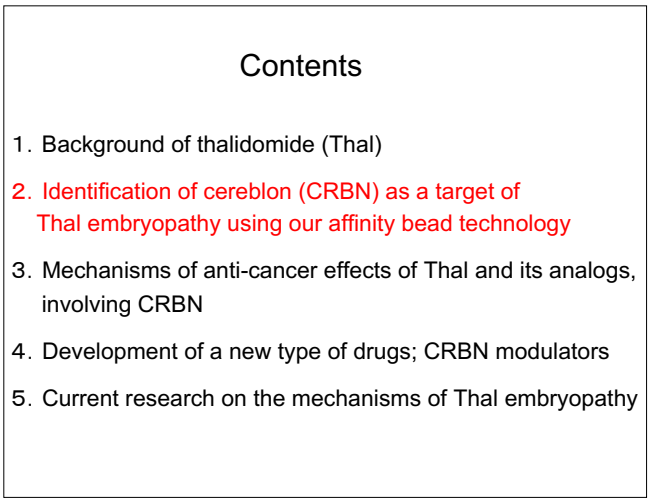


Fig. 7

As shown here, one-step affinity isolation is performed by mixing drug-fixed FG beads with cell lysates for more than 4 hours, and then washing the beads several times by magnetic separation. Then, drug-binding proteins, including targets, are eluted by adding excess drug or surfactant. A single 1.5-mL centrifuge tube is sufficient for the whole process. (Fig. 9)

This bead technology has further advantages. First, the binding specificity of the target to the drug can be assessed using a competitive inhibition assay or a competitive drug elution assay. I will introduce some practical examples of these assays later. Second, binding mode and binding affinity can be roughly estimated by altering the binding, washing, and eluting conditions. Therefore, a potential target that is involved in drug actions can be identified from the acquired information.

Here, I will show an example of the advantages of our bead technology. Alendronate, a drug for osteoporosis, was fixed to the beads through its amino group and mixed with cell lysates for 0.5, 1, 2, 3, and 4 hours, at which time, the proteins binding to the drug-fixed beads were eluted by detergent treatment and analyzed by SDS-PAGE and silver staining, as shown here. (Fig. 10)

The amounts of bound proteins varied with time, and were divided into three groups, namely those showing increased binding, decreased binding, and no change. Competitive inhibition assays showed that the group of proteins showing increased binding with time was selectively competed by the addition of excess alendronate, indicating that they are specific alendronate-binding proteins.

These results indicated that specific drug-binding proteins become concentrated with time, and that our simple bead technology with easy operation is useful for isolating specific drug-binding proteins directly from protein libraries. By the way, these isolated proteins were identified as dynamin 2, which binds directly to alendronate, and its associated protein, sorting nexin 9.

Here is a list of various ligands, including pharmaceuticals, biomolecules, and toxic chemicals, for which we have identified targets using our bead technology and published our findings, as shown here. As you can see, the list includes thalidomide. And now, I'll talk about our identification of

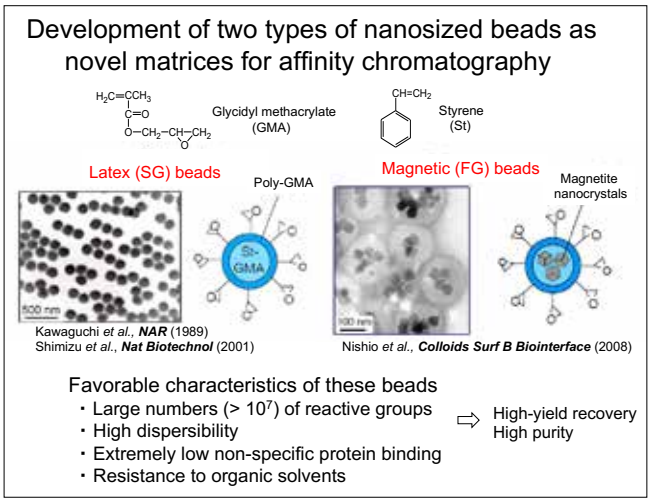


Fig. 8

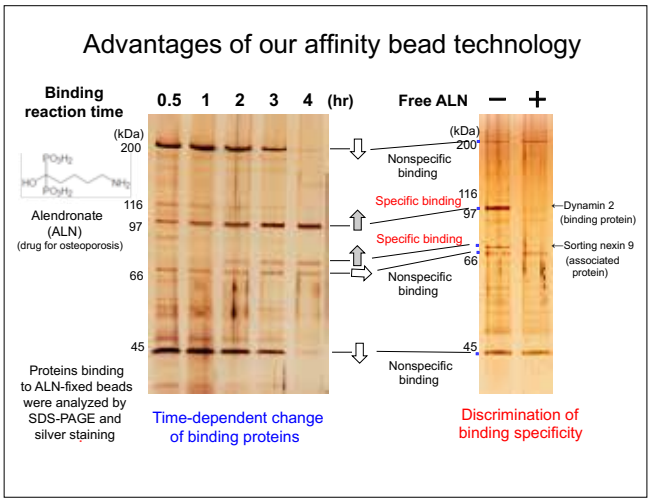


Fig. 10

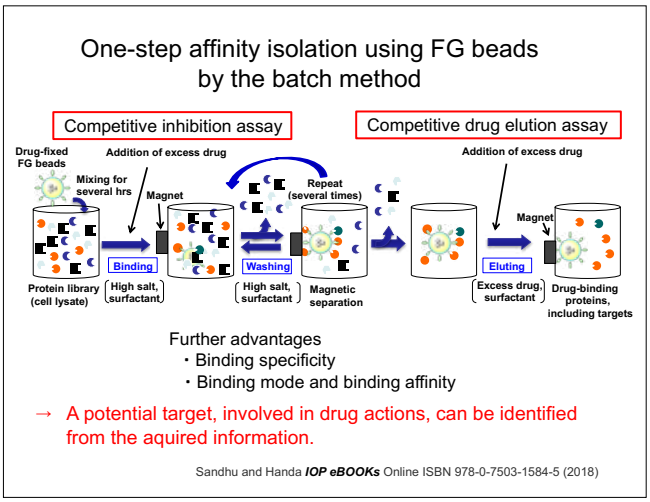


Fig. 9

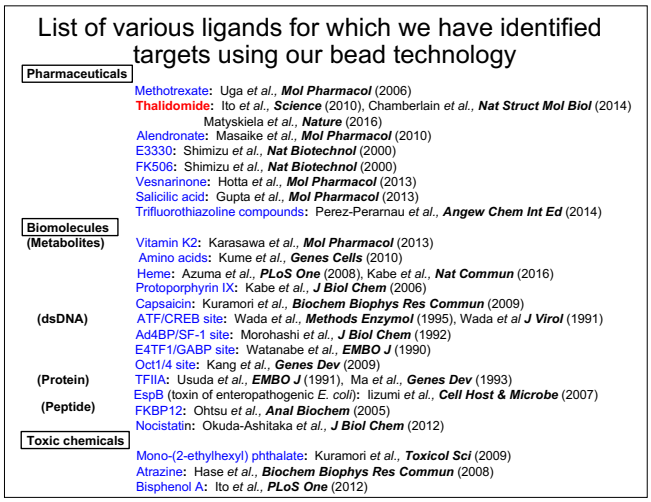


Fig. 11

the target of thalidomide.(Fig. 11)

To isolate and identify the molecular targets of thalidomide, we fixed a carboxylated derivative of thalidomide to our beads and then treated the beads with acetic anhydride to mask unreacted amino groups via acetylation and deduce nonspecific protein-binding caused by ionic interactions. (Fig. 12)

Then, the beads were mixed with cell lysates for several hours. After washing, the bound proteins were eluted by adding excess thalidomide, which is known as a competitive drug elution assay. (Fig. 13)

We isolated two proteins that selectively bind to thalidomide, which were competed by adding excess thalidomide to the binding reaction, which is known as a competitive inhibition assay. Then, we identified these proteins as damage-specific DNA-binding protein 1, called DDB1 for short, and cereblon by mass spec analysis. Both proteins were confirmed by immunoblotting using their specific antibodies.

Using the recombinant proteins and our affinity bead technology, we found that thalidomide directly binds to cereblon, but not to DDB1. (Fig. 14)

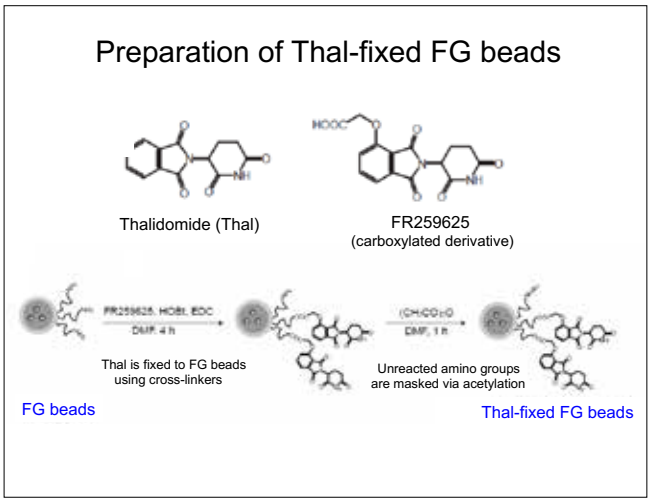


Fig. 12

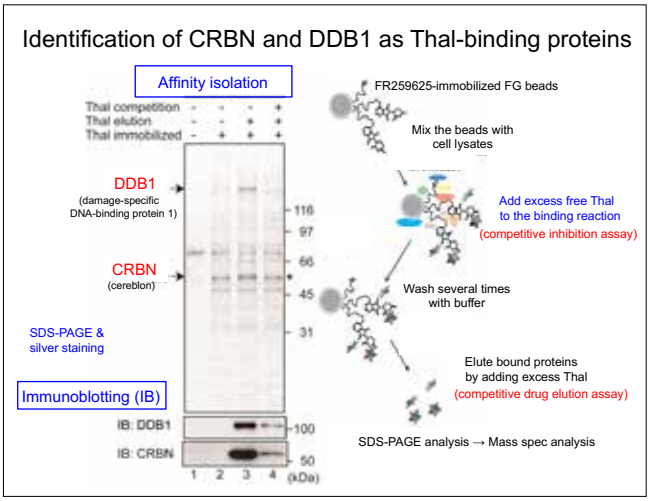


Fig. 13

We also found that cereblon is part of a ubiquitin ligase complex. Co-immunoprecipitation experiments showed that cereblon interacts with DDB1, CUL4, and ROC1. It is widely known that DDB1, CUL4, ROC1, and an established substrate receptor, such as DDB2, CSA, etc., form an E3 ubiquitin ligase complex, which is involved in the ubiquitination and degradation of substrate proteins. The question here was whether cereblon functions as a substrate receptor, and if so, whether it would compete with DDB2 for binding to DDB1. (Fig. 15)

As shown here, the amount of DDB1 co-precipitated with cereblon was gradually reduced as the amount of DDB2 was increased, indicating that DDB2 competes with cereblon for binding to DDB1. This suggested that cereblon works as a substrate receptor.

As the previously identified substrate receptors were known to undergo auto-ubiquitination, we analyzed cereblon ubiquitination in cells treated with the proteasome inhibitor MG132. As shown here, cereblon was found to be ubiquitinated, and its ubiquitination was sensitive to thalidomide. (Fig. 16)

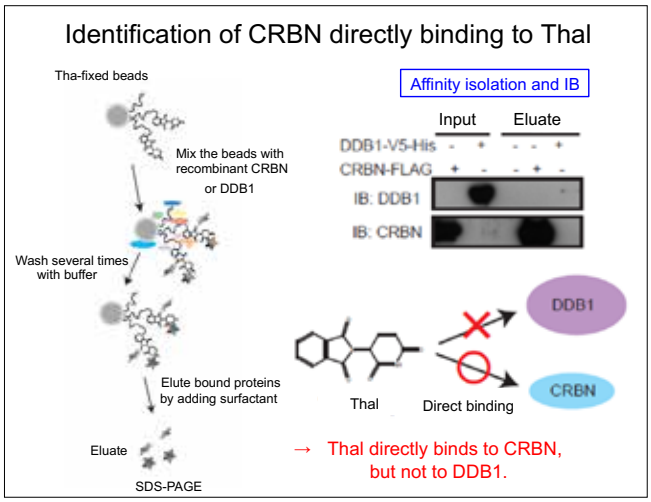


Fig. 14

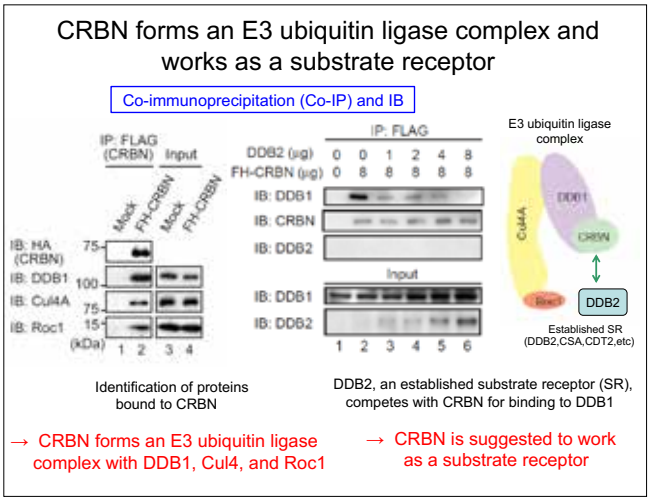


Fig. 15

We also examined the expression of thalidomide-binding cereblon and DDB1 in various cells using our affinity bead technology. We found that cereblon and DDB1 are ubiquitously expressed in all cells that were tested. Unexpectedly, mouse cereblon also binds to thalidomide, although rodents do not develop TE. (Fig. 17)

Next, we investigated the possible association between cereblon and TE in zebrafish, which has several advantages as an experimental animal, as shown here. Zebrafish cereblon shared 70% homology with human cereblon. The first thing we did was to make sure that zebrafish has a human cereblon homolog that can bind to thalidomide and interact with human DDB1. As the effect of thalidomide on zebrafish development was not yet known, fertilized zebrafish eggs were allowed to develop in media containing thalidomide. (Fig. 18)

When treated with thalidomide, there were no gross morphological changes except for in the pectoral fin, which was significantly smaller than that of control embryos. The fin defects were clearly detected by alcian blue staining of cartilage. We also found that the development of the otic vesicle, which is the zebrafish equivalent of the ear, was significantly affected. These results indicated that thalidomide causes similar developmental anomalies in zebrafish and in humans. (Fig. 19)

Our next question was how can we definitively prove that cereblon is the true target of thalidomide involved in embryopathy? If TE is suppressed by a cereblon mutant that does not bind to thalidomide, but is otherwise functional, we can confirm that cereblon is the true target of thalidomide, leading to embryopathy. Thus, we designed cereblon mutants that do not bind to thalidomide. (Fig. 20)

We first identified the thalidomide-binding site as the C-terminal region of cereblon. Then, we found that that the tyrosine 384 and tryptophan 386 of cereblon are important for binding to thalidomide, and the double-point mutant does not bind to thalidomide. (Fig. 21)

The double-point mutant formed the E3 ubiquitin ligase complex with DDB1, CUL4, and ROC1, and was auto-ubiquitinated. The mutant was co-localized with wild-type cereblon. As expected, the ubiquitination of the double-point mutant was not affected by thalidomide. So we successfully

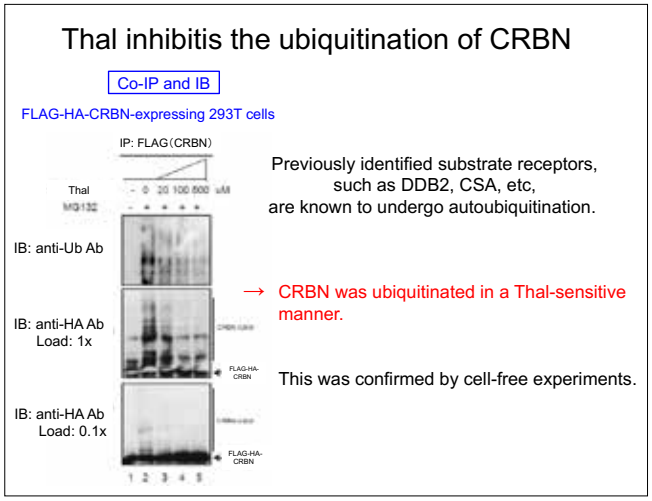


Fig. 16

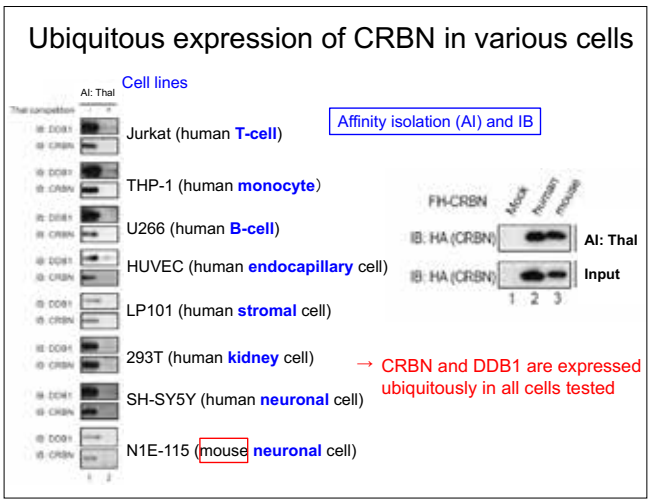


Fig. 17

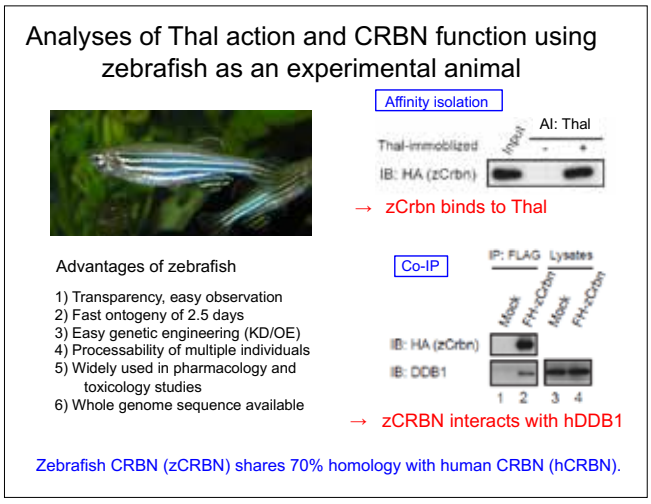


Fig. 18

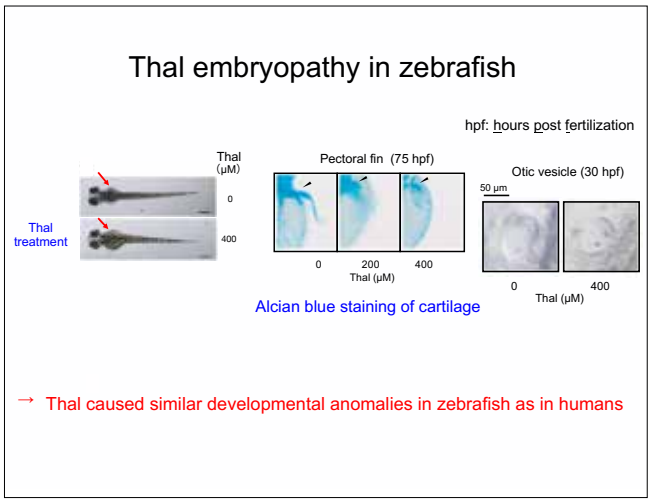


Fig. 19

identified a double-point mutant of cereblon that does not bind to thalidomide, but is otherwise functional.

I show here that the expression of our double-point mutant suppresses thalidomide-induced embryopathy in zebrafish. Embryos expressing wild-type cereblon were still sensitive to thalidomide as much as control embryos, but embryos expressing the double-point mutant were resistant to thalidomide. Essentially, the same results were obtained when analyzing the otic vesicles. We therefore confirmed that cereblon is a bona fide target of TE. (Fig. 22)

Next, we analyzed the potential involvement of the key signaling molecules such as FGF8 and Sonic hedgehog in TE. FGF8 is essential for pectoral fin formation along the proximal–distal axis, and is expressed in the apical ectodermal ridge, called AER for short. Sonic hedgehog is crucial for the pectoral fin development along the anterior–posterior axis, and is expressed in the zone of polarizing activity, called ZPA. (Fig. 23)

Thalidomide significantly reduced FGF8 expression, as shown here, but had little effect on Sonic hedgehog expression. In addition, the expression of the double-point mutant suppressed the thalidomide-induced downregulation of FGF8. These results hence indicated that FGF8 is a main downstream factor of cereblon and thalidomide.

We also investigated the possible connection between cereblon and TE in chicks, which had been routinely used as an animal model for TE. We first confirmed that chick cereblon can also bind to thalidomide and interact with human DDB1. Next, we administered thalidomide to this region of the egg, which strongly inhibits formation of the forelimbs only at the site of administration. This result indicated an important issue that thalidomide itself, rather than its active metabolites in the liver, is a causative agent of embryopathy, because the opposite forelimb is not affected at all. (Fig. 24)

Expression of the double-point mutant of cereblon significantly inhibited thalidomide-induced embryopathy and the downregulation of FGF8/FGF10 expression in chicks. Therefore, our findings in zebrafish were validated in chicks. (Fig. 25)

It had been considered that thalidomide-induced disruption of angiogenesis is a major cause of the developmental defects of pectoral fins. To address this issue, we analyzed TE using fli1:EGFP transgenic zebrafish that express a GFP

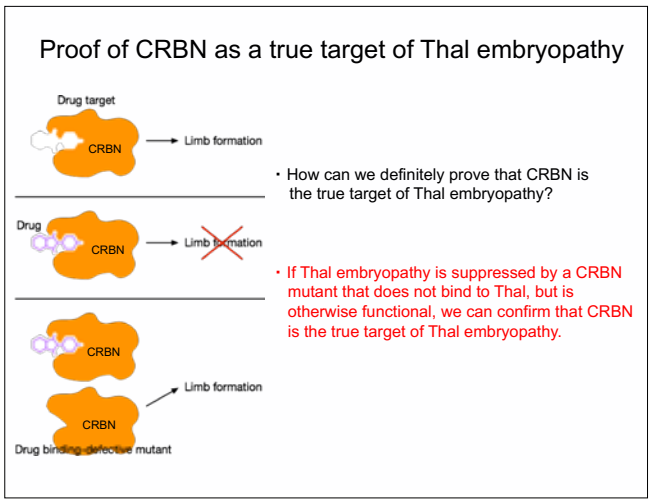


Fig. 20

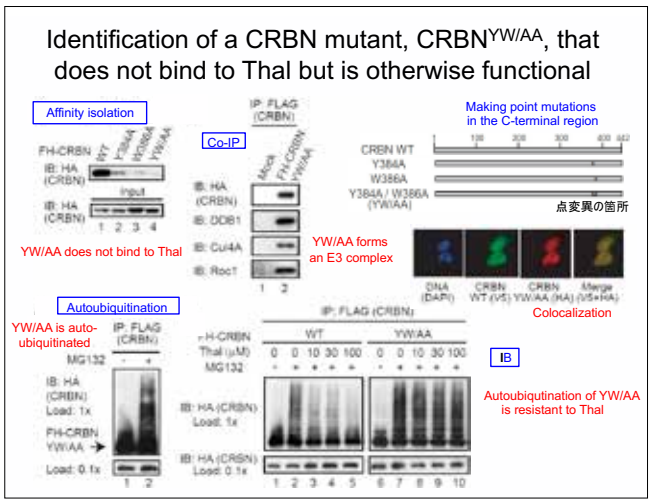


Fig. 21

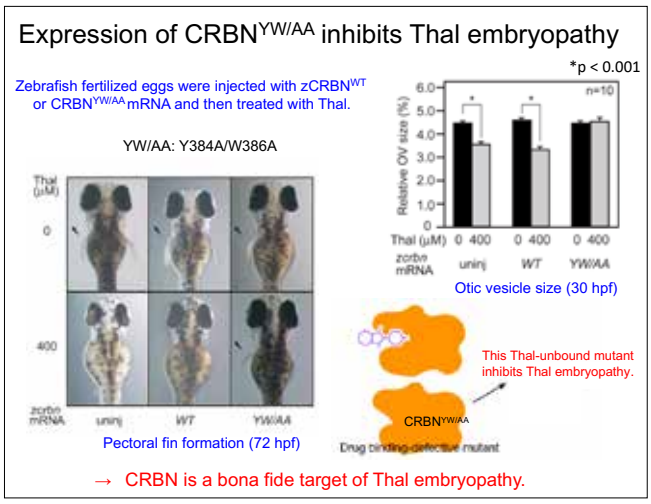


Fig. 22

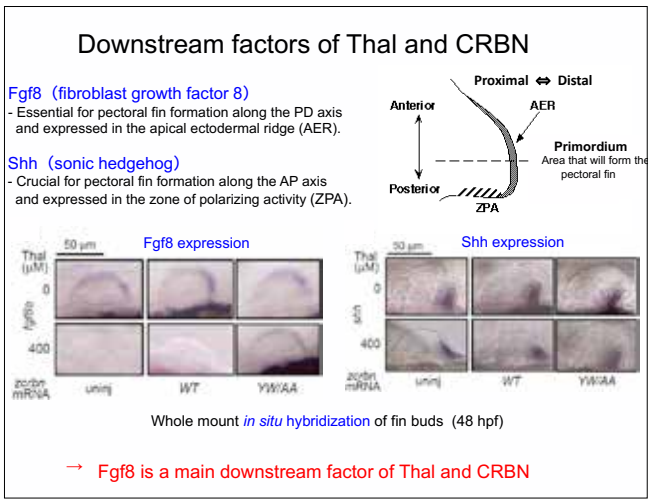


Fig. 23

fusion protein in the marginal blood vessels to visualize angiogenesis. (Fig. 26)

At 52 hours post-fertilization, both angiogenesis and pectoral fin formation were inhibited by thalidomide treatment. But at 48 hours post-fertilization, the marginal blood vessels were not yet formed, whereas pectoral fin development was clearly inhibited. These results showed that the thalidomide-induced deformity of pectoral fins occurs prior to angiogenesis.

Here is a summary of our major findings regarding cereblon up to this point, which were published in Science. We identified cereblon as a thalidomide-binding protein using our affinity bead technology. Cereblon forms an E3 ubiquitin ligase complex with DDB1, Cul4, and Roc1, works as its substrate receptor, and contributes to the normal development of the limbs and otic vesicles in zebrafish and chick models. Cereblon is a target of TE, and thalidomide exerts its teratogenic effects by binding to cereblon and altering cereblon E3 ubiquitin ligase activity. (Fig. 27)

Thus, our results indicated that thalidomide affects cereblon E3 ubiquitin ligase activity by binding to cereblon, suggesting two possible mechanisms of thalidomide action. One is that thalidomide blocks the binding of a natural substrate to cereblon. The other is that thalidomide alters the substrate specificity of cereblon. I will discuss a possible answer to this later in my talk. (Fig. 28)

Now, I will talk about the involvement of cereblon in anticancer effects of thalidomide and its analogs, and the mechanisms of their anticancer effects via cereblon. (Fig. 29)

In recent years, second-generation thalidomide analogs, including lenalidomide and pomalidomide, have been developed and commercialized. Lenalidomide and pomalidomide are much more effective than thalidomide against multiple myeloma. Lenalidomide is also approved as a treatment for MDS 5q minus syndrome and T-cell leukemia/lymphoma. (Fig. 30)

In addition to the activity of inhibition of multiple myeloma cell growth, these three drugs have immunomodulatory activity, that is, T-cell activation activity. Therefore, they are called immunomodulatory drugs, or IMiDs for short. We

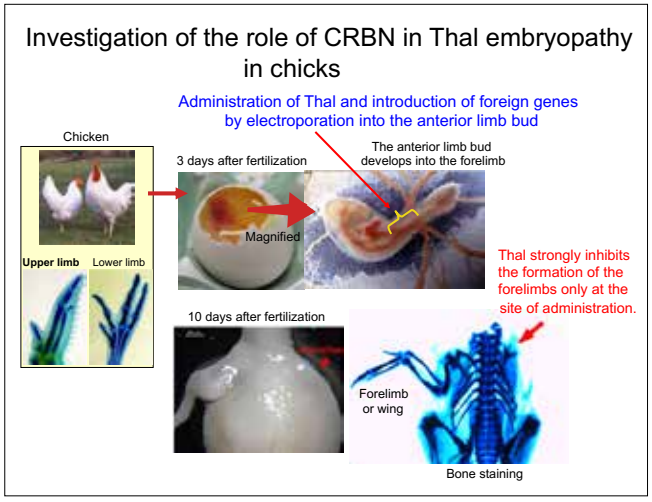


Fig. 24

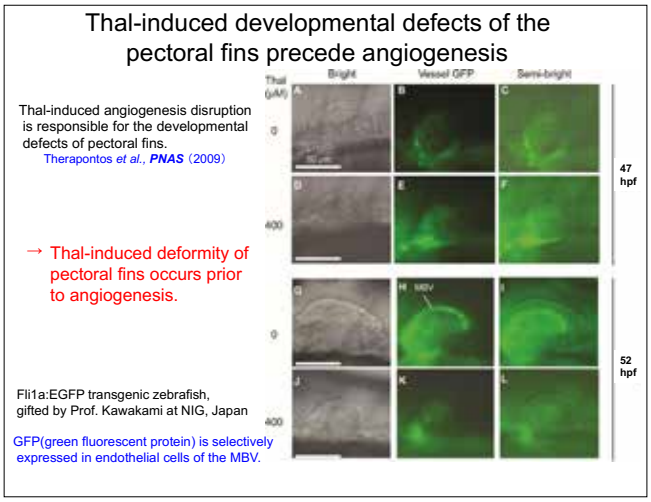


Fig. 26

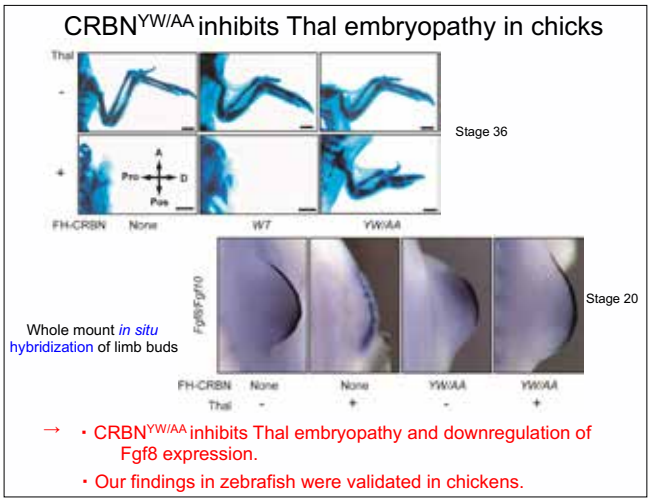


Fig. 25

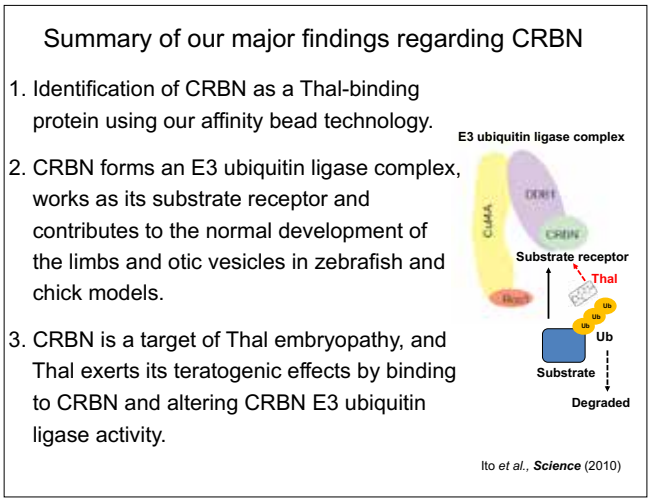


Fig. 27

hence tried to demonstrate whether cereblon is involved in the anticancer effects of IMiDs in collaboration with Celgene, which is the pharmaceutical company that returned thalidomide to the market and developed and commercialized second-generation thalidomide analogs.

To answer this question, we first investigated the association between cereblon and the anticancer activities of IMiDs. We used multiple myeloma-derived OPM2 cells, which are sensitive to IMiDs, as shown here. However, cereblon-knockdown resulted in the resistance of the cells to IMiDs. Then, we established lenalidomide-resistant cells by culturing multiple myeloma-derived DF15 cells in the presence of lenalidomide for a long time, which resulted in the cells becoming resistant to lenalidomide and pomalidomide. In the resistant cells, cereblon expression was clearly decreased. These results indicated that cereblon is involved in the anticancer activity of IMiDs. A research group at the Mayo Clinic also reported the same results. (Fig. 31)

Previous studies and our results showed that when OPM2 cells are treated with IMiDs, IRF-4, and c-myc, which reciprocally regulate each other and are essential for the growth and survival of multiple myeloma cells, they are usually downregulated, but p21, which inhibits cell cycle progression, is upregulated, though not in all cell lines. However, these IMiD-induced gene expression changes were not observed upon the silencing of cereblon, indicating that IMiDs downregulate the expression of IRF-4 and c-myc via cereblon, leading to the growth inhibition of multiple myeloma cells. (Fig. 32)

We then elucidated the 3D structure of the IMiD-human cereblon complex by X-ray crystallographic analysis. We found that the glutarimide ring common to IMiDs is inserted into a triple tryptophan hole in the C-terminal region of cereblon. (Fig. 33)

This slide shows the novel substrates identified that bind to the cereblon–IMiD complex. Novel substrates of cereblon, common to IMiDs, were identified as Aiolos and Ikaros, which are zinc finger transcription factors involved in lymphoid development and differentiation. The binding of IMiDs to cereblon recruits Aiolos and Ikaros as novel substrates

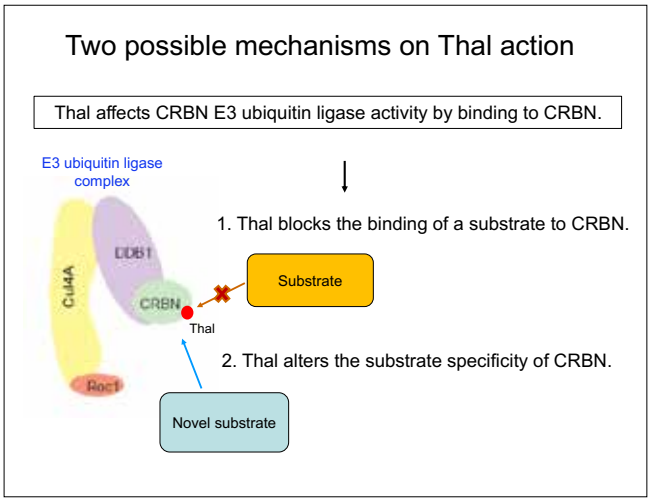


Fig. 28

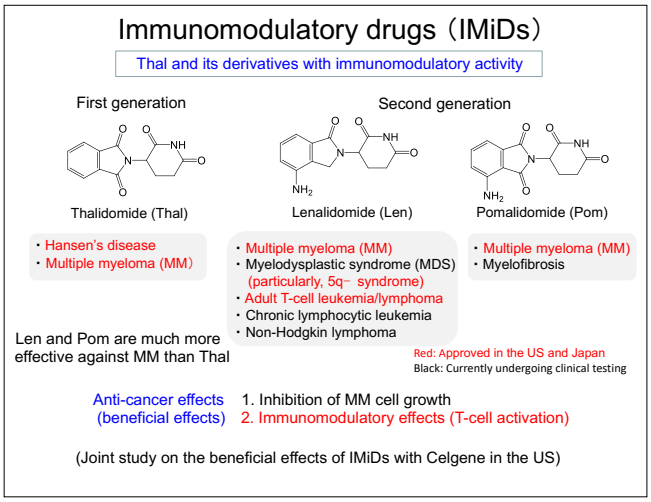


Fig. 30

Contents

1. Background of thalidomide (Thal)
2. Identification of cereblon (CRBN) as a target of Thal embryopathy using our affinity bead technology
3. Mechanisms of anti-cancer effects of Thal and its analogs, involving CRBN
4. Development of a new type of drugs; CRBN modulators
5. Current research on the mechanisms of Thal embryopathy

Fig. 29

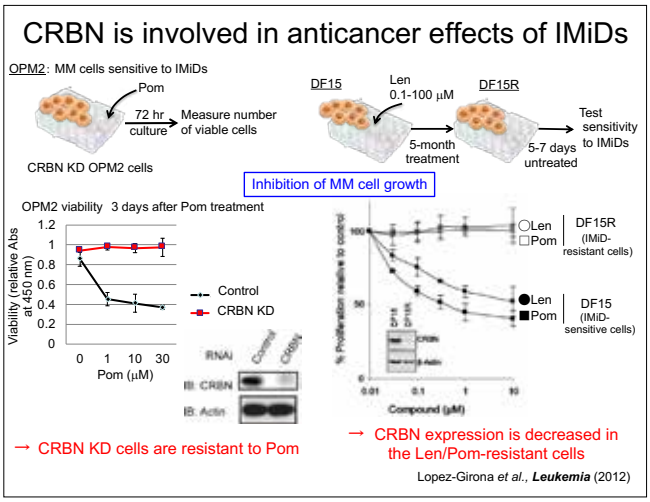


Fig. 31

and induces their ubiquitination and degradation, leading to a therapeutic effect against multiple myeloma. (Fig. 34)

In addition, a novel lenalidomide-specific substrate of cereblon was also identified as the enzyme casein kinase 1A1 or CK1a. The binding of lenalidomide to cereblon induces CK1a ubiquitination and degradation, leading to an effective treatment for 5q minus syndrome.

Now, I will talk about the optical isomers of thalidomide, which have an asymmetric carbon, named S-thalidomide and R-thalidomide. In 1979, Blaske proposed the hypothesis that S-thalidomide and R-thalidomide are involved in the side effects and main effects of thalidomide, respectively. As we identified cereblon as a target of both the main effects and side effects of thalidomide, we were in the best position to prove this hypothesis scientifically, although the main effects are not sedative effects, but anticancer effects. (Fig. 35)

Thus, we analyzed whether the optical isomers of thalidomide interact differently with cereblon and have different functions, in collaboration with Professor Hakoshima at the NARA Institute of Science and Technology and Professor Shibata at the Nagoya Institute of Technology.

I will not go into the details of our experimental data. I will simply talk about our conclusion. (Fig. 36)

Our biochemical and 3D structural analyses indicated that S-thalidomide has a much higher affinity for cereblon than does R-thalidomide, and that S-thalidomide is mainly involved in both the anticancer and teratogenic effects of thalidomide. Furthermore, thalidomide is easily racemized under physiological conditions. Therefore, S-thalidomide preferentially binds to cereblon, and then, the remaining R-thalidomide will be readily racemized, leading to a supply of S-thalidomide. So, we concluded that the optical isomers of thalidomide are not a crucial issue for its drug action.

Next, I will talk about the development of a new type of drug, cereblon modulators. (Fig. 37)

Here's a summary of the development of cereblon modulators. Second-generation thalidomide analogs have been developed and used for the treatment of multiple myeloma and 5q minus syndrome. More recently, third-generation thalidomide analogs have been developed. These analogs,

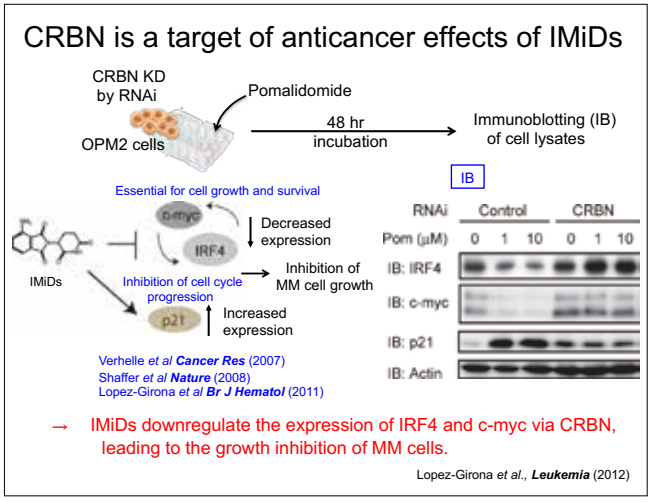


Fig. 32

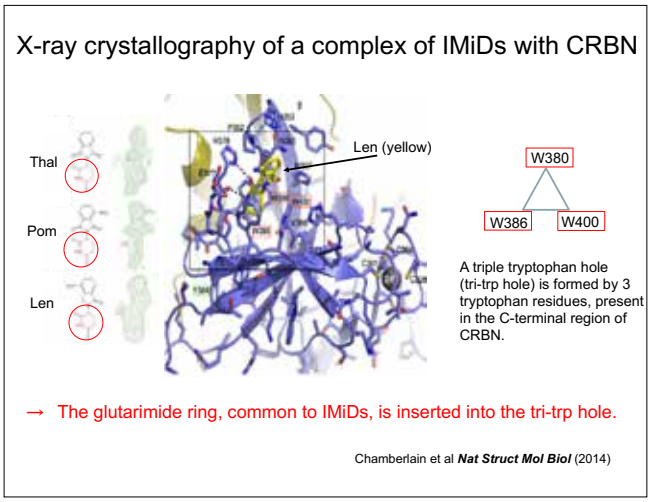


Fig. 33

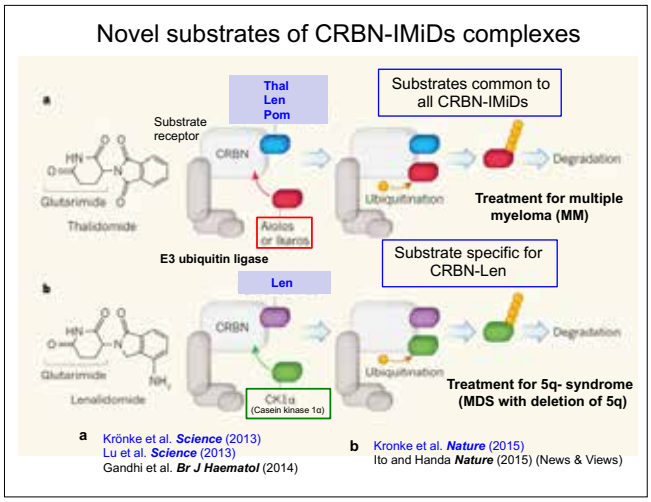


Fig. 34

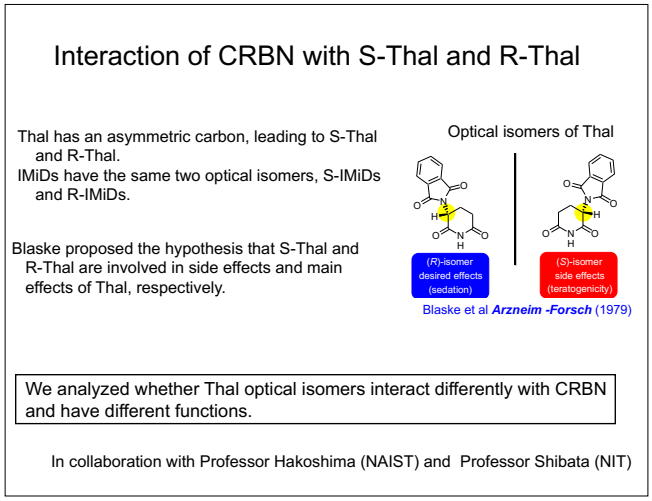


Fig. 35

CC-122 and CC-885, were found to exert favorable therapeutic effects against diffused large B-cell lymphoma and acute myeloid leukemia, called AML for short. (Fig. 38)

For CC-122, the neosubstrate, which is what these types of substrates are called instead of substrates, is not yet known, but the key neosubstrate of CC-885 was identified as GSPT1, a regulator of translational termination. As these analogs do not fit the category of IMiDs, thalidomide and its analogs are now collectively called "cereblon modulators".

We reported the 3D structure of the complex of cereblon, CC-885 and GSPT1, which was published in Nature.

I will just talk about our results on CC-885. CC-885, which has the structure shown here, exerts anticancer effects on various types of cancers, and is particularly effective against AML. Here, I show that the leukemic cells of AML patients are highly sensitive to CC-885 compared with normal lymphoid cells. I also show here that knockout of cereblon abolishes the anticancer activity of CC-885, indicating that CC-885 exerts anticancer effects via cereblon. (Fig. 39)

We identified GSPT1 as a novel neosubstrate of cereblon in the presence of CC-885 by co-immunoprecipitation experiments, as shown here. CC-885 induced the cereblon-dependent degradation of GSPT1. (Fig. 40)

We found that glycine 575 of human GSPT1, which is not present in yeast GSPT1, is essential for the CC-885-induced degradation of GSPT1, because the G575N mutant is resistant to CC-885. AML cell lines expressing this substitution mutant are resistant to CC-885, indicating that GSPT1 is a novel neosubstrate of cereblon and involved in the anticancer effects of CC-885.

Here, I show images of GSPT1 binding to the CC-885/cereblon/DDB1 complex, taken by cryo-electron microscopy. X-ray crystallographic analyses showed that CC-885 binds to cereblon and works as a molecular glue that attaches GSPT1 to cereblon. (Fig. 41)

We found various similarities between the actions of thalidomide and its analogs. Thalidomide and its subsequently developed analogs, which collectively are called cereblon modulators, bind to cereblon, recruit their unique neosubstrate, induce ubiquitination and degradation of the neosub-

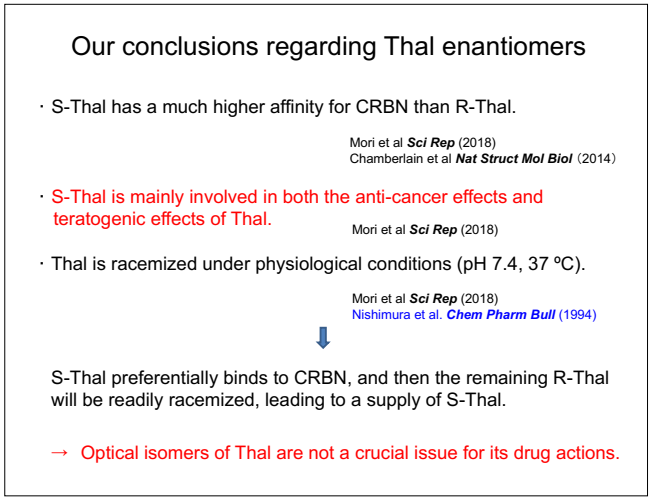


Fig. 36

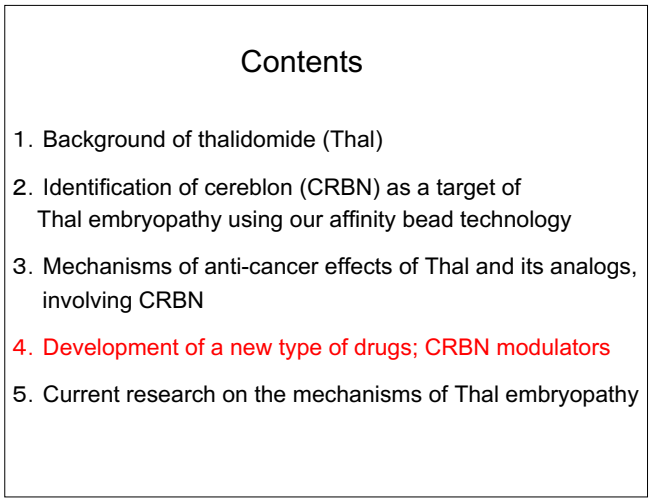


Fig. 37

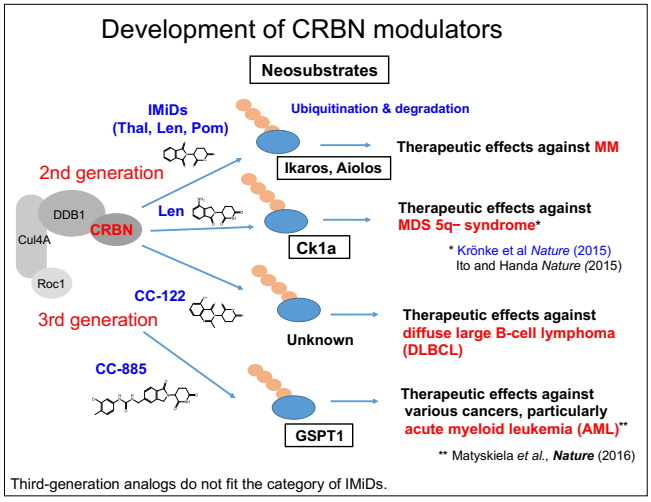


Fig. 38

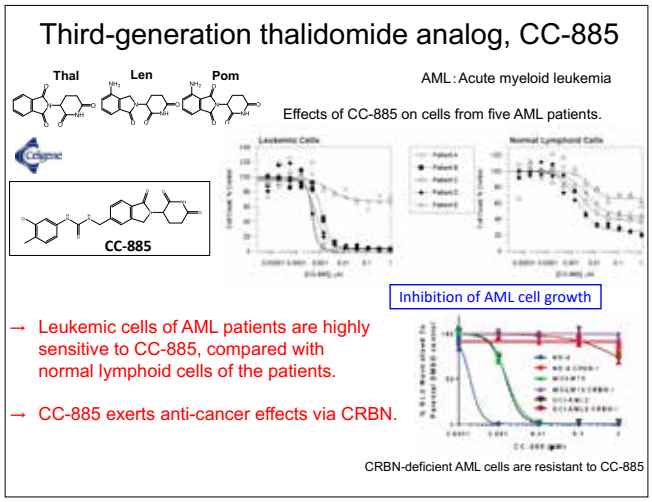


Fig. 39

strate, and exert anticancer effects. (Fig. 42)

I presented two possible mechanisms on the actions of thalidomide a while ago. And now, it is reasonable to predict that thalidomide alters the substrate specificity of cereblon.

In the last part of my talk, I will discuss the mechanisms of TE. (Fig. 43)

We have shown that when thalidomide forms a complex with cereblon, Aiolos and Ikaros are recruited as novel neosubstrates to the complex, and then ubiquitinated and degraded, leading to the anticancer effects of thalidomide. So, it is imaginable that thalidomide also exerts its teratogenic effects via cereblon in a similar way. (Fig. 44)

On that note, two research groups in the US reported that Sall4, which regulates the induction of differentiation, is a neosubstrate of thalidomide. They found that Sall4 degradation was most enhanced when iPS cells were treated with thalidomide. Thalidomide treatment in fact caused cereblon-dependent Sall4 degradation in iPS cells, and also decreased Sall4 expression in the forefoot of rabbit embryos. There was also a report that a genetic disease of humans involving malformation of the hands and eyes is caused by a mutation in Sall4. (Fig. 45)

These research groups also showed that, in the presence of thalidomide, Sall4 binds to cereblon in the case of humans, but not in the cases of zebrafish or mice.

These studies have two weak points. The first is that although TE develops in primates, rabbits, chicks, and zebrafish, Sall4 degradation does not occur in chicks and zebrafish.

The second is the absence of a rescue experiment for TE using wild-type Sall4 and its thalidomide-unbound mutant. Therefore, Sall4 might be partly involved in the multiple phenotypes of TE, and there may be neosubstrates other than Sall4.

We have actually found novel neosubstrates in collaboration with Luisa Guerrini at the University of Milan, Italy. I would like to talk about the details, but they are still unpublished results. So I ask you for your understanding and will call it LD1 here. There are reports of genetic diseases caused by LD1 mutations in humans and mice. Thalidomide induced the binding of LD1 to cereblon and the ubiquitination

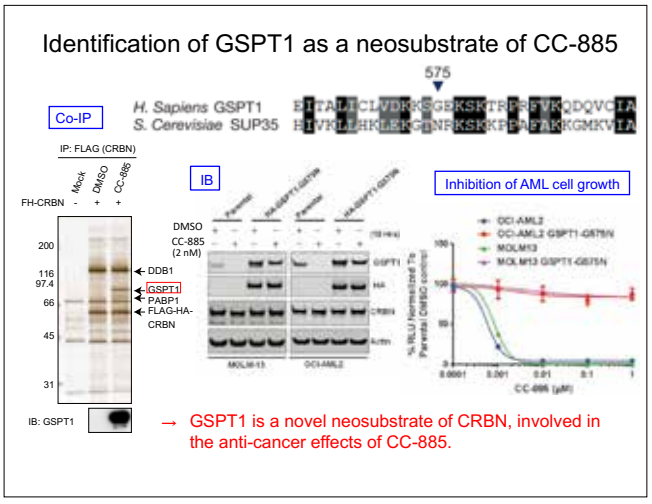


Fig. 40

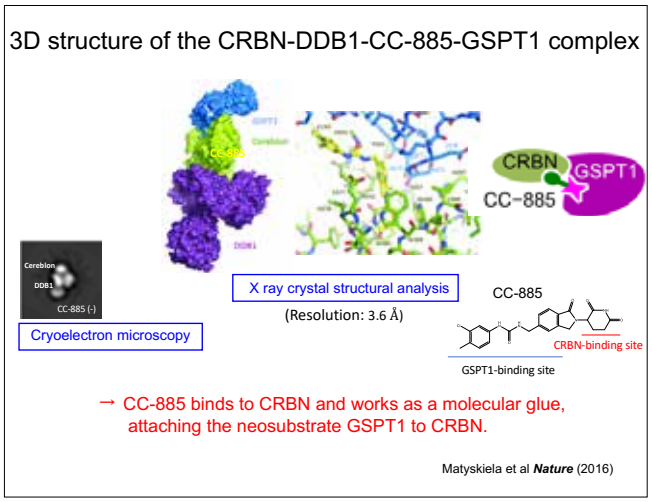


Fig. 41

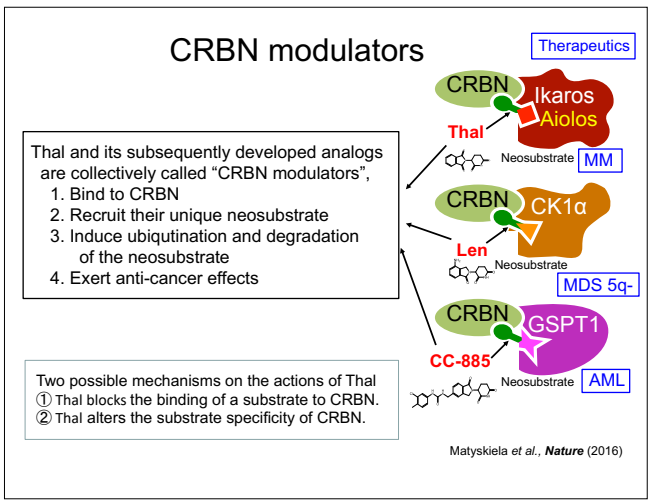


Fig. 42

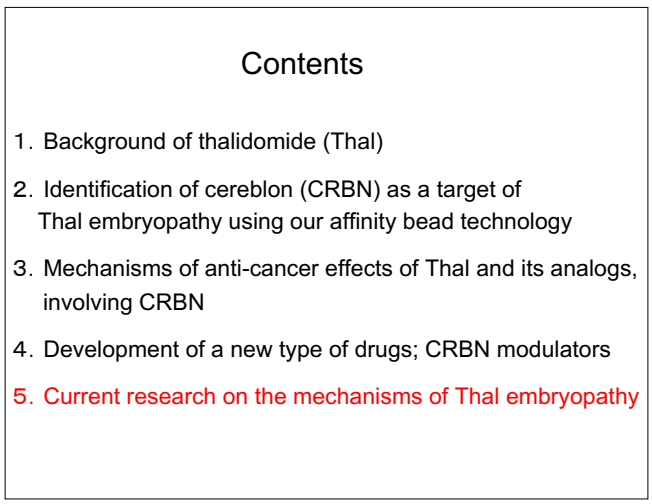


Fig. 43

and degradation of LD1 via cereblon.

We identified an LD1 mutant, named GA, which does not bind to thalidomide. Wild-type LD1 was degraded by thalidomide, but the GA mutant was not. We performed rescue experiments using this GA mutant. The results showed that the expression of the thalidomide-binding defective GA mutant blocked or rescued TE of pectoral fins in zebrafish more efficiently than that of wild-type LD1, indicating that LD1 is a true neosubstrate involved in thalidomide-induced embryopathy of the limbs. (Fig. 46)

At present, Sall4 and LD1, used here, have been identified as cereblon neosubstrates involved in TE. Other new neosubstrates are expected to be identified in the future. Furthermore, I believe that the mechanisms of thalidomide-induced embryopathy, which shows multiple phenotypes and develops in time- and site-specific manners, will be elucidated before too long.

Finally, I would like to thank the following colleagues and collaborators who participated in this research. (Fig. 47)

Thank you for your kind attention. (Fig. 48)

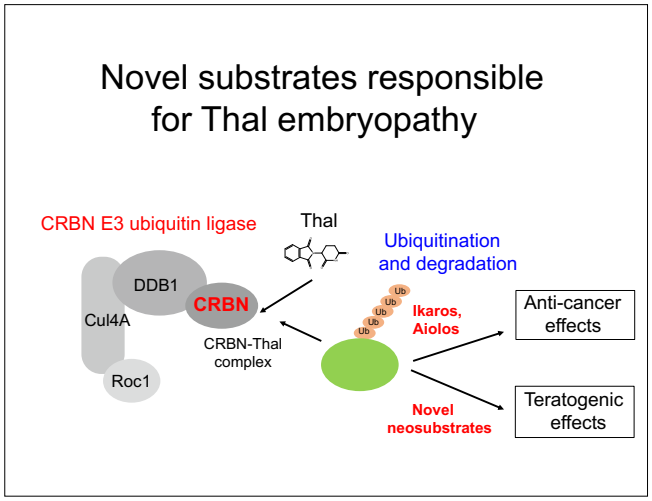


Fig. 44

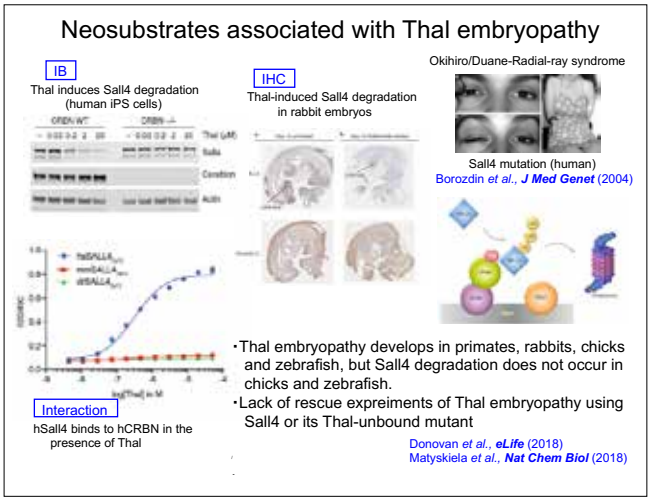


Fig. 45

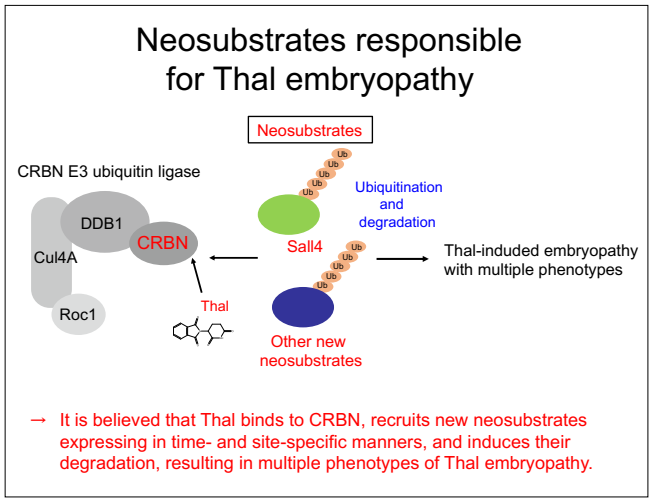


Fig. 46

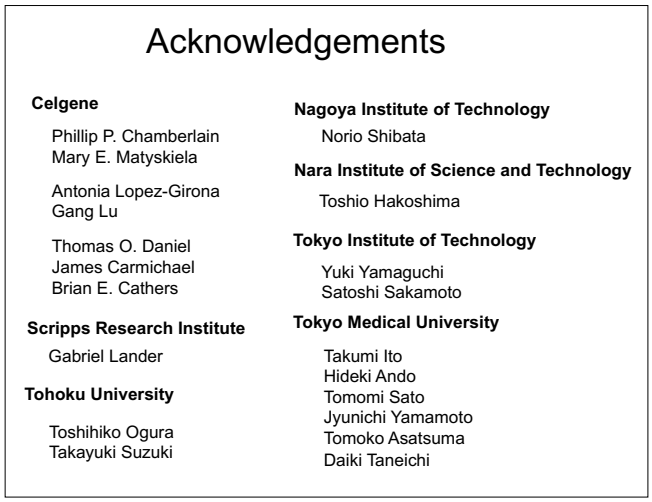


Fig. 47



Fig. 48

Q&A

Nobuhiko Haga: Thank you very much, Professor Handa. And now it's open for discussion. Are there any comments? Okay, yes.

Dee Morrison: Thank you Dr. Handa for a very detailed explanation. I first heard about cereblon when I attended the World Health Organization Conference in 2014, and it was a great surprise for me to learn about it then. It's been very interesting to follow the work since. I'm not sure whether you can answer my question, but I thought I'd ask it. Dr. Beyer in Germany who, unfortunately is not here, published a paper earlier this year showing altered vasculature around the body and the organs, particularly around the kidney and heart in those with TE.

He was reassuring us that those affected by thalidomide still had normal function of the heart and kidneys. The pattern of abnormal vasculature didn't seem to match the pattern of the external abnormalities. So, in looking at this and the cardiovascular risk, which is, I understand, slightly different in Japan, where we think there is a slight increased risk of cardiovascular disease, though we have no evidence, it is linked to thalidomide at present. But in talking to cardiologists, they were uncertain whether an area of the body could be more susceptible to the effects of abnormal vessels during fetal development, and then later to disease processes, depending on when thalidomide was given and the timing of the pregnancy. Now, for those affected by thalidomide, just to reassure you, we have no evidence and this is hypothetical, but in asking you and looking at your research, it would allow us to perhaps pick up a pattern of external damage that might be more susceptible to a certain area of the body and administer medication to try and prevent it.

So, for instance, whether a certain pattern of timing in the pregnancy might make those with TE more at risk of stroke, but not necessarily of heart attack. So, is your research at any point going to lead toward this, and what are your thoughts on it?

Hiroshi Handa: Thank you. I am not sure that thalidomide affects the altered or abnormal vascularization as you mentioned. We have checked the effects of thalidomide on the development of heart. The results showed that thalidomide definitely affects heart development in zebrafish. We have submitted our paper on the target of TE of pectoral fins and otic vesicles in zebrafish. I think that we have described just a little bit on heart in the paper.

Dee Morrison: Yes I know, I know it is a fact and I know obviously there were deaths. Those who are living at the moment…[Not recorded]

Hiroshi Handa: I think that multiple cereblon substrates, which are targeted for TE in a time-dependent manner, are present in different organs, and that thalidomide impairs the early development of various organs, such as the heart, blood vessels, limbs, and ears, via degradation of an organ-specific substrate.

Nobuhiko Haga: Okay, I can accept only one more question today. This is the last question.

Tetsuya Tagami: Then let me ask you this in Japanese. There are a couple of derivatives, and of course, their effects should be different. In the case of zebrafish or chicks, is there teratogenicity?

Hiroshi Handa: Thalidomide and its second-generation analogs, including lenalidomide and pomalidomide, cause developmental defects of the fins/limbs in different species, such as chicks and zebrafish.

Tetsuya Tagami: Yes, I understand that. But if we just limit this to zebrafish, are there three or four derivatives that might have…

Hiroshi Handa: Our data using zebrafish showed that thalidomide causes developmental defects of pectoral fins and otic vesicles more strongly than pomalidomide or lenalidomide.

Nobuhiko Haga: We will now finish this section. Thank you very much.

Activities of the Japanese Research Group on TE and Nation-wide Survey of Actual Life Situations in Subjects with TE in Japan, 2018

Fumihiko Hinoshita

Department of Nephrology, National Center for Global Health and Medicine, Tokyo, Japan

Tetsuya Tagami (Moderator)

I watched the Federer tennis match on television until 3 AM, so I am a little sleepy. Anyway, today's first speaker is Dr. Hinoshita. The title of his presentation is "Activities of the Japanese Research Group on TE and Nationwide Survey of Actual Life Situations in Subjects with TE in Japan, 2018". Dr. Hinoshita, please.

Thank you, Dr. Tagami. Anyway, looking around this venue, I feel that none of you are sleepy, or I hope so anyway. I am Dr. Hinoshita from National Center for Global Health and Medicine. So, let's go ahead to the first slide. (Fig. 1)

More than 300 thalidomide-impaired babies have been born in Japan. Thus, from 1959 through 1969, we had about 300 thalidomide victims. I will explain a little bit about the history of thalidomide or Contergan® in Japan. (Fig. 2)

Thalidomide victims and their relatives initiated legal proceedings against the Japanese government and pharmaceutical companies selling thalidomide-containing drugs in 1961. Both sides legally arrived at an amicable settlement in 1974. Based on the above settlement, a public interest incorporated foundation for thalidomide-impaired people, the Ishizue Foundation, was established in 1974. (Fig. 3)

Yesterday, the President of the Ishizue Foundation, Dr. Sato, gave opening remarks. Dr. Sato is also a pharmacology scientist.

Anyway, an official research group to study and support programs for the health and living situations in thalidomide-impaired people was newly organized for study and support by Ministry of Health, Labour and Welfare (MHLW) in 2011. The second official research group was organized by MHLW in April 2014, and I was appointed head at that time. The third group was renewed in 2017 under my direction, adding some new members. Basically, this official research



Fig. 1

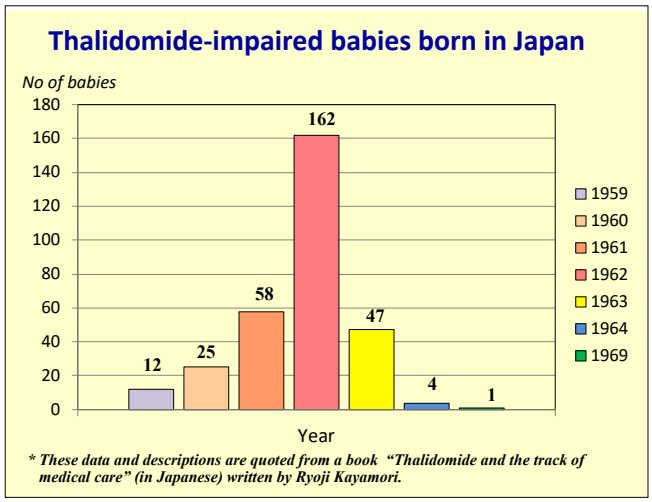


Fig. 2

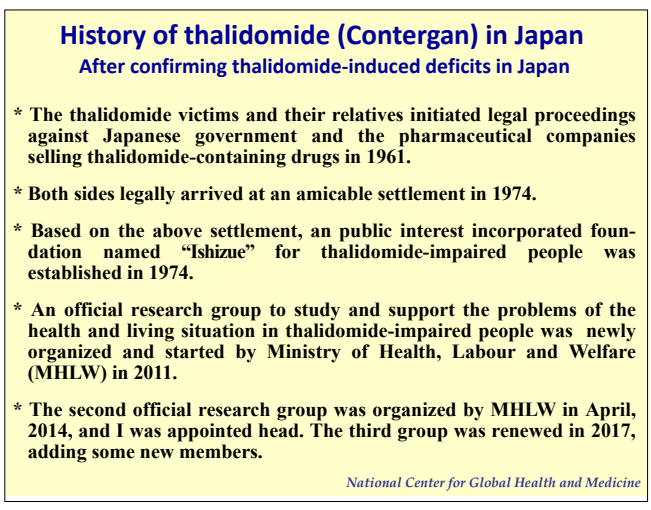


Fig. 3

group was renewed every 3 years.

Next, I will talk about the major activities of the Japanese research group. We have continuously conducted medical checkups every year. At its peak, this has involved 24 people with TE every year. In addition, we have also focused on visiting specialists of TE in Europe. For example, we visited Conterganstiftung in Cologne, Germany, The Thalidomide Trust in the UK, and the Ex-Center in Sweden, as well as some specialists on TE in Germany, the UK, and Switzerland. (Fig. 4)

As you know, the first international symposium on TE was held in Tokyo in 2015. We have established a working group on TE and its homepage in the Internet, and a workshop is held every 2 years in Japan. This workshop is held only for Japanese researchers and associates. We made a list of physicians, physiotherapists, researchers, pharmacists and so on, who can deal with TE in Japan. We also created a comprehensive guidebook on TE for clinical practice, as well as an English edition, called "Guide for the Management of Thalidomide Embryopathy 2017". Maybe we have already given this edition to the attendees who are participating in this symposium.

We also carried out a second nationwide survey on the health and living situations of thalidomide-impaired people in 2018. We have also been conducting new interviews with thalidomiders by rehabilitation specialists since 2017.

Now, I will show you some slides from when we previously visited Europe. This is a photograph taken when we visited Europe for the first time. This photo was taken at the Conterganstiftung in Cologne, Germany. In the same year, we visited an experienced specialist on TE, Dr. Jürgen Graf. He is now working in Nuremberg, Germany. (Fig. 5, 6)

Some of you may remember this photograph. This is the first international symposium on TE in Tokyo. (Fig. 7)

In 2016, we visited Europe for the second time. This photo shows when we visited the Ex-Center in Solna, Sweden. The other photo was also taken in the same year when we visited Dr. Jan Schulte-Hillen & Dr. Bettina Ehrt at St. Anna Clinic in Lucerne, Switzerland. (Fig. 8, 9)

Last year, we visited Europe for the third time. This photo was taken with Dr. Christina Ding-Greiner. The second photo was taken at the Dr. Becker Rhein-Sieg-Klinik, Nüm-

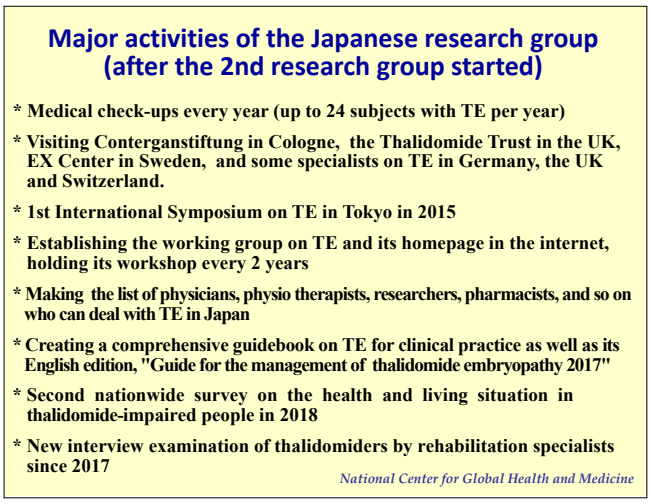


Fig. 4



Fig. 5



Fig. 6



Fig. 7

brecht, with thalidomide victims. In the center of this photo, Mr. Udo Herterich and Ms. Claudia Herterich, are both thalidomiders living in Germany. And next, the third photo is with the staff of The Thalidomide Trust. We can see Dr. Morrison and Ms. Newbronner here in the photograph. (Fig. 10, 11, 12)

And finally, we visited Dr. Beyer to share some discussions on TE. (Fig. 13)

Some visiting staff discovered this very precious thing in Heidelberg by chance. This photograph shows the original Contergan/thalidomide at Deutsche Apotheken-Museum in Heidelberg. (Fig. 14)

This is the guidebook for the management of thalidomide embryopathy (TE), which was created in 2017, and later



Fig. 8



Fig. 9



Fig. 10



Fig. 11



Fig. 12



Fig. 13

translated into English by the Japanese research group. (Fig. 15)

May I ask you who took a look at this homepage before? Oh, okay. If you haven't, please take a look at this homepage later, the homepage of the Japanese research group. You can find our website easily. (Fig. 16)

Then, from here, I would like to show you the results of the second nationwide survey of life situations of subjects with TE in Japan.

The aim of this survey was to clarify the actual medical health status of thalidomiders. A multicenter investigation was previously conducted in Japan from 2011 to 2014 to investigate the manifestation of TE in individuals aged around 50 years. That was the first survey. (Fig. 17)

The study above deals with socioeconomic programs and reveals the gaps in terms of health and social problems between thalidomiders and the general population of the same age in Japan. Therefore, we further carried out a nationwide survey mainly focusing on life situations in thalidomiders living in Japan in early 2018, and compared the results with those of the comprehensive survey of living conditions (CSLC) in the general population carried out by the government in 2016. A questionnaire was sent to 274 thalidomiders living in Japan whose mail addresses were recognized. The questionnaire included a great variety of questions, 38 items mainly, covering health, medical care, welfare, pension income, and some other basic items of living. Each form of the questionnaire was filled in based on the situation as of December 20, 2017. The questions were almost the same as those of the governmental survey, CSLC, in the general population. Responses were received from 173 thalidomiders, so the response rate was 63.1%. The results of the survey were compared with those of the governmental survey. (Fig. 18)

Okay, I'll show you a part of the questionnaire. For example, number 1, what do you think of your health condition? The answers were good, relatively good, average, relatively bad, and bad. And number 2, do you think your health problems influence your daily life, yes or no? And so on. (Fig. 19)

First, I should show you the basic characteristics of thalidomiders. The short-arm group, 126; hearing loss group, 27; the mixed group, 13. In total, there were 173 subjects. Regarding family structure, one-person household, 33; sharing



Fig. 14

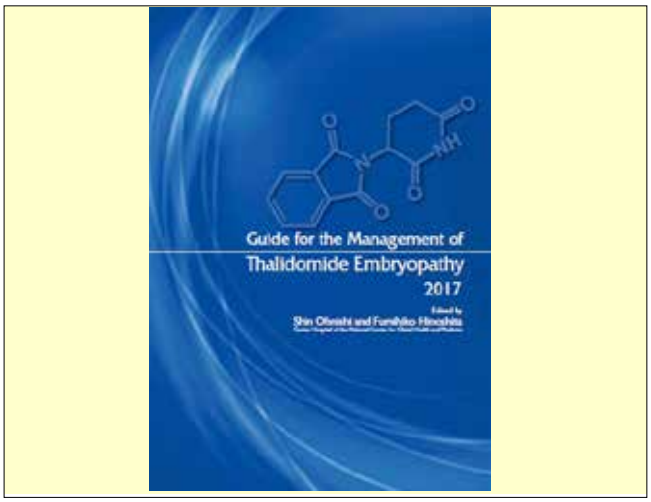


Fig. 15



Fig. 16

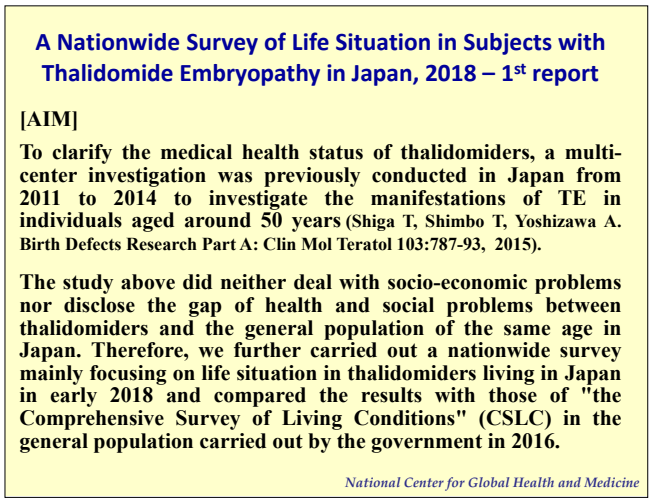


Fig. 17

household with parents only, 32; and other type of household, 102. (Fig. 20)

Family structure classified by type of disorder is shown here. Okay, so the hearing loss group tended to live with their parents, 28.1%. Sixty-nine percent or almost 70% of the subjects were living by themselves, especially those in the short-arm group. (Fig. 21, 22)

As for marriage, about half of the subjects with TE were married. Family structure classified by marital status showed that single unmarried persons were living by himself or herself, or only with his or her parents. Married thalidomiders were living with other family members. It's the bottom column. (Fig. 23, 24)

Okay, next, health condition. From here, I will show you

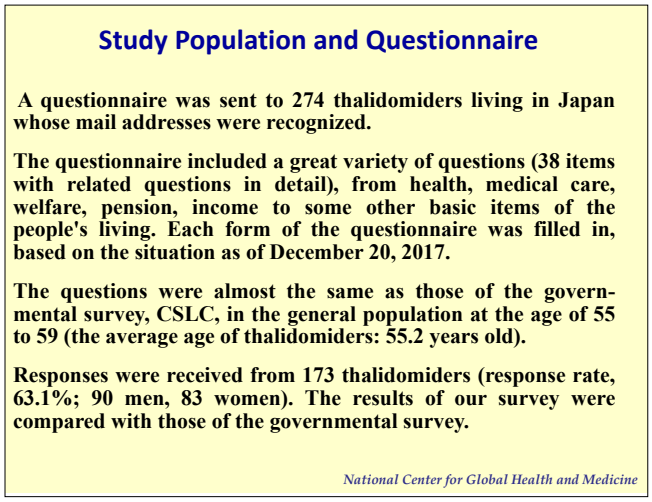


Fig. 18

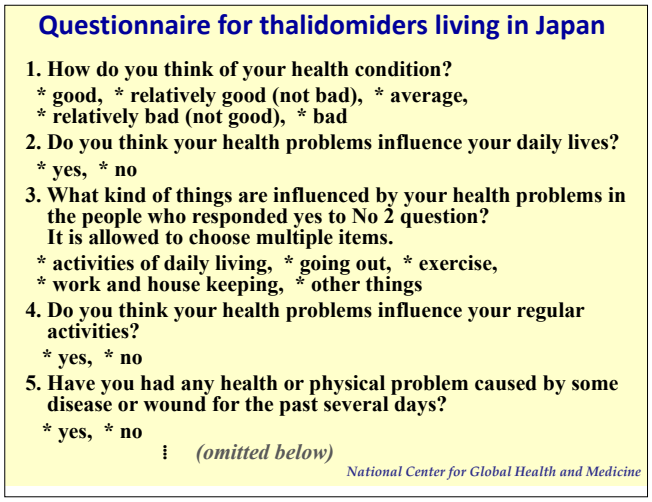


Fig. 19

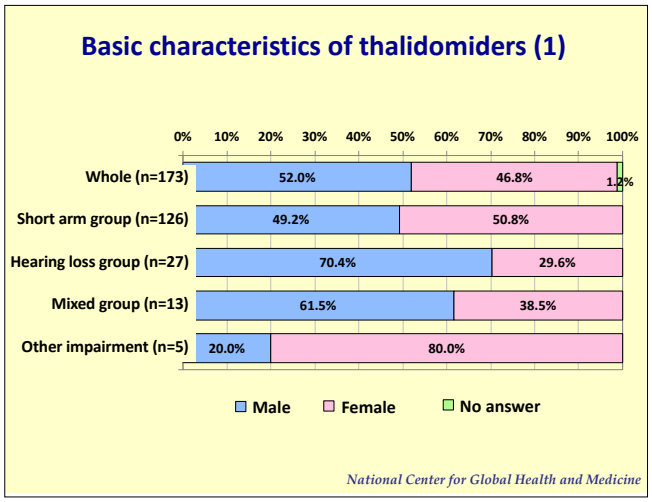


Fig. 20

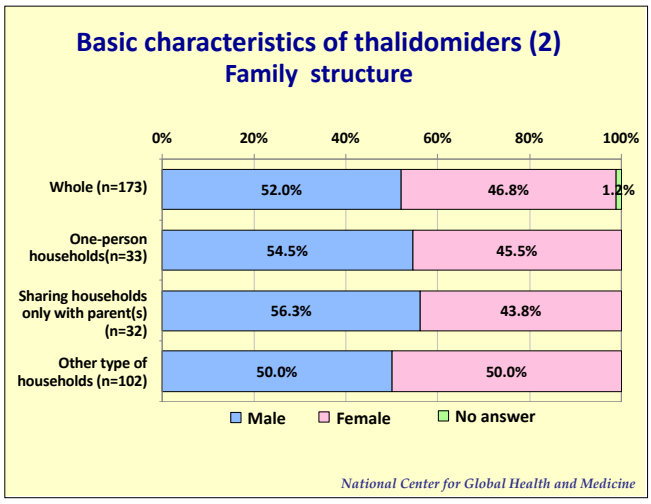


Fig. 21

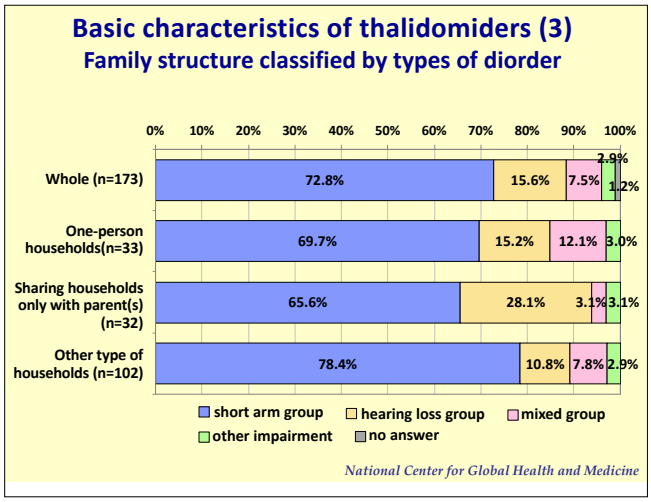


Fig. 22

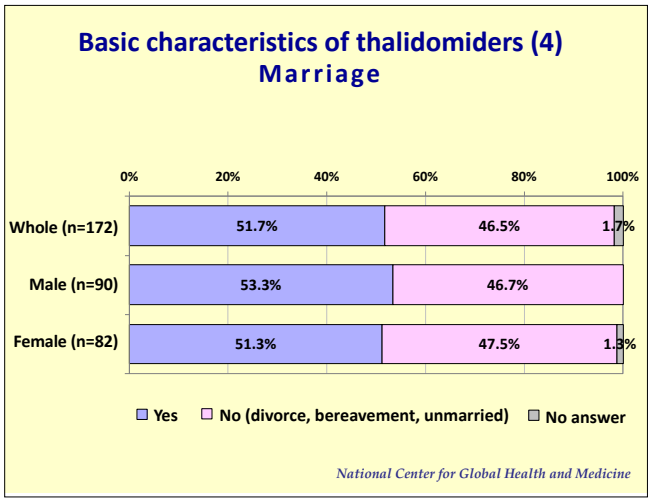


Fig. 23

the study items we focused on. As for health condition, most of the thalidomiders did not feel bad compared with the age-matched general population. (Fig. 25)

This slide shows the influence of health condition on daily living. More thalidomiders felt that their health condition greatly influenced daily living. In detail, for example, you know, work and housekeeping are greatly influenced by health condition. And also, for example, health condition might influence going out and exercising. (Fig. 26, 27)

This slide shows the influence of health condition on all of the regular activities in life; in total, the health condition influences thalidomiders greatly. (Fig. 28)

This slide shows the health and physical problems caused by disease or wounds at the time of the survey. Many more

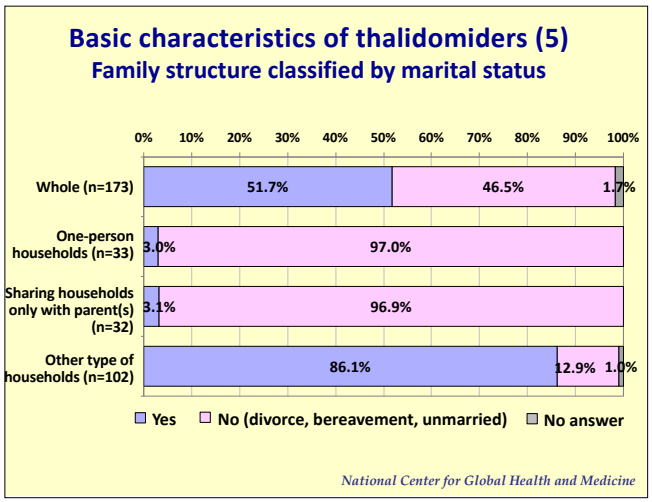


Fig. 24

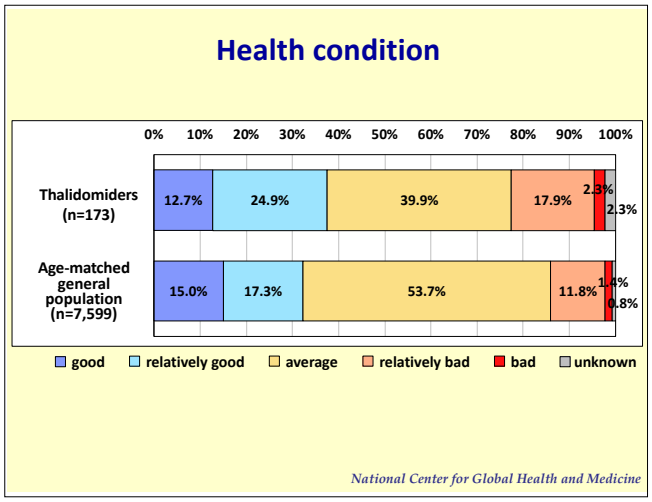


Fig. 25

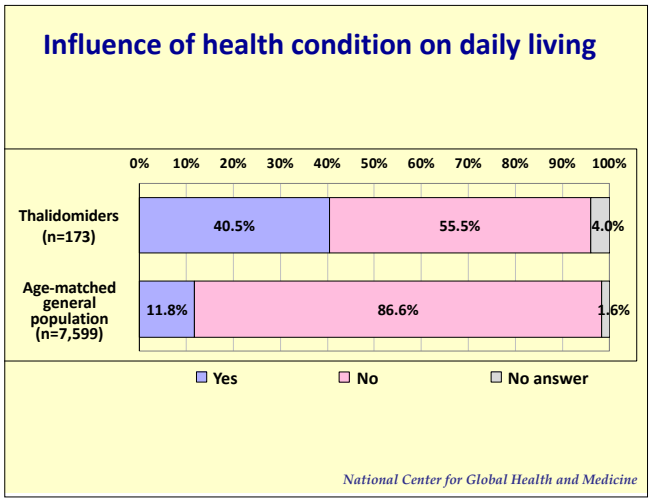


Fig. 26

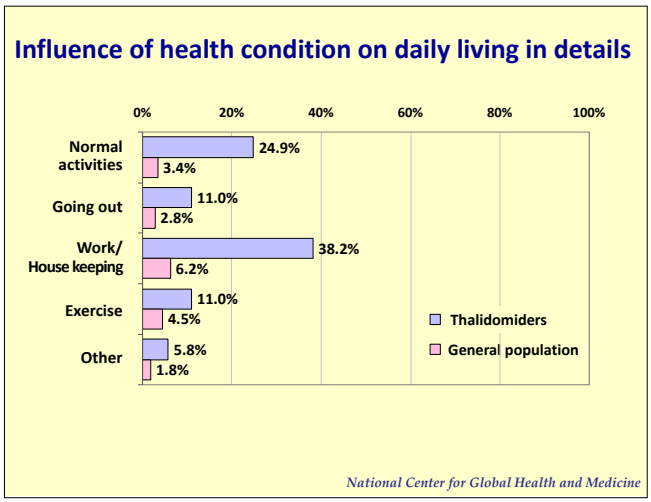


Fig. 27

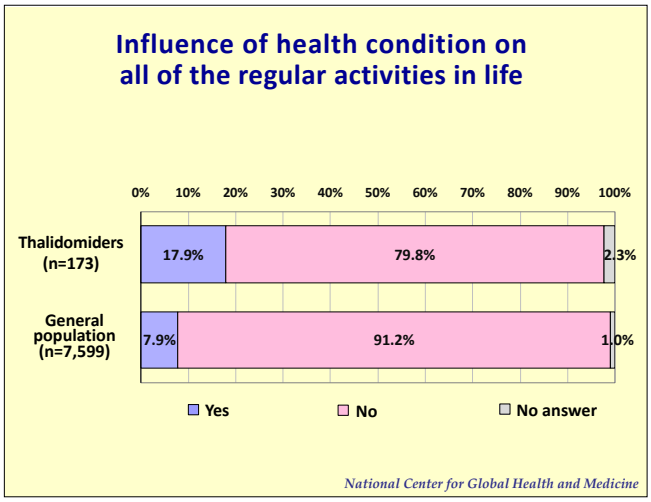


Fig. 28

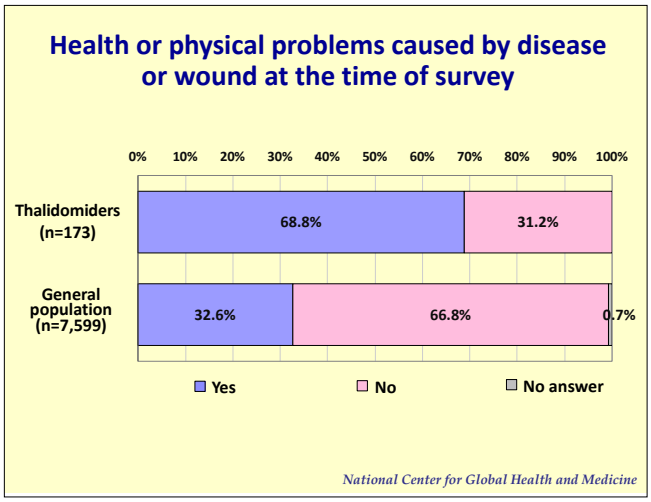


Fig. 29

people with TE thought disease or wounds were caused by health and physical problems. The next slides show the diseases and physical problems in detail. Thalidomiders had a higher prevalence of diabetes mellitus (12.7%), hyperlipidemia (13.9%), ocular diseases (19.1%), and dental diseases (17.9%) than the general population, as well as arthropathy, stiff shoulders, and lumbago or lower back pain. But interestingly, the percentage of subjects with hypertension was almost the same as that in the general population, at least in this national survey. (Fig. 29, 30, 31)

Next, this slide shows the visiting situation in subjects with symptoms and/or problems. As for this theme, there was no great difference between thalidomiders and the general population, but please pay attention to utilizing massage and acupuncture as well as chiropractic as shown in the slide. In this respect, more thalidomiders depend on these medical services. (Fig. 32)

This slide shows the distribution of annual income. Unexpectedly, no great difference was found between thalidomiders and the general population. (Fig. 33)

We also asked about general family circumstances. This means in short whether they feel good or bad, happy or unhappy, or uneasy, not only in regard to economic status, but also mental condition. (Fig. 34)

Anyway, interestingly, fewer thalidomiders felt that their general family circumstances were very difficult; more of those in the general population felt that their lives were difficult now.

Next, we also asked the current work situation. You know, we should focus on this important point. I mean, many thalidomiders, 9.2%, are unemployed, even if they want to work. But in the general population, no many persons are unemployed. (Fig. 35)

Next, this slide shows the results regarding worry and stress. More thalidomiders felt worry and stress, obviously. (Fig. 36)

From this slide, I will show you the results of the nation-wide survey, which were not previously revealed. I have shown the previous slides to part of the attendees here from the UK, Germany, or Japan. But from this slide, I newly show the other results on pain. Please keep in mind that these items were not compared with the results of the general population.

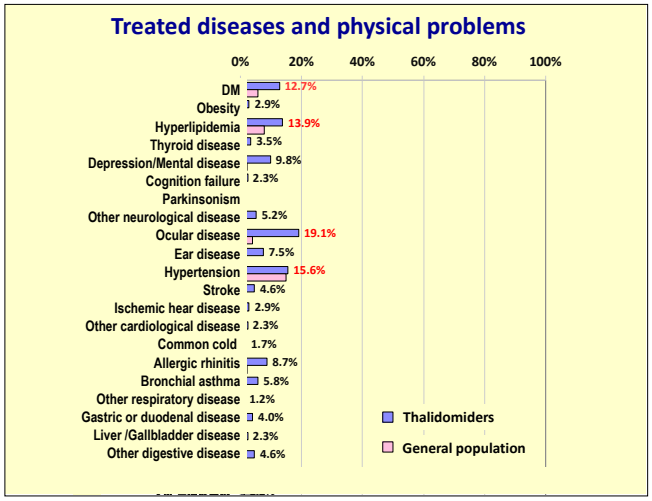


Fig. 30

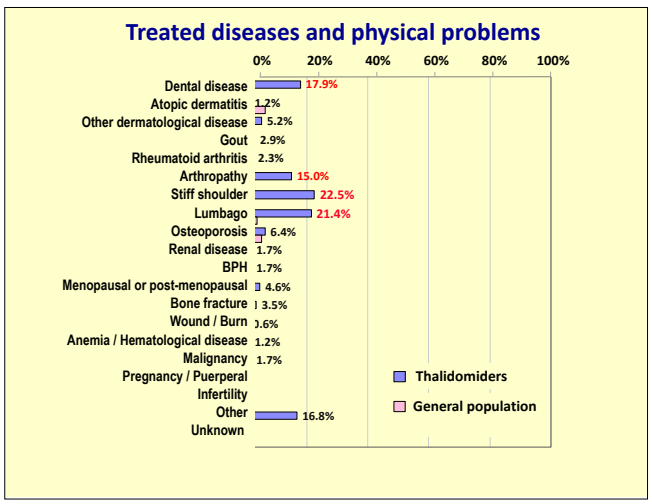


Fig. 31

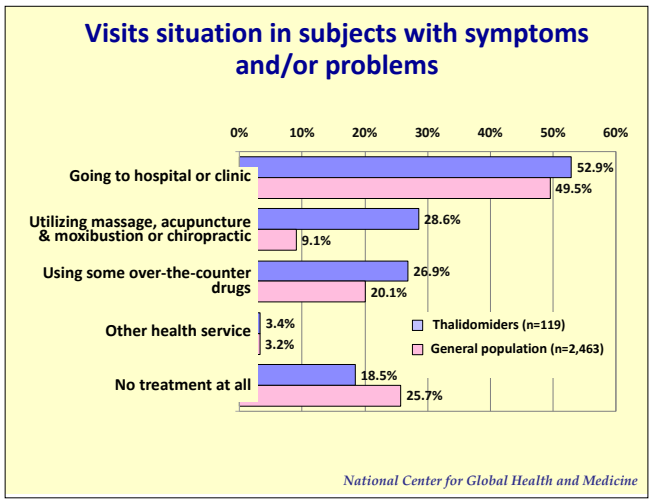


Fig. 32

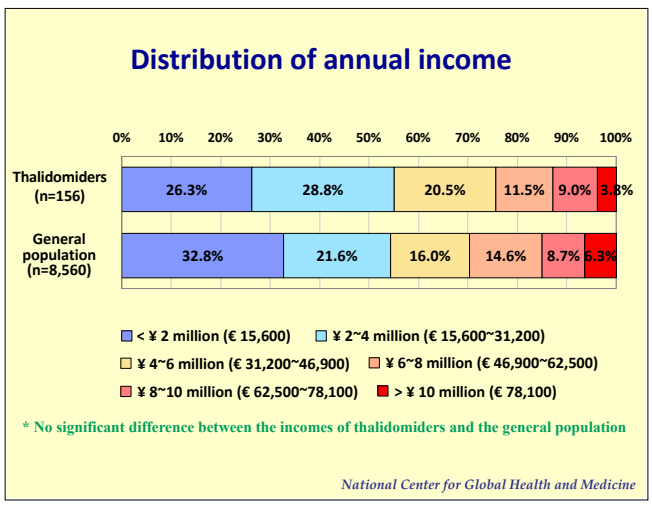


Fig. 33

As for persistent pain, more than half of the thalidomiders feel persistent pain every day. Especially in the mixed-type group, there are many people with TE who feel persistent pain. (Fig. 37)

We also asked about the body parts or locations with pain. We found, for example, pain was frequently reported in the shoulder and upper arm, neck and around the neck, and next hands and fingers. As for females, hip joint pain was remarkable. We also asked about changes in the pain grade for the past 5 years. Most of the thalidomiders responded that their pain had become stronger since 5 years ago. (Fig. 38, 39)

Now I will summarize the main results. More thalidomiders feel that their health condition is worse or relatively worse than that of the general population. More thalidomiders are influenced by their health condition in general than the general population. Especially, there are great gaps in conducting normal activities, going out, working, and housekeeping. Many more thalidomiders have health or physical problems caused by disease or wounds than the general population. Generally, thalidomiders have significantly more diseases, physical problems, and treatments than the general population, except for hypertension.

No significant difference was found between the annual income of thalidomiders and that of the general population. As for work, thalidomiders are at a disadvantage compared with the general population. There are more unemployed

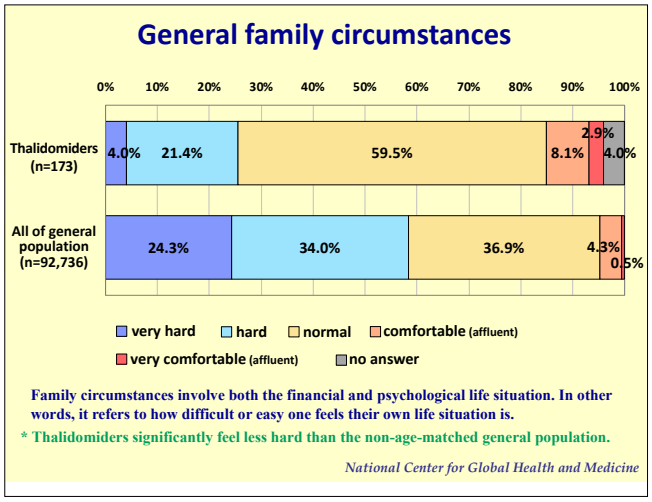


Fig. 34

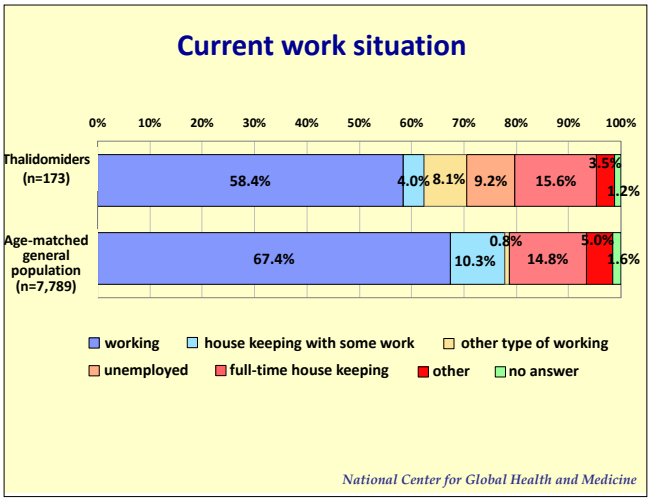


Fig. 35

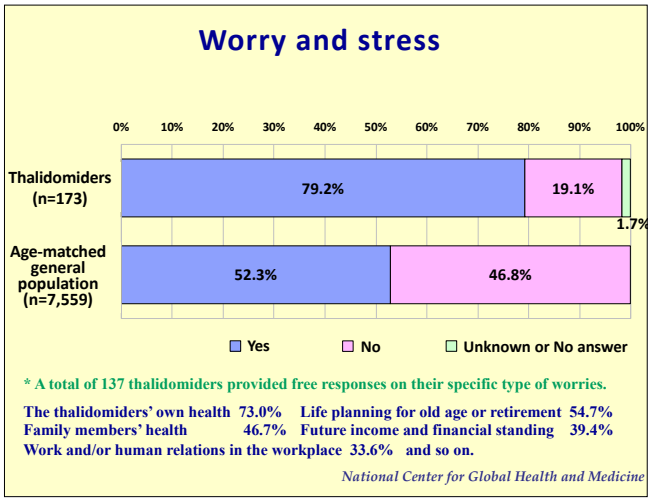


Fig. 36

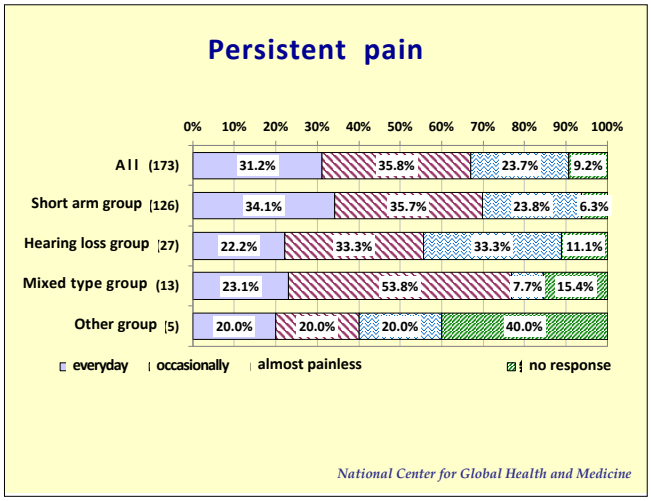


Fig. 37

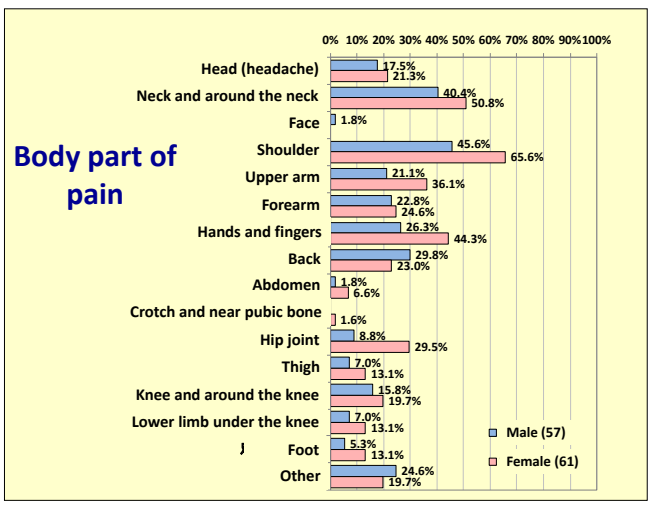


Fig. 38

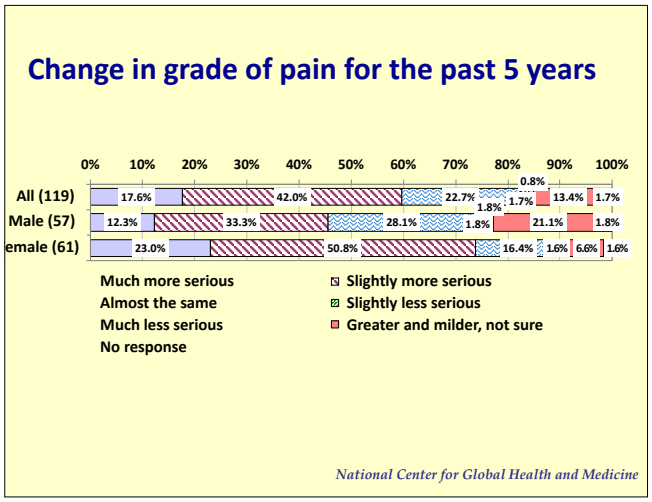


Fig. 39

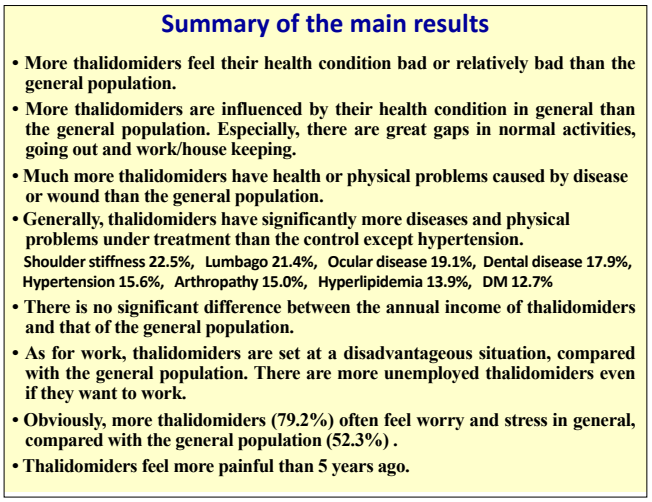


Fig. 40



Fig. 41

thalidomiders, even though they want to work. Obviously, more thalidomiders, 79.2%, feel worry and stress compared with the general population. Thalidomiders also feel more pain now than 5 years ago. (Fig. 40)

Therefore, I think all of us should continuously work towards the resolution of TE-associated problems. Hopefully, this global network on TE will successfully push forward and function well in the future, too. Thank you for your attention. That's all. (Fig. 41)

Q&A

Tetsuya Tagami: Thank you, Dr. Hinoshita. Are there any comments or questions?

Elizabeth Newbronner: Thank you very much, Dr. Hinoshita, for the very interesting presentation. It was nice to see some of your new data as well. Thank you. I was just interested in income, which you said was similar to that of the general population. Does that income level include people's compensation payments, so it's their whole income?

Fumihiko Hinoshita: We did not ask about that in detail, but I think the income shown here includes compensation, namely money from the fund or the government.

Elizabeth Newbronner: Yes. And I just wondered have you received any feedback from thalidomide survivors here about how adequate they think their income is in terms of covering the cost of living with their disabilities?

Fumihiko Hinoshita: Yes, as I showed, most of the thalidomiders think that their lives are not so bad, that they are doing well financially and in their activities, except for work, namely unemployment. But I believe they need to spend more, for example, on massages or chiropractic or other medical services or treatment, compared with the general population. So, we Japanese researchers think that in reality, they get less income than they need because of their greater expenses for medical services and so on.

However, I don't know about the thalidomiders in European countries, but at least in Japan, thalidomiders are patient and have become accustomed to a poorer situation. So they do not have great stress or worry, maybe because in a sense, they have been mentally strengthened in their physical activities from youth. That's it.

Elizabeth Newbronner: Thank you.

Klaus M. Peters: I think there are lot of parallels between the Japanese results and the German data. I think also that German thalidomiders need more medical treatment and have more pain than the others, and the retirement quote is much higher than the normal range of the German population up to now. A lot of them have retired in the last 5 years because of pain and poor health conditions.

Fumihiko Hinoshita: Yes, thank you. Thank you for your comment. We know there are more thalidomiders in Ger-

many who would retire from their job because of great pain or such other problems. And, according to your report, you said that German thalidomiders would not like to visit hospitals or clinics for their pain or so on. But based on our national survey in Japan, most Japanese thalidomiders can rely and depend on regular medical services, including massages and some medical examinations at hospitals or clinics.

Shadi-Afarin Ghassemi: Thank you very much. That was a very nice presentation. I have two questions. The first is from what I understand, you conducted your survey through e-mail and it didn't cover all thalidomiders or…?

Fumihiko Hinoshita: Just postal mail, not e-mail.

Shadi-Afarin Ghassemi: Okay, but anyway, I mean that you reached more than 200 of the over 300 you had. My question is why do you think you couldn't reach all of the thalidomiders in Japan? If you had answers from them, would it have changed the outcome of your studies? That's my first question. My second question is although it was very interesting, I wonder why you used your own survey according to your own questionnaires instead of validated questionnaires, such as the SF-36 or SF-12?
With respect to cultural differences, it would be nice to hear. I mean, the answers and outcomes were still quite similar, but why did not you use the outcomes, sorry, the validated questionnaires? That would be interesting to know. Thank you.

Fumihiko Hinoshita: Okay. As for your first question, we, the Japanese research group, did not know all of the addresses of the thalidomiders in Japan, partly because of privacy issues. The Ishizue Foundation, you know, the public incorporated foundation, knew almost all of the addresses of the thalidomiders in Japan. But I heard that they did not know all of the addresses because a small portion of the thalidomiders did not wish to disclose their address, situation or other private things. Then, as you pointed out, there might be the possibility that we cannot grasp or understand the actual situation of all of the thalidomiders living in Japan, especially in regard to the non-responders, who might be very sick or hospitalized with some serious mental diseases or such. Therefore, we could neither check nor know the situation of those specific patients.
To answer your second question, as you said, we did not use a global standard questionnaire, for example, the SF-36. But in parallel, the staff of the psychiatric subgroup in our TE research group are and have been carrying out a survey on thalidomide victims in Japan using the SF-36 or similar tool. Therefore, especially this time, I focused on the gaps and differences or similarities between Japanese thalidomiders and the age-matched general population.
Therefore, we adopted the standard questionnaires or question items of the survey regularly carried out by the government, the CSLC. That's it. Okay?

Junichi Horiuchi: I will speak in Japanese. My name is Horiuchi. I am the director of the Ishizue Foundation and I would like to thank all of the attendants here today at the symposium. This is just my personal view, but in terms of work, the staff members of the public organization entity made a contribution at the time to support and promote thalidomiders to be hired and employed by blue chip companies. In terms of work, this is often mentioned in dialogue and communication as a topic. In Japan, work–life balance is considered, and they have to work until 65 or 70 years of age, the retirement age.
But because of pain in the neck or shoulder area, thalidomiders and the disabled are wondering if they actually can work until age 65 or 70. When we pose them a question like that, they say, "No, I don't think I will be able to work until that age due to this persistent pain in my shoulder and neck and so forth," and 50% are single without a family, so what sort of support will be required for aging thalidomiders? This is something that we need to consider as a major issue.
Therefore, on this topic, support from MHLW as well as pharmaceutical companies will be necessary, with the cooperation and support of stakeholders. In terms of the use of massage, for the past some years, pharmaceutical companies have been providing support and some kind of subsidies or financial contributions. Amazingly, there are so many applications for subsidies for massage services. We receive many applications for the subsidization of massage services. I hope that the government will consider this as well.

Fumihiko Hinoshita: You know, massage, physical massage, is very popular in not only Japan, but also Germany, Sweden, and the UK. Most of the TE researchers and specialists think that massage is very advantageous and meaningful. However, I'm sorry to say that based on recent discussions, we think that massages would not be effective for a long period unless carried out on a consistent basis. That is a great problem. So, perhaps most Japanese thalidomiders would use massage often, I mean many times, which would have a steep cost.
Thus, not only the official research group, but also responsible pharmaceutical companies and the government should think about the great costs by thalidomiders. Yes, exactly, I think so.
Tetsuya Tagami: Anymore comments? Okay. Time is up. Thank you, Dr. Hinoshita.

Preserved Pulmonary Function in Thalidomide Embryopathy in Japan

Hiroyuki Nagase

Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University, Tokyo, Japan

Tomoko Shiga (Moderator)

Good morning, everyone. I am Tomoko Shiga from Division of General Medicine, Tokyo Women's Medical University. I will be chairing this session. The next presentation will be given by Professor Hiroyuki Nagase from Department of Medicine, Division of Respiratory Medicine and Allergology, Teikyo University. The title of his presentation is "Preserved pulmonary function in Thalidomide Embryopathy in Japan". Please, go ahead.

Thank you very much, Dr. Shiga. My name is Nagase and I am a respiratory physician from Teikyo University. In my talk, I want to focus mainly on pulmonary function testing for thalidomiders. (Fig. 1)

I will discuss three topics in this session. First, I will present the pulmonary function data from a health check surveillance study of people with thalidomide embryopathy (TE). (Fig. 2)

We previously performed pulmonary function testing the patients at 50 years of age to assess the percent of vital capacity (vital capacity / predicted normal vital capacity). I will call this %VC. This value was 89.6%. The forced expiratory volume in 1 second / forced vital capacity (FEV1%), which reflects obstructive dysfunction, was 81.7%. (Fig. 3)

The normal %VC value is 80% and the normal FEV1% value is 70%. So, these data were within normal limits. At that time point, no specific pulmonary disease or dysfunction was identified in patients with TE aged 50 years. We are continuing health checkups for these patients, and I want to show here the results from recent health checkups in 2017–2018. At this point, the patient's age was 55 years. (Fig. 4)

These are the results regarding smoking status in Japanese thalidomiders who visited Teikyo University. The number of patients was 11. We excluded patients with asthma and cerebrovascular disease from this analysis. The average

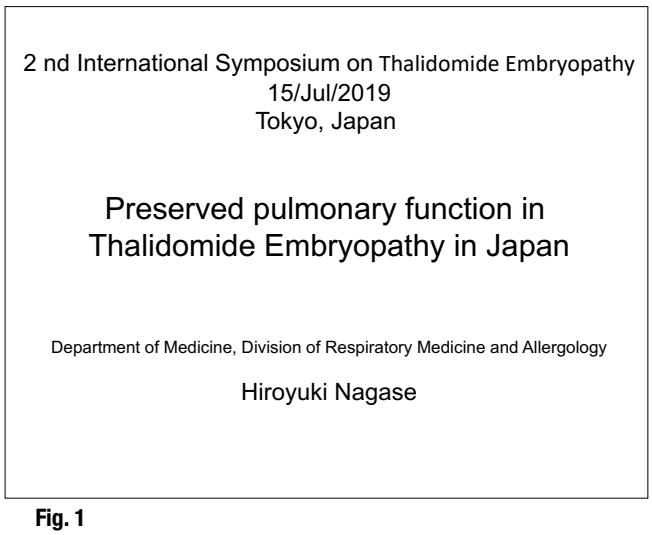


Fig. 1

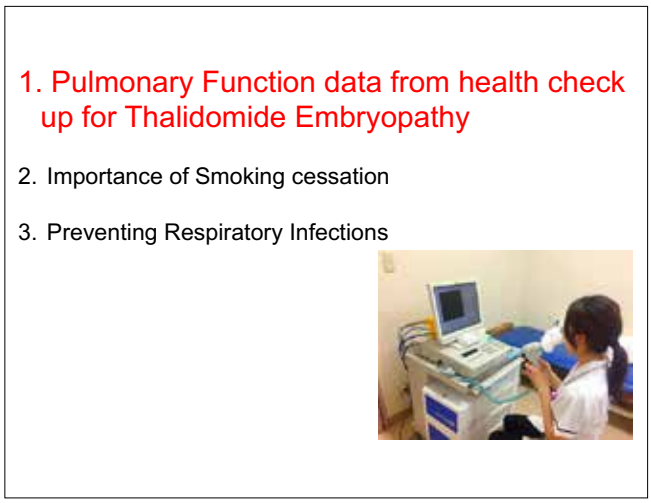


Fig. 2

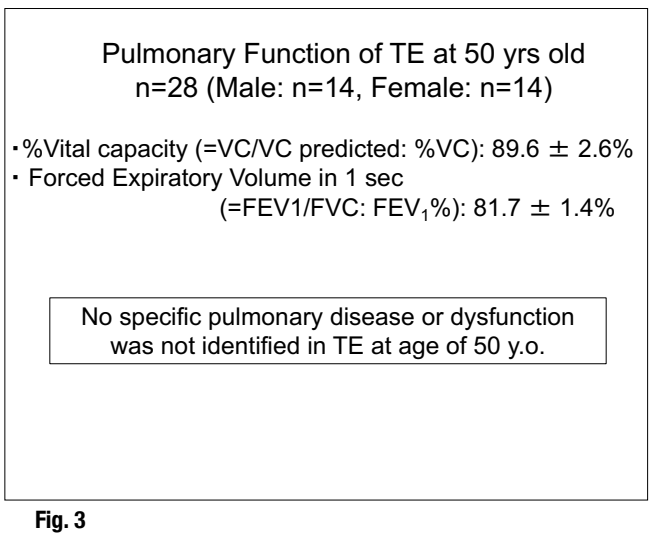


Fig. 3

age was 55.5 years old, and eight patients were male. And as you can see, the prevalence of current smokers was 23%, previous smokers was 39%, and never smokers was 38%. As shown here, a considerable proportion of thalidomiders were still smoking. (Fig. 5)

This slide shows the pattern of respiratory dysfunction and corresponding diseases. Restrictive dysfunction is defined as %VC below 80%, and the representative diseases are interstitial pneumonia or neuromuscular disease. Obstructive dysfunction is defined as FEV1% below 70%, and representative diseases include chronic obstructive pulmonary disease (COPD) and asthma. (Fig. 6)

This slide shows the flow volume curve, which is very useful for detecting peripheral airway dysfunction or obstruction. The y-axis shows expiratory flow velocity, and the x-axis shows lung volume. V.25 is defined as expiratory velocity at %FVC of 25%. This reflects peripheral airway obstruction. The V.50/V.25 ratio is also useful to detect peripheral airway obstruction because in patients with peripheral airway obstruction, the V.25 value decreases, so the ratio increases as peripheral obstruction progresses. Peripheral obstruction is suggested when this ratio is over 3. (Fig. 7)

From here, I will show the results of pulmonary function testing in recent health checkups. As you can see, %VC was not different between smokers and never smokers. The average value was 111, which is within the normal range. There was no problem. (Fig. 8)



Fig. 4

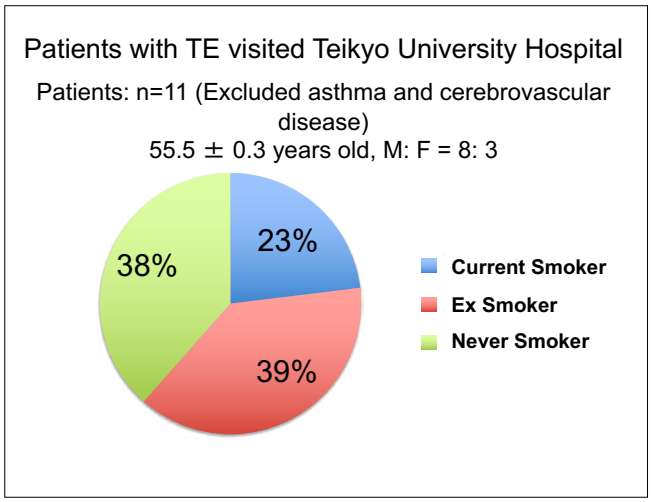


Fig. 5

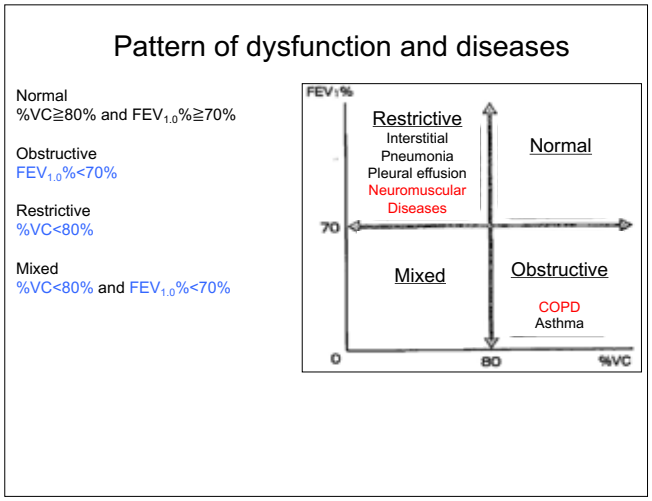


Fig. 6

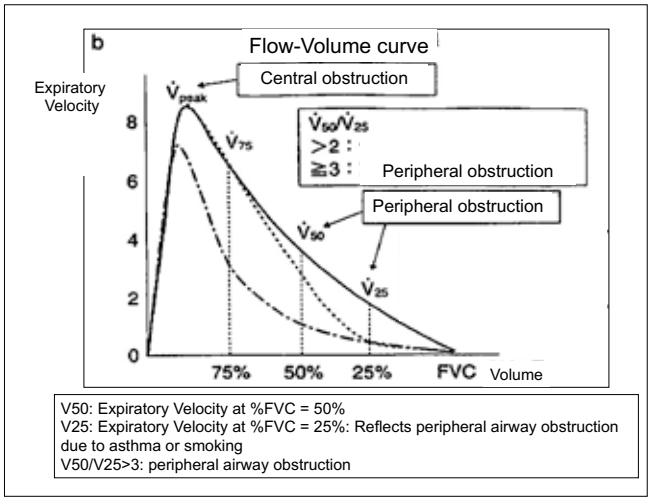


Fig. 7

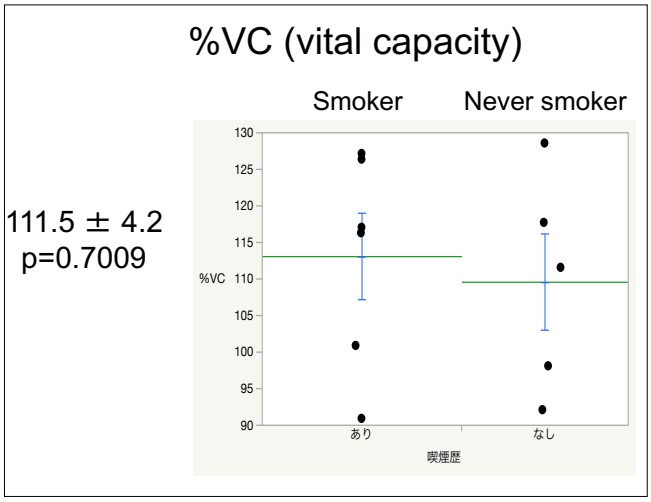


Fig. 8

Also, in case of FEV1%, there was no significant difference between smokers and never smokers. The average value was 79.1%, and this was also within the normal range. In general, FEV1% is considered to reflect central airway obstruction, not peripheral airway obstruction. Concerning the central airway, it was within normal limits. (Fig. 9)

By contrast, %MMF reflects peripheral airway obstruction. As you can see, there was a difference between smokers and never smokers. The value was numerically lower in smokers, but not statistically significant. (Fig. 10)

Here, I show the data for %V.75, %V.50, and %V.25. As you can see, %V.75 to %V.25 reflects the data for central to peripheral airway obstruction. For %V.75 and %V.50, there was no significant difference between smokers and never smokers. However, for %V.25, which reflects peripheral airway obstruction, the value was numerically lower in smokers. As you can see, central airway obstruction was within normal limits, even in smokers, but peripheral airway obstruction was observed in smokers. (Fig. 11)

This is the V.50/V.25 ratio. A value over 3 indicates peripheral airway obstruction. As you can see, the ratio was higher in smokers than in never smokers, which suggests peripheral airway obstruction. (Fig. 12)

This slide shows pulmonary function data from patients with or without block vertebrae. As you can see, there was no difference in %VC or FEV1% between patients with or without block vertebrae. The data were completely similar between groups. (Fig. 13)

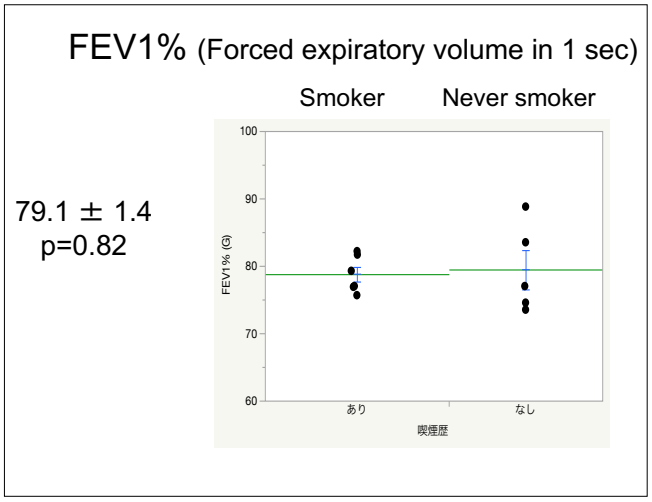


Fig. 9

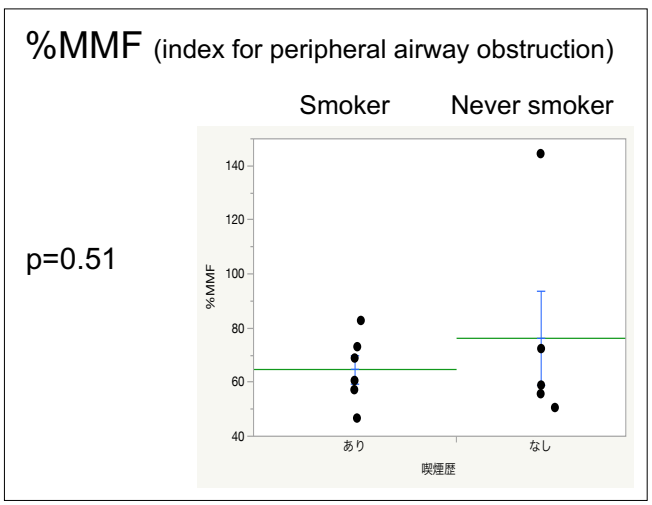


Fig. 10

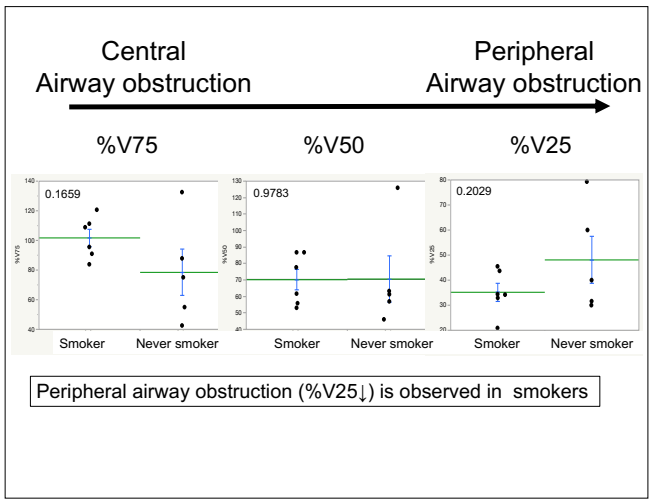


Fig. 11

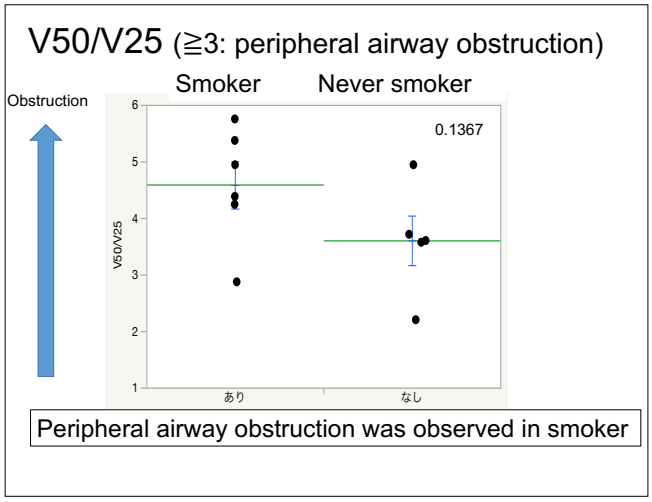


Fig. 12

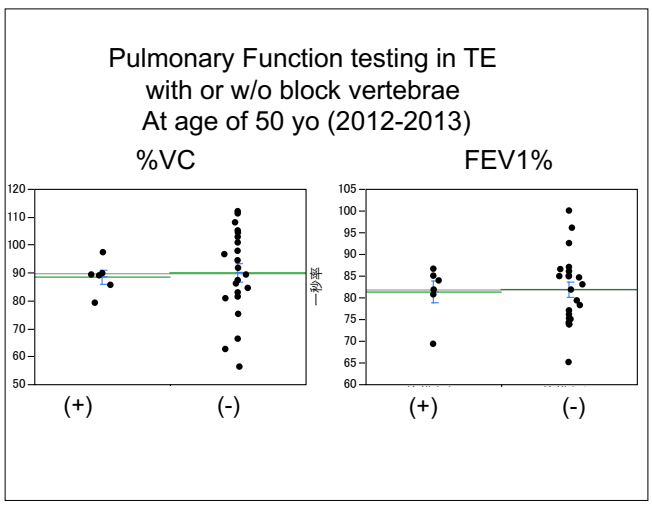


Fig. 13

This slide shows data concerning patients with upper limb defects. Concerning %VC, there was no difference. But the FEV1% value was slightly lower in patients with upper limb defects. The value was 80.2%, which was still within the normal limit, but the data were slightly lower in patients with upper limb defects. (Fig. 14)

This slide shows a summary of the results. The proportion of smokers in TE was 23%, which seems to be a little bit higher than the average value in Japan. The %VC and FEV1% values were preserved and within the normal range in all patients. I think this is good information. Especially in smokers, peripheral airway obstruction was observed, and FEV1% tended to be lower in patients with upper limb defects. Therefore, I think smoking cessation is very important for such patients. (Fig. 15)

This slide shows a photo of the alveolar space and enlargement in the elderly. These patients were never smokers, but alveolar space enlargement occurs spontaneously with aging. This alveolar space enlargement causes peripheral airway obstruction. Thus, aging is an important factor in peripheral airway obstruction. (Fig. 16)

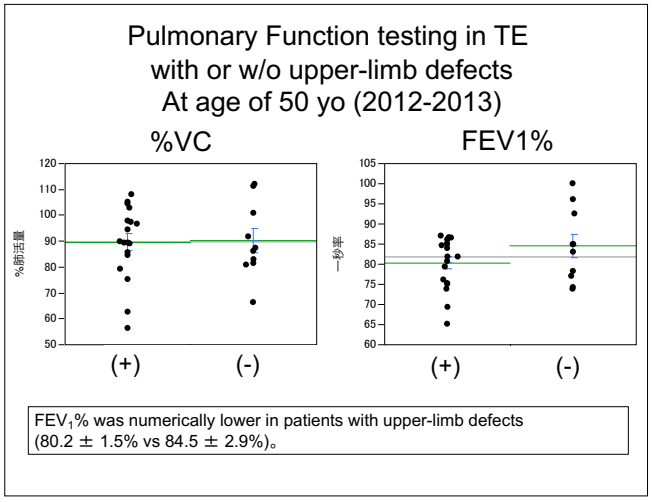


Fig. 14

Results

The proportion of smoker in TE was 23% (Average 17.9% in Japan).

The value of %VC and FEV1% was preserved and value in all patients was within normal range.

Peripheral airway obstruction was observed in smokers.

FEV1% tended to be lower in patients with upper limb defect.

Fig. 15

As you can see, these data depend on age. In the peripheral airway, aging greatly affects %V.25 as compared with the central index FEV1%. Thus, obstruction with aging is more dominant in the peripheral airway. Thalidomiders are now about 55 years old. The effects of aging are important for this generation, so we have to recommend smoking cessation, especially for current smokers. (Fig. 17)

In summary, pulmonary function in TE at age 55 years was within the normal range. But peripheral airway obstruction, especially in smokers, could be observed. As peripheral airway obstruction leads to COPD, smoking cessation is very important, especially for patients with upper limb defects. (Fig. 18)

Next, I want to mention the importance of smoking cessation. In Japan, smoking is generally prohibited in public spaces, but smoking is still permitted in designated areas around various public spaces. (Fig. 19)

These data show the prevalence of smokers in Japan, which has been continuously decreasing. In 2018, the average prevalence was 17.9%: 27.8% in males and 8.7% in females. (Fig. 20)

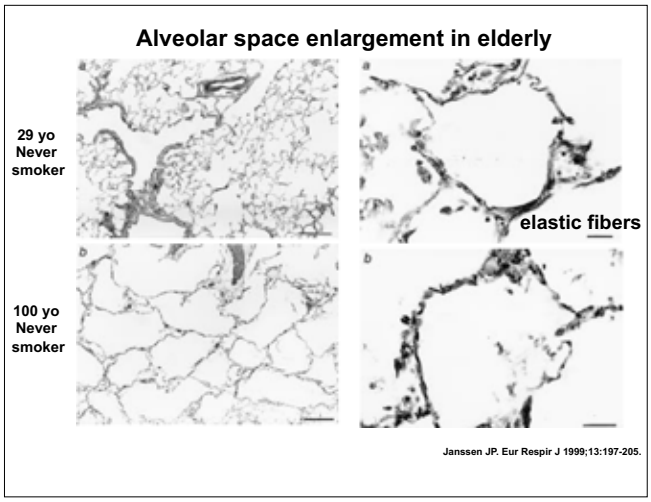


Fig. 16

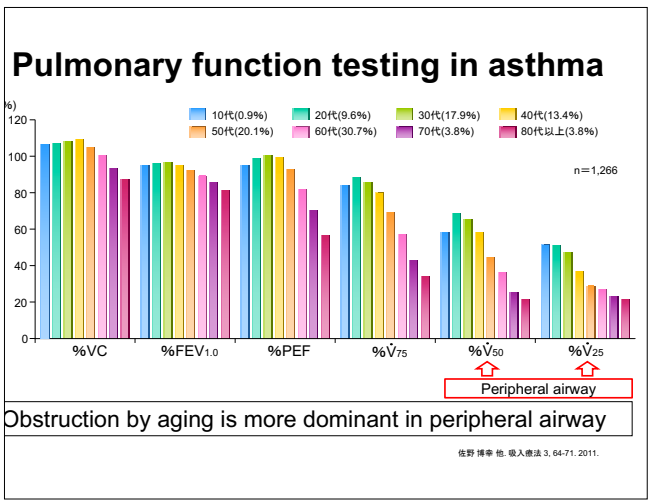


Fig. 17

As you know, smoking causes various diseases, including cancer, cardiac diseases, pulmonary diseases such as COPD, and various other diseases. (Fig. 21)

The problem concerning smoking in Japan is that tobacco vaping products, which contain nicotine, are becoming more prevalent. Three devices—iQOS, PloomTech, and glo—are currently available in Japan. Minors under the age of 20 cannot purchase these products, but they are becoming increasingly popular among the youth in Japan. The popularity of iQOS is rising, from 1.3% in 2015 to 4.9% one year later. And I think it's even more popular now. (Fig. 22)

The problem is that most prevalent use is the youth. This device is frequently used by males aged 20 to 49 years and by females in their 20s. In addition, 98% of all iQOS prod-

Summary

- Although pulmonary function in patients with TE at age 55 yo was within normal range, peripheral airway obstruction, which can lead to COPD was observed in smokers.
- As %FEV1 was numerically lower in patients with upper-limb defects, smoking cessation is highly recommended to such patients.

Fig. 18

1. Pulmonary Function data from health check up for Thalidomide Embryopathy

2. Importance of Smoking cessation

3. Preventing Respiratory Infections



Fig. 19

Prevalence of Smokers in Japan

2018年: 17.9% (Male 27.8%, Female 8.7%)

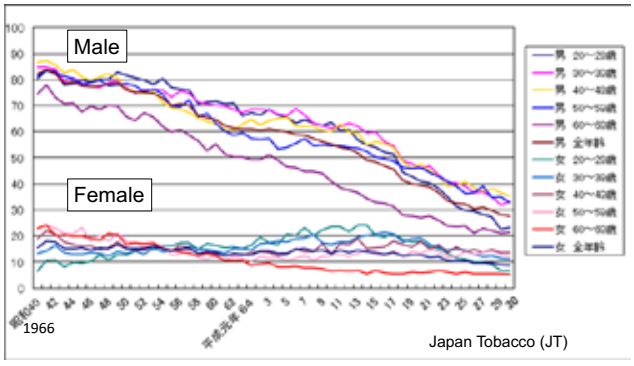
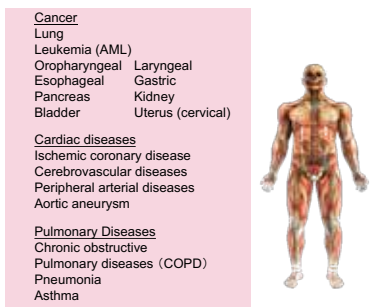


Fig. 20

Effect of Smoking on various diseases



Cancer
Lung
Leukemia (AML)
Oropharyngeal Laryngeal
Esophageal Gastric
Pancreas Kidney
Bladder Uterus (cervical)

Cardiac diseases
Ischemic coronary disease
Cerebrovascular diseases
Peripheral arterial diseases
Aortic aneurysm

Pulmonary Diseases
Chronic obstructive
Pulmonary diseases (COPD)
Pneumonia
Asthma

Reproduction
Low weight birth
妊娠合併症
不妊
Sudden infant death syndrome(SIDS)

Others
Osteoporosis
Cataract
Gastric Ulcer
Diabetes
Metabolic syndrome

Centers for Disease Control and Prevention: Surgeon General's Report—The Health Consequences of Smoking: 2004
1)Uchimoto, S. et al.: Diabet Med 16(11): 951, 1999
2)Ishizaka, N. et al.: Atherosclerosis 181(2): 381, 2005

Fig. 21

Prevailing Heated tobacco products in Japan





20 pieces ¥460 ($ 4)



- Contains nicotine
- iQOS (Philippe Molis) Oct/2014~
- PloomTech (Japan Tobacco) Sep/2015 ~
- glo (British American Tobacco) Oct/2017 ~
- Minor under age of 20 cannot purchase.

Fig. 22

Recent data concerning heated tobacco products

- Prevalence of iQOS is rising
  1.3% in 2015 → 4.9% in 2016
  The most prevalent age:
  Male: 20～49 yo、Female: twenties

- Ninety-eight percent of iQOS is sold in Japan.

- Used by previous smoker who wants to quit smoking: 19% > Never smoker: 1.3%
→suggesting the possibility of gateway for smoking.

Fig. 23

ucts are sold in Japan. iQOS is a product of Philip Morris. Another problem is the user: 1.3% of users are never smokers, which suggests that vaping can serve as a gateway for smoking. (Fig. 23)

This slide shows the mechanism for nicotine dependence. If a person smokes, nicotine binds to the alpha-4 beta-2 nicotinic receptor and causes dopamine release. Dopamine release induces satisfaction, and once dopamine levels decrease, the person feels the urge to smoke again. (Fig. 24)

In Japan, treatment for smoking cessation is covered by health insurance, and patients can be treated once a year for 3 months. Patients have to pay 30% of the total cost, which is about 200 USD for 3 months of treatment. In Japan, two drugs are covered by health insurance, one of which is varenicline. (Fig. 25)

Varenicline binds to the nicotinic receptor and blocks binding of nicotine, which decreases the satisfaction gained by smoking. The binding of varenicline also causes the release of a small amount of dopamine, which reduces the urge to smoke. Another drug used is the nicotine patch. (Fig. 26)

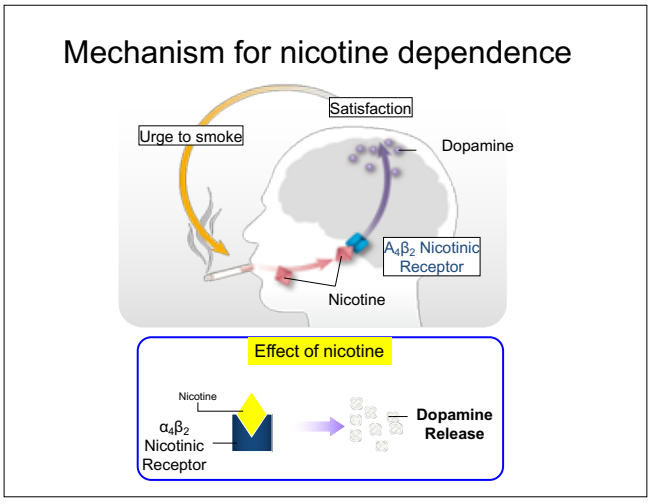


Fig. 24

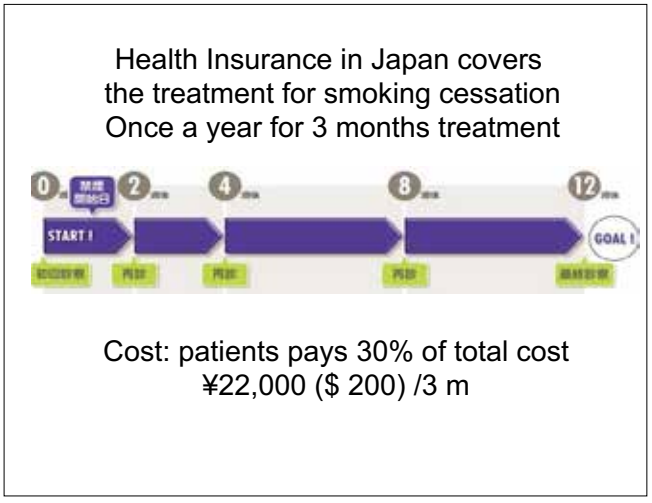


Fig. 25

This figure shows the time course of serum nicotine concentration. The nicotine patch achieves approximately half of the nicotine concentration as that from actual cigarette smoking; this level is continuously maintained, reducing the urge to smoke. (Fig. 27)

The success ratio was slightly but significantly higher in the varenicline group. Therefore, I recommend varenicline as the initial treatment for smoking cessation. (Fig. 28)

These data concern the ratio of successful smoking cessation depending on the month of starting treatment. The best months were March and April, and the worst month was November. I think this may be due to the drinking that occurs at many parties at the end of the year. So, the current season is not bad, and I can recommend current smokers to attempt smoking cessation now. (Fig. 29)

Here is a summary of this section. In Japan, treatment for smoking cessation is covered by national health insurance, and two drugs are available. As smoking rates in TE patients might be higher than the Japanese average, I think we have to inform such patients about the harmful effects of smoking

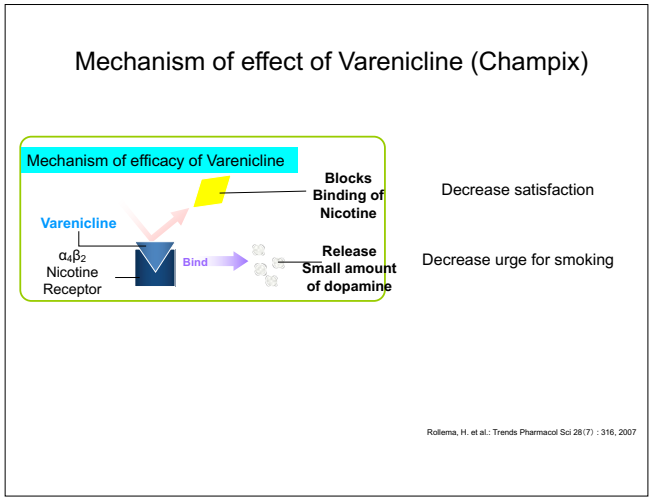


Fig. 26

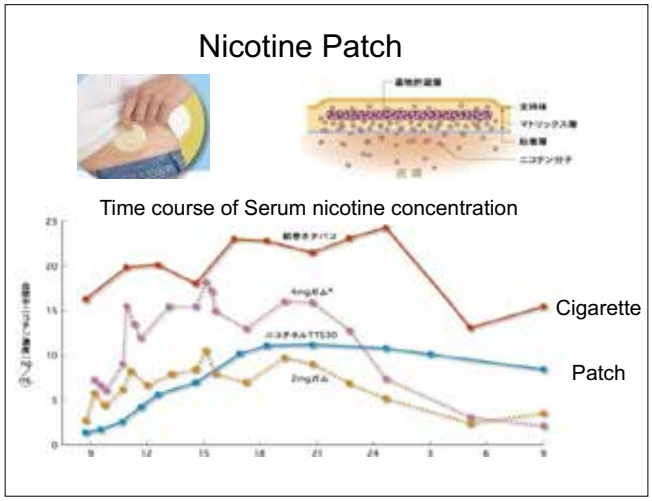


Fig. 27

to promote good health status. (Fig. 30)

I also want to mention the prevention of respiratory infections. This photo shows a crowded train in Tokyo. Very crowded trains are common in Tokyo, and viruses can easily be transmitted to other persons in such a situation. (Fig. 31)

As Dr. Hinoshita showed, I previously mentioned ways to prevent viral infections in a TE management guide published in 2017. I would now like to give some tips for preventing infections. Influenza virus infections generally peak around the winter season, in February of each year. (Fig. 32)

Viral transmission typically occurs through two main routes. One is droplet transmission, and the other is contact transmission. Droplet transmission occurs when one breathes virus from droplets expelled by patients. Contact transmission occurs when someone picks up virus from doorknobs or other surfaces touched by patients. (Fig. 33)

Wearing a mask and avoiding crowded locations are effective to prevent droplet transmission. There are such masks available in Japan. Masks for people with microears are available, and for example, there are masks with long straps, or strapless masks that can be adhered to the cheeks without any straps. In Japan, cedar pollinosis is very common, and these masks are also helpful for preventing such symptoms. (Fig. 34)

Alcohol disinfection is effective to prevent contact risk transmission of influenza virus. There are alcohol spray and gel products available in Japan. This photo shows automatic hand sanitizers that can be operated with one hand and can also be used for the feet. (Fig. 35)

In that guide, we stressed keeping appropriate humidity levels, adequate rest, nutrition, and vaccinations for the management of TE. (Fig. 36)

This brings me to my conclusion. Pulmonary function in TE at the age of 55 was within normal range. It was very good. But peripheral airway obstruction was observed, especially in smokers. And FEV1% values were lower in patients with upper limb defects. Therefore, smoking cessation is highly recommended for such patients.

In Japan, treatment for smoking cessation is covered by national health insurance, and two drugs are available. As

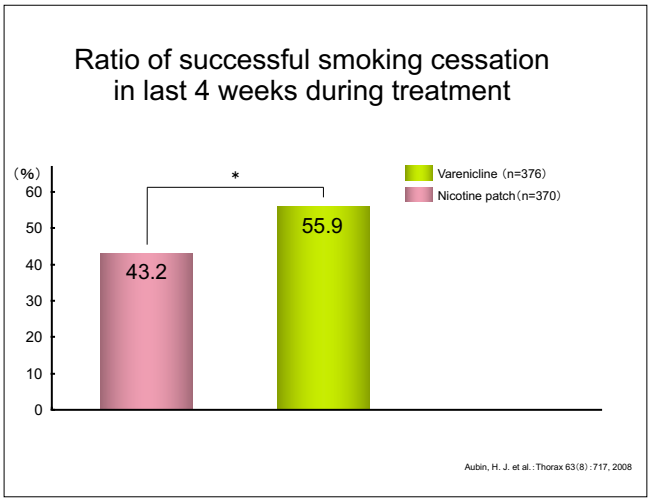


Fig. 28

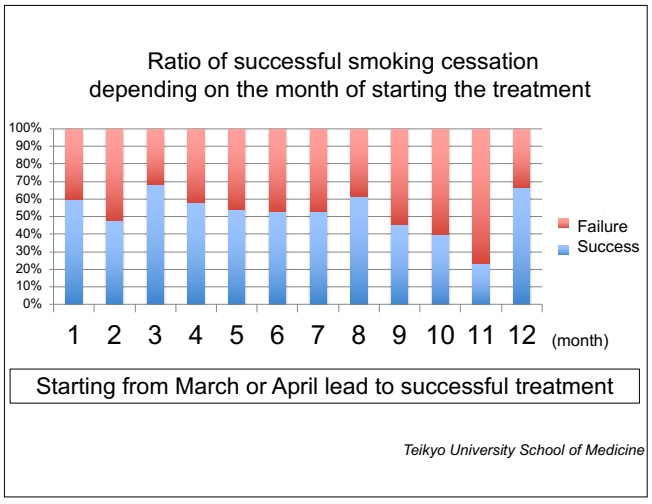


Fig. 29

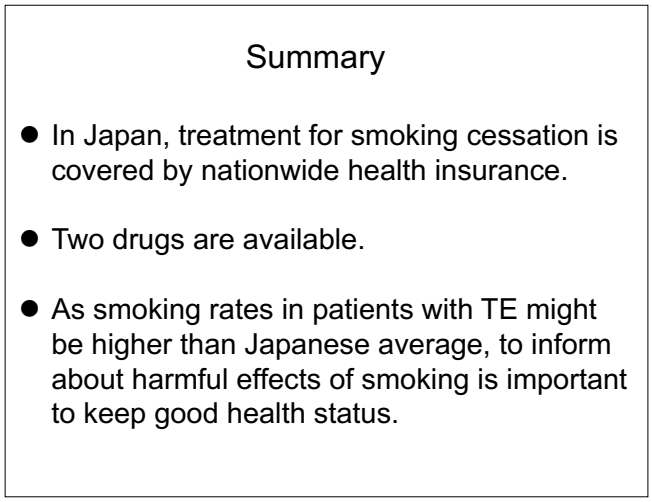


Fig. 30

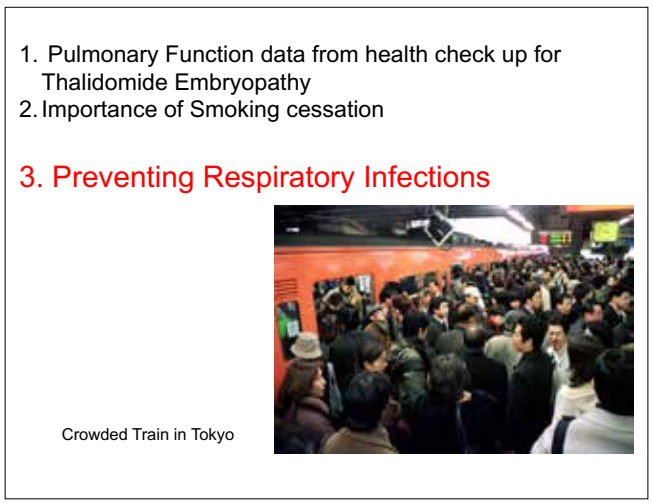


Fig. 31

smoking rates in TE might be a little bit higher than the average Japanese, it is important to inform such patients about the harmful effects of smoking. And because the physical activity of patients with TE potentially becomes lower because of muscle and skeletal pain, the development of COPD also leads to decreased physical activity. Thus, quitting smoking could help prevent the development of COPD. Various devices are also available in Japan to help patients avoid respiratory infections. (Fig. 37))

That is the end of my presentation. Thank you for your attention. (Fig. 38)

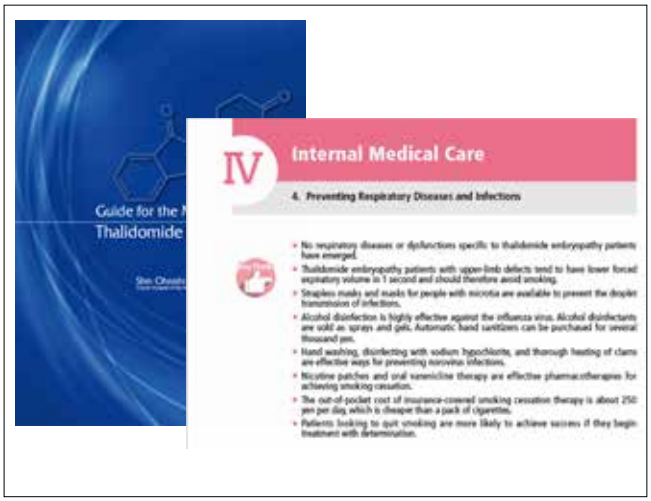


Fig. 32

Preventing Respiratory Infections

Focusing on prevention strategies aimed at the influenza virus

- Influenza virus infections generally peak around February of each year. Infections are generally transmitted via two routes.
- Droplet transmission occurs when someone inhales virus particles contained in droplets coming from the cough of an infected person.
- Contact transmission occurs when someone touches a doorknob or other surface touched by an infected person and then touches their nose or mouth.

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 33

Strategies for preventing infection
Preventing droplet transmission

- Wear a mask and avoid going to crowded locations. Masks for people with microtia are commercially available. Examples are masks with long straps and strapless masks that are adhered to the cheeks with silicone tape.
- These masks also help prevent pollen allergies.



Mask with long straps



Strapless mask

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 34

Preventing contact transmission

- Wash and disinfect hands after going out. Remember to wash your hands after returning home.
- Alcohol disinfection is highly effective against the influenza virus. Disinfecting the hands with an alcohol product is useful for people unable to rub their hands together.
- Alcohol sprays, such as Welpas, and gels, such as Softy Hand Clean, are available. Gel products can be dispensed and applied with one hand. Automatic hand sanitizers can be purchased for several thousand yen. They can be operated with one hand and can also be used for feet.



Guide for the Management of Thalidomide Embryopathy 2017

Fig. 35

- Maintaining optimal humidity levels: Breathing dry air reduces the defensive properties of the airway mucosa, which increases the chance of getting sick. A humidifier should be used to maintain proper humidity levels (50–60%).
- Getting enough rest and eating nutritious, well-balanced meals.
- Getting a flu vaccination: Influenza vaccination reduces the chance of getting the flu and prevents influenza infections from worsening. Flu shots require about 2 weeks to become effective and should therefore be given by mid-December. Only one shot is needed. A shot is needed every year because the effects wear off after about 5 months and prevalence strains change from year to year. Flu shots contain an inactivated vaccine free of pathogens and therefore cannot cause influenza. Adverse reactions, which include redness and swelling at the injection site, fever, headache, and fatigue, normally resolve within 2–3 days.

Guide for the Management of Thalidomide Embryopathy 2017

Fig. 36

Conclusion

- Although pulmonary function in patients with TE at age 55 yo was within normal range, peripheral airway obstruction, which can lead to COPD was observed in smokers.
- As %FEV1 was numerically lower in patients with upper-limb defects, smoking cessation is highly recommended to such patients.
- In Japan, treatment for smoking cessation is covered by nationwide health insurance. Two drugs are available.
- As smoking rates in patients with TE might be higher than Japanese average, to inform about harmful effects of smoking is important to keep good health status.
- As the physical activity of patients with TE potentially becomes lower due to muscle skeletal pain, development of COPD, which can lead to low physical activity, should be avoided.
- To avoid respiratory infections, masks with long straps and strapless masks are available.

Fig. 37



Teikyo University Hospital (Itabashi, Tokyo, Japan)

Fig. 38

Q&A

Tomoko Shiga: Thank you, Dr. Nagase. Are there any questions or comments?

Dee Morrison: Thank you for your presentation. About smokers in the UK, 25% with TE smoke compared with the national average of 17% to 19% according to gender. So this is an important topic for us, too, and we haven't yet tackled it. Obviously, it's quite a sensitive topic, and we are wondering about how to go about it as best we can. It's important that thalidomide survivors like the Trust, and we don't put them off because we are doing lots of other work as well. I am not sure how many really want to stop smoking at the moment. I wondered if you had any idea of how many of your smokers were receptive to stopping smoking and how they are going to go about it?

Hiroyuki Nagase: Yes, thank you very much. I think that some but not all patients with TE get a health checkup within this project. So there is a bias for accessing different types of patients. My impression is that TE patients who smoke do not like to visit the hospital frequently or have checkups regarding their health status. They don't want to see the real status of their health.

So I think it's very difficult to access such patients, especially current smokers. I want to ask the Ishizue Foundation to provide information on the importance of smoking cessation, and if possible, I want more access to patients with TE who smoke. Thank you for your question.

Junichi Horiuchi: Thank you very much. According to your statistics, there are many patients with TE who smoke. Well, I work in a hospital, and I don't have any statistics myself. But those born with birth defects tend to smoke more than others at around the age of 20, that's my feeling. And when they become adults, they would like to show others that they are adults, for example. Your statistics are of the general public. So, if you could present data for the young adults, that will be very helpful in showing that thalidomiders tend to smoke more than the general public. I would like to also emphasize to my fellow people to stop smoking. Thank you.

Hiroyuki Nagase: Thank you very much for your comment. The prevalence of smoking, especially in young females, is a big problem in Japan. The prevalence in males is continuously decreasing, but the ratio in young females is not. So, as you say, it's an important problem. Thank you.

Shadi-Afarin Ghassemi: Thank you very much. I feel like I have comments in every session. So, please excuse me. It's just a comment. I mean I think, a lot of work has to be done to prohibit smoking. And as you say, it's right for smoking thalidomiders to just seek free healthcare.

Actually, in Sweden, we have started to ask patients with prosthesis, endoprosthesis, and total hip or knee prosthesis not to smoke at all at least 6 weeks before their surgery, whether they are thalidomiders or non-thalidomiders. If they show that they have been smoking days or weeks before the surgery, the surgery is off. So, yes, we actually cancel that, yes.

And from this year, July 1, there is a new law that you cannot smoke even outside a restaurant. We usually have some places for smokers, like in a courtyard or outside the hospital, but not inside. It's been, I mean it's been forbidden for many years now. But from July 1, you cannot smoke even outside. So, if anybody is passing by the bus station or train station, it's free air, I mean, but you are not allowed to smoke.

So, I think these things don't make it personal when it comes from the governor. You know it's, you don't need to ask any person please stop smoking. You say, this is the law, and that's it. So it's much easier to handle that really. That was just a comment.

Hiroyuki Nagase: Thank you very much for your comment. I completely agree with you.

Fumihiko Hinoshita: An additional comment from me. You know, in Japan, there is also a tendency for the government to strengthen the regulation of smoking, year by year. And recently, some new acts were enacted by law, not to smoke in restaurants or public places, not only inside, but also outside of those buildings. Okay.

Hiroyuki Nagase: We are changing. For the 2020 Olympic Games in Tokyo, things are changing.

Klaus M. Peters: Thank you for your presentation.

Hiroyuki Nagase: Thank you.

Klaus M. Peters: I think the rate of smokers in Germany is also higher among thalidomiders than among the general population. But there are also other things being abused, especially alcohol. Alcoholism is higher in thalidomiders than in the general population in Germany, as is other types of drug abuse. I think that's a problem. This could be due to chronic pain.

Hiroyuki Nagase: Thank you for your comment.

Fumihiko Hinoshita: Thank you very much, Dr. Peters, for your nice comment. I should respond to that question. In Japan, I'm sorry to say, we did not examine how many thalidomiders abuse alcohol or drugs. So we cannot show you the exact percentage or ratio of thalidomiders who are alcoholics or drug abusers. Do you have any information about this, Mr. Sato?

Tsugumichi Sato: No, I don't have any information about drug abuse or alcoholism.

Fumihiko Hinoshita: Do you feel that there are many such thalidomiders?

Tsugumichi Sato: I've never heard it this among thalidomiders, Japanese thalidomiders. I don't know any Japanese thalidomiders affected by drug abuse.

Christina Ding-Greiner: We should think of the fact that thalidomiders have a higher percentage of psychic diseases, more bouts of depression, and more anxiety disorders. We know that people with mental diseases are the strongest smokers. I read a paper that said about 80% of people with psychic diseases smoke. So, I suppose it's comprehensible that there are more smokers among thalidomiders.

Hiroyuki Nagase: Thank you very much for your comment, and I completely agree with you. I work at a smoking cessation clinic, and in that clinic, the success rate of smoking cessation is significantly lower in patients with depression. The overall success rate is 67%, but in patients with depression, it is 33%. I think it's very difficult, but 30% of patients can quit smoking. So, we continuously have to say to patients, "let's try to quit smoking". Thank you very much for your comment.

Tomoko Shiga: So, the time is up. That's the end of this session. Thank you, Dr. Nagase.

Hiroyuki Nagase: Thank you very much.

Mortality in Thalidomiders in Germany: Is Underdiagnosed Hypertension the Cause?

Jan Schulte-Hillen

Notfallzentrun Klinik St. Anna, Luzern, Switzerland

Ryoji Kayamori (Moderator)

I am glad to be here with Dr. Jan Schulte-Hillen. He earned his medical degree at the University of Münster in 1988 and his PhD from the University of Münster in 1991. Currently, he is working as a GP in Lucerne, Switzerland. His clinical experience has been expanding, partially because he is multilingual. He has a good command of German, as it was his mother's tongue, in addition to English, French, Spanish, Italian, and Portuguese. His hobbies are also diverse, including sailing, skiing, motorcycle riding, skateboarding, vintage cars, and flying. This is unbelievable for Japanese people who grew up on a small island country.

One more thing, as you know, his father is Mr. Karl-Hermann Schulte-Hillen, the famous lawyer. Without him, there would be no thalidomide story. Jan was born on April 25, 1961 with short arms. In June, 1961, his father visited and asked Dr. Widukind Lenz in Hamburg why were lots of malformed babies born with so-called Wiedemann syndrome. What was going on in West Germany? Sadly, Mr. Karl-Hermann Schulte-Hillen passed away on January 14, 2017. Now, Jan's theme is mortality in thalidomiders in Germany and the prevalence of hypertension as a cause. Could you please begin your talk? Thank you.

Jan Schulte-Hillen

Thank you very much for the kind words, especially for my father. It is a big honor for me to speak to you today.

Yes, let me jump to the main slide of my discourse here. (Fig. 1)

What really concerns me and what really annoys me and puts a big question mark in my mind are the two graphs you are seeing here. This is the mortality, the age-related mortality of the German population data derived from the Federal Bureau of Statistics in Wiesbaden. And this is the same data for the thalidomiders. And here you see the first mistakes. I put the comma at the wrong place. It should read 1.24. That means that in the year 2017, a German person born in 1961 would have a 0.5% chance of dying that year. Whereas, a thalidomider born in 1961 would have a probability almost twice as high in 2017.

How did I get these data? I got these data by comparing the data from the statistics bureau or the federal bureau in Germany with the mortality rates issued and published by the Thalidomide Trust in Germany. (Fig. 2)

This is the same, only with the numbers in it. I think it's safe to say that at least in Germany, thalidomiders may be a population at risk with double the mortality of age-related groups.

The reason for this is not known, to my knowledge. I think we do not precisely know why this is so, and we do not know if the data from Germany are representative of the worldwide situation. (Fig. 3)

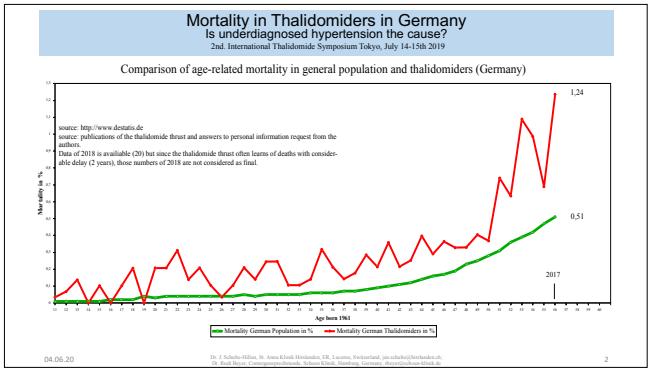


Fig. 1

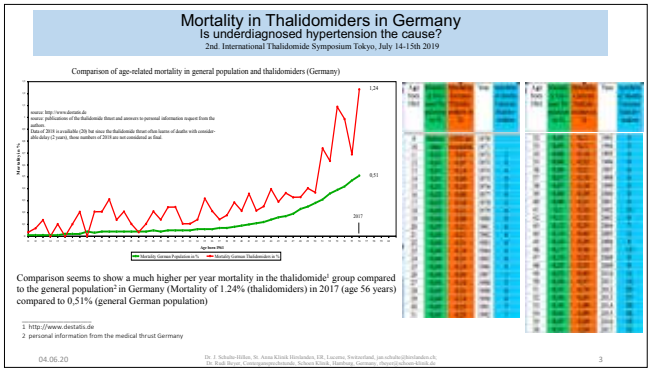


Fig. 2

What could be discussed may be a general accelerated aging due to unknown reasons or maybe social isolation, psychological problems, or a higher, let's say, "wear and tear," because of the limited range of motion and limb defects.

I mean, if you have to move your entire body to reach a glass of water every time in your life, this is not going to be without consequences on the tissue. And maybe there are higher stress levels, income issues, family life, and social aspects. We already heard from several sources that thalidomiders tend to have a much higher prevalence of metabolic syndrome, perhaps also due to the limited possibility of physical exercise.

And of course, a big issue is also limited access to public managed care programs due to limited mobility and iatrophobia. When I talk to peers and ask them why they don't go to see a doctor, many of them reply, "I don't want to stay in the waiting room and be stared at it." It can be as simple as that. There might be several reasons for the higher mortality, and I would like to focus on this one: possible arterial hypertension. (Fig. 4)

Is there any evidence for hypertension as a problem in thalidomiders? Yes, there is. We just heard from Dr. Hinoshita that he compared the rates of hypertension in thalidomiders with the normal Japanese population and did not find any significant difference. As I remember, Dr. Tomoko Shiga found a higher risk for cardiovascular diseases in her Japanese study group and a prevalence for hypertension of almost 50%, which would be an enormous number. We are comparing thalidomiders in Japan with normal people and non-thalidomiders in Germany. But the prevalence of hypertension in Germany in the normal population in an age-related group is 31%. So, this is much lower.

We have no idea why this is so, and there are no groups for comparison, so I really had to dig very, very deep, and what I found was a publication from Nallegowda, reported in 2012. He found a significantly higher prevalence of cardiovascular diseases in amputees, and he assumed the observed higher prevalence of hypertension in this group to be the reason for this.

In 2015, Kowalski found a higher prevalence of cardiovascular diseases in a Brazilian study group of thalidomiders. I have no idea how old this study group was, but I think the thalidomiders in Brazil should be about 10 years younger than us? No?

Lavinia Schuler-Faccini

The same age, no. I will show this later.

Jan Schulte-Hillen

This is very interesting, yes. I am looking forward to that. Okay. Just a couple of words about hypertension in general. (Fig. 5)

Like you all know, I don't have to put emphasis on this. Elevated blood pressure is considered the major risk factor for long-term multiorgan diseases involving the heart, brain, kidney, and eyes. Because most of the time, it becomes clinically relevant at the end point of a disease, it's called a silent killer because it does not show any preliminary symptoms. High blood pressure doesn't cause pain. The correct self-measurement of blood pressure is mandatory for prophylaxis of these diseases, and is part of every single modern health program. Every health program involves self-measurement of blood pressure. And this is the situation for thalidomiders. Due to anatomic reasons, thalidomiders with upper extremity defects show problems in measuring

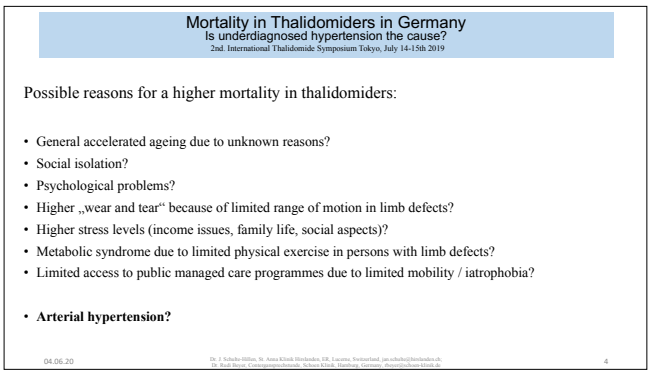


Fig. 3

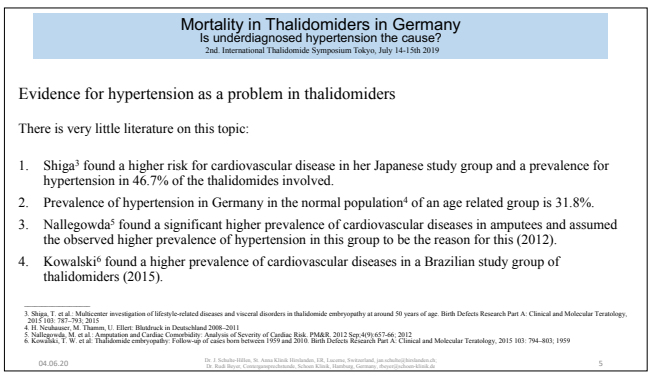


Fig. 4

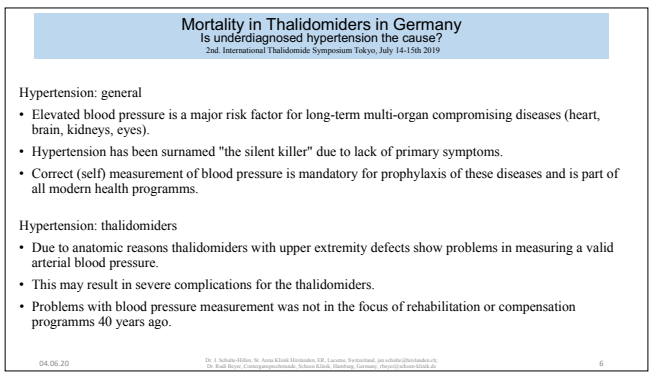


Fig. 5

valid arterial blood pressure. I will come to the reasons for that later. This may result in severe complications among thalidomiders.

I would like to put emphasis on the fact that problems with blood pressure measurement were not the focus of any rehabilitation or compensation program 40 years ago. Blood pressure, hypertension—no blood pressure as "blood pressure 'period'" was only an issue during surgical interventions when anesthetists just tried to figure out how to keep the systolic blood pressure above 120 mmHg or something like that, and then everything was safe. Nobody ever had any concern about diastolic blood pressure. And as you all know, this is more important in terms of the long-term defects of high blood pressure. (Fig. 6)

Indications for incorrect blood pressure measurements in thalidomiders. I do not have any doubt that you can take blood pressure in thalidomiders. But, as an educated guess, I would say most of them are wrong. What would be an indication for such an assumption? I told you I was working for the Thalidomide Trust in Germany, who have no idea that I am standing here now. My work is in no way endorsed by them. As one of the experts of the medical committee, I have come to read many, many medical reports of patients who, for example, apply for a higher compensation because they say "the hips don't work anymore," "I can't move my hands," or "I developed carpal tunnel syndrome."

Reading between the lines, I find strong evidence of a history of stroke and myocardial infarction from the age of 40 and upwards, which is mentioned only in as a side remark. This is one thing where I say that something must be going on. The other thing is that many, in many ophthalmologic investigations, fundus hypertonicus in random eye investigations for other indications has been found, in spite of the family physician having always stated blood pressure to be normal.

So, whatever the doctor measured was not the correct blood pressure. They also found elevated blood pressure with invasive measurements in surgical interventions without the patient having any history of documented hypertension. (Fig. 7)

So, these are what are regarded as mandatory conditions for correct blood pressure. A correct cuff diameter in relation to diameter of the arm and hand. However, in thalidomiders, this is not possible. The cuff must be fixed snugly and the arm must be at the height of the heart. In thalidomiders, this is often not possible. An upper arm with normal anatomy must be patent. It is not. The diameter of the arm artery must be in normal relation to the diameter of the upper arm, but there are no data available. The arterial brachialis should be in the normal anatomical location, but this is very questionable in thalidomiders. And in the case of, you know, wrist measurement devices, the arteria radialis on the radial side of the wrist must be patent for wrist blood pressure measurement devices. The arteria radialis is very often miss-

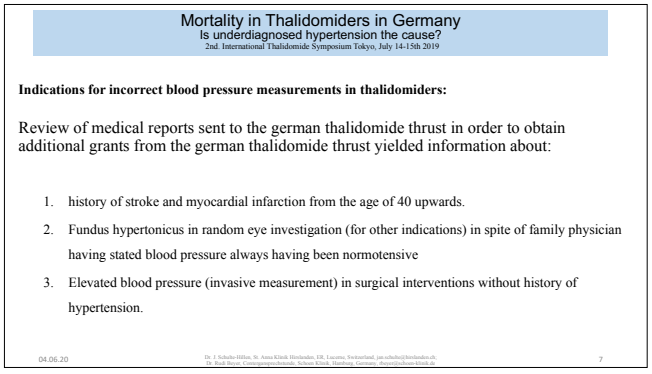


Fig. 6

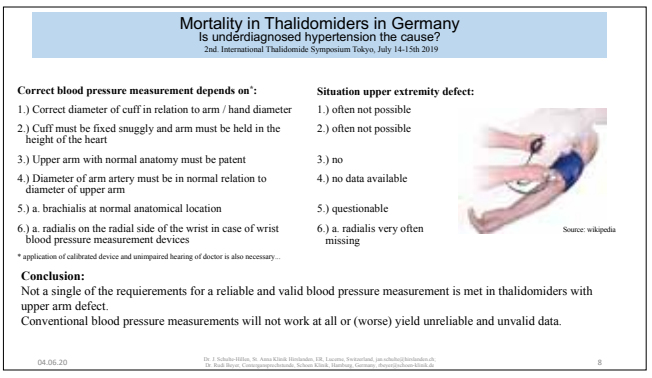


Fig. 7

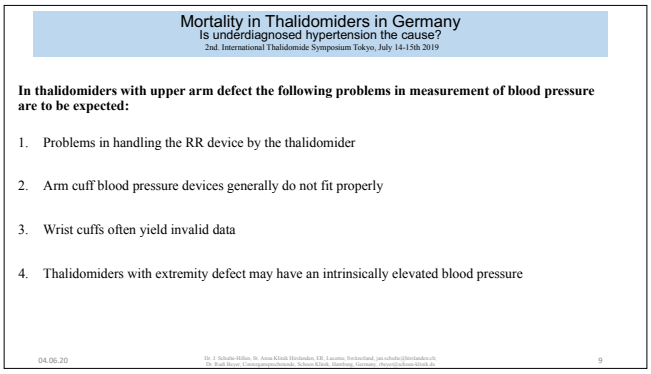


Fig. 8

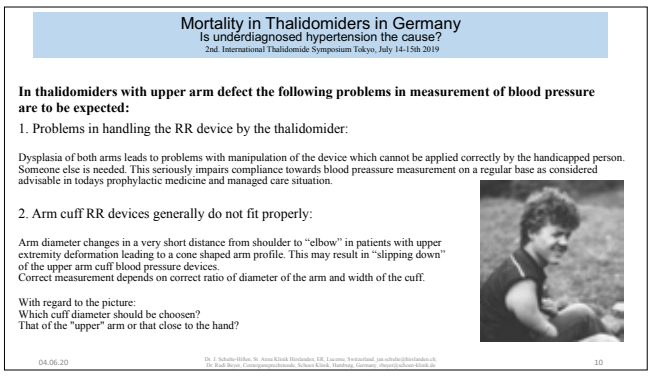


Fig. 9

ing in thalidomiders.

Concerning the radial artery, I understand that in Japan, there are many, many long-armed thalidomiders, and I would like to tell you that we have many long-armed thalidomiders in Germany with a missing arteria radialis. This goes to the extreme, where the hand is anatomically normal, and hypoplasia of the thenar is the only sign or indication of thalidomide damage you see.

Many of them are missing the radial artery, so wrist cuffs do not work properly, not even in long-armed thalidomiders. (Fig. 8)

Therefore, not a single requirement for reliable and valid blood pressure measurement is met in thalidomiders with an upper arm defect. Conventional blood pressure measurements will not work at all, or worse, will yield unreliable and invalid data. (Fig. 9)

In thalidomiders with upper arm defects, the following problems in terms of blood pressure measurement are to be expected. Handling the device itself is going to be problematic. I couldn't handle it with my arms. Arm cuff blood pressure devices generally do not fit properly. Wrist cuffs yield invalid data, and thalidomiders with upper extremity defects may have intrinsically elevated blood pressure, as I showed, compared with an amputee group. Handling the device is kind of self-explanatory, and the cuff generally does not fit properly. So, you see, this is a more conical shape, so the cuff is going to slip down. With regard to the correct diameter of the cuff, which arm diameter do you choose, up here or down here? This is very questionable. (Fig. 10)

This is a radiograph of an upper extremity. I would like to ask, where do you expect the arteria radialis to be? There is none at all. And, yes, I will skip this. I already told you that perhaps they have intrinsically elevated blood pressure due to the reduced overall diameter of the blood vessels. (Fig. 11)

So, thalidomiders in Germany seem to have higher age-related mortality than the general population. After all, the prevalence of arterial hypertension seems to be high in the thalidomide population, as mentioned by Dr. Shiga, but it still might be underdiagnosed because of the problems I described. (Fig. 12)

Thalidomiders are therefore excluded from one of the most basic and most important types of biometer monitoring. Higher mortality and underdiagnosed arterial hypertension could be related, and there is need for guidelines concerning blood pressure evaluation for thalidomiders. (Fig. 13)

We talked about this already. Suggestions for future mortality data and the prevalence of hypertension should be compared with those from other countries. (Fig. 14)

I did not find much on this topic in the literature. The development of the mortality rate should be subject to close follow-up, and family physicians and clinical doctors should be notified about problems when blood pressure measurements are not correct.

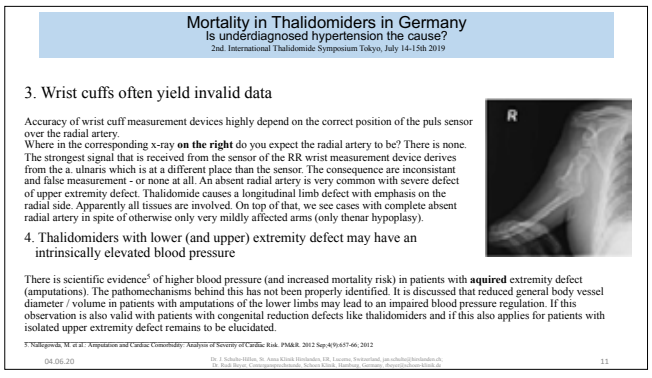


Fig. 10

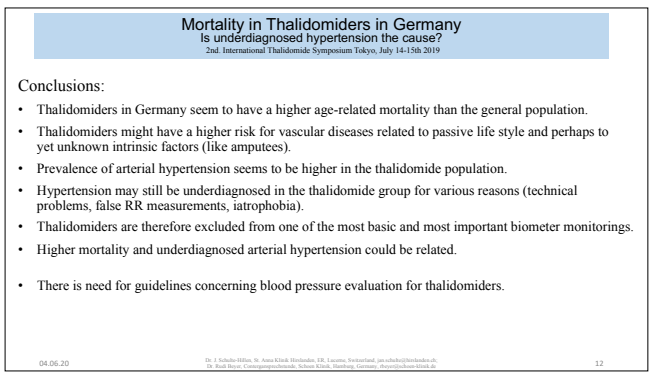


Fig. 11

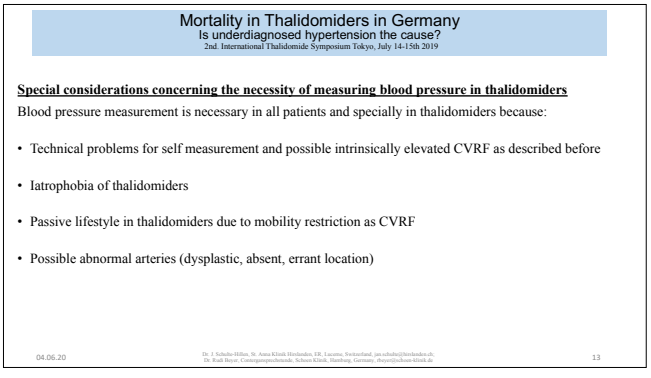


Fig. 12

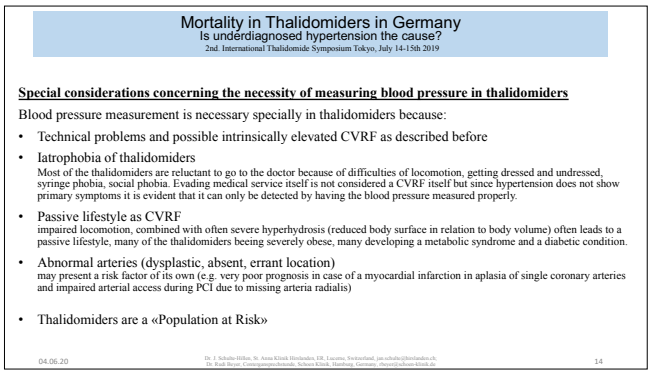


Fig. 13

I also think we are in dire need of clinical research on noninvasive blood pressure measurement devices that use something like pulse wave analysis instead of the traditional Riva-Rocci approach. All investigations in that direction should strongly be encouraged. There is also a need for guidelines, as I said.

I mean, the Riva-Rocci approach, if you come to think of it, is more than 100 years old. We are still working with it and it works well, except for three conditions that yield incorrect data. The first is thalidomiders, the second is diabetic angiopathy, and the third is arteriosclerosis. (Fig. 15)

My suggestions for thalidomiders and blood pressure measurement at this time is as follows. Patients with isolated leg defects and normal upper extremities should measure their blood pressure in the same way as every other patient with normal arms. Patients with upper arm defects should have their blood pressure measured once on both legs and both arms, and if the result yields a difference of more than 20 mmHg in the legs compared with in the arms, the legs should be used for future blood pressure measurements; that is, the arteria tibialis posterior correction factor, as mentioned above and shown by Yoshizawa.

The literature on this remains very limited. Yoshizawa found that he could get reasonable results if he took the systolic blood pressure of the arteria tibialis posterior, added 8 mmHg, and multiplied this by 0.88 mmHg. He considered this a valid correction factor.

Another possibility that I find quite appealing is measurement by proxy, that is, if possible, you find a healthy reference person not affected by extremity defects who matches the thalidomide patient in terms of age, sex, and leg circumference, and you take the blood pressure in the legs and arms with cuffs of adequate size. The ratio between arm and leg blood pressure in the normal person can be applied to evaluate the actual blood pressure in the legs of the thalidomider. You don't have to do this very often. I think it might be okay to get a correction factor once per year, maybe even less.

Then, I think patients with defects of the upper and lower extremities should have their intra-arterial blood pressure taken once as an equation for a personal ratio between the daily blood pressure taken at the determined localization, like, let's say a shortened limb, and the correct intra-arterial pressure. This can either be done with a planned surgical intervention, or especially for this purpose, after careful consideration of the risks and benefits, of course. I mean, it's an invasive procedure.

In general, as I said, for blood pressure measurement on the legs, the problems of false results in diabetic arteriopathy and atherosclerotic lesions must be taken into account because you get wrong results in those scenarios. (Fig. 16)

Talking about invasive blood pressure measurement, this is a plot that I had done during a surgical intervention, and I had the anesthesiologist take intra-arterial invasive blood

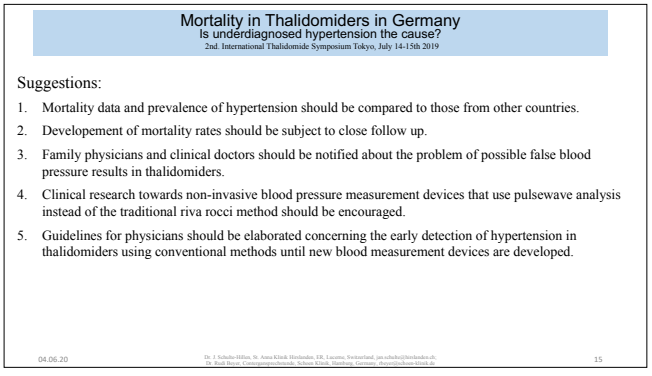


Fig. 14

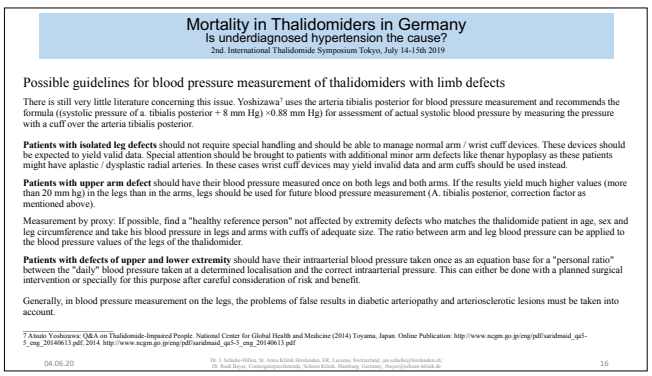


Fig. 15

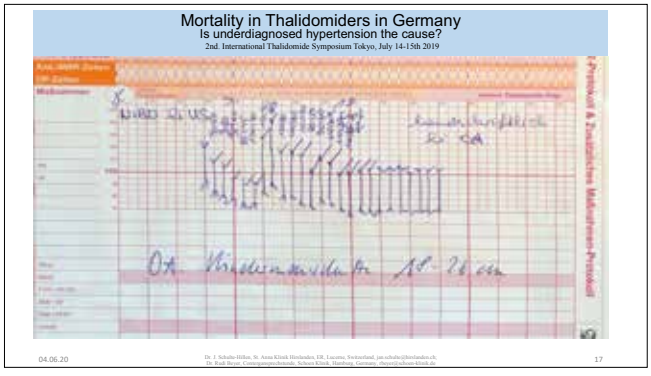


Fig. 16

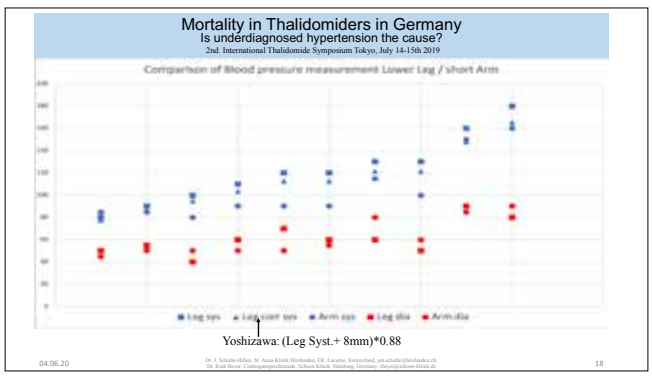


Fig. 17

pressure. Afterwards, he said, "I didn't want to. I didn't do the invasive measurement. What I did instead is noninvasive blood pressure on the left side, lower leg, and left side upper arm". I would like to show you what the problem is. (Fig. 17)

What you see here is not a graph. I just plotted several singular measurements. Blue is systolic. Red is diastolic. The square is a leg and circle is an arm. The triangle is this thing with a correction factor from Yoshizawa, which of course, shows an excellent correlation because it's a mathematical function.

If you take a look at this, systolic leg and systolic arm differ by up to 30 mmHg, which is completely unacceptable. And even in the diastolic, you have a difference up to, well, at least in my case, up to 20 mmHg; completely useless for any prophylactic program concerning or involving blood pressure. (Fig. 18)

Generally, and for all thalidomiders, we suggest the following procedures. As long as there is no other method available, we still suggest Yoshizawa's method, as described above, and a correction factor. And please, in all planned surgical interventions where invasive intra-arterial blood pressure is taken anyway, you should try to talk your patients and the anesthesiologist into making comparisons between invasive and noninvasive blood pressure measurements. And please note the diameter of the cuff that was involved, and the place where the blood pressure was taken. This is absolutely mandatory.

With this, you could establish your personal ratio for this patient between intra-arterial blood pressure and cuff measurement results. As an additional measure, I would suggest that regular laboratory investigations should include lipids, cholesterol, and uric acid, but not creatinine, because many thalidomiders have very reduced muscle mass. So, creatinine wouldn't work; however, a rise in creatinine would show you something, whereas isolated creatinine would not.

I was told that the more sensible thing would be to do the cystatin C, and of course, glucose and electrolytes and renal analysis should include microalbumin, and then, of course, further examinations like ECG, echocardiography, duplex sonography of extracranial brain vessels and 2D-echo vessels, 24-hour blood pressure measurements if possible, and then perhaps pulse wave assessment. In addition, I would send thalidomiders to a doctor once per year to see if they could find any sign of fundus hypertonicus because this is not a sign; this is proof of hypertension that is not well corrected.

This is a bit of a look into the future. There are possible technical approaches for blood pressure measurement. One is called ClearSight and another is called SOMNOtouch. But they do not work with our patients because they need a cuff measurement as a reference point. So, this does not work. (Fig. 19)

I think the most promising approach, which is still in the development stage, is Dr. Aflex's device. He measures in the buccal cavity. He measures blood flow in the arteria facialis. And I think this is very interesting. The approach is, I don't know if I get the word correct, photoplethysmography, that's low intensity infrared signal combined with an inflatable pad. So, he inflates the pad to the very point where the arteria facialis does not pass any blood anymore, and then he opens it and looks at how fast it recovers or something like that. I have not entirely understood the procedure, but I think this is a very interesting thing because I don't think the buccal or facial artery was affected in a single thalidomider, and you could use it for everybody else as well.

The gentleman in the picture is Gernot Stracke, one of the big players in thalidomide in Germany, from Hamburg, who works together with Dr. Beyer. If you could post this, if you could fix it to a wall or to a socket or something like that, the thalidomiders, even those without any arms, wouldn't even have to touch it to use it. All they have to do is to let their mouth use the system.

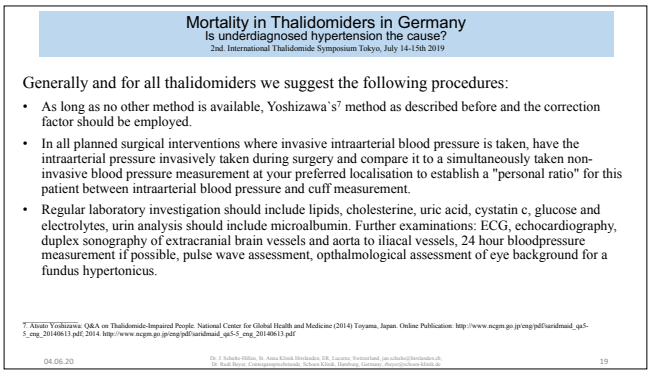


Fig. 18

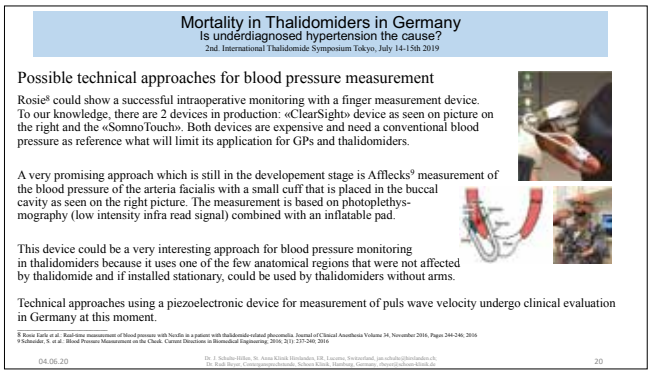


Fig. 19

And I think this looks like the shape of things to come, something like this. Okay, that's it. Thank you very much.

Ryoji Kayamori: Thank you, Jan. Lots of comments and questions would be expected, but time-wise, I have to move to another presentation. Thank you, Jan.

Jan Schulte-Hillen: Okay.

Lessons from Thalidomide Embryopathy and Sharing Information with the Next Generation: From the Physiatrist's Point of View

Nobuhiko Haga

Department of Rehabilitation Medicine, The University of Tokyo, Tokyo, Japan

Ryoji Kayamori (Moderator)

The next presentation is Professor Nobuhiko Haga from the University of Tokyo. The title of his presentation is "Lessons from Thalidomide Embryopathy and Sharing Information with the Next Generation: From the Physiatrist's Point of View". Could you start please?

Good morning, everyone. My name is Haga from the University of Tokyo. I work in the Department of Rehabilitation. I joined the research group 2 years ago. (Fig. 1)

So, what we as physiatrists have done since 2017 is participate in a mobility symposium in Hamburg in 2017, hold health meetings in five Japanese sites from 2017 to 2018, visit Germany and UK to meet experts, including some of you, last year, and examine thalidomiders in clinics. On every occasion, we had the chance to hold discussions with thalidomiders. (Fig. 2)

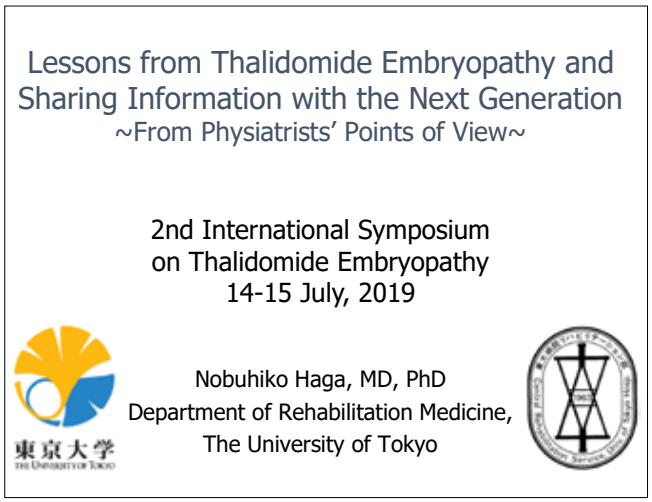


Fig. 1



Fig. 2

So, this is the mobility maintenance of people with thalidomide embryopathy (TE): prevention, pain therapy, and alternative therapeutic procedures. This symposium was held in September in 2017 in Hamburg by Dr. Rudolf Beyer. I have heard that around 200 thalidomiders participated from all over Europe. (Fig. 3)

This is the schedule for the first day. We had many topics related to rehabilitation medicine. (Fig. 4)

This is the schedule for the second day. On the second day, we had several topics on complementary and alternative medicines. From that symposium, I learned the importance of mobility maintenance, the use of assistive devices, a personalized rehabilitation approach, especially for pain, and the application of complementary and alternative medicines. (Fig. 5)

We then had health meetings at five Japanese sites. During these meetings, held at local thalidomiders' meetings, we discussed problems with health and daily living with thalidomiders. (Fig. 6)



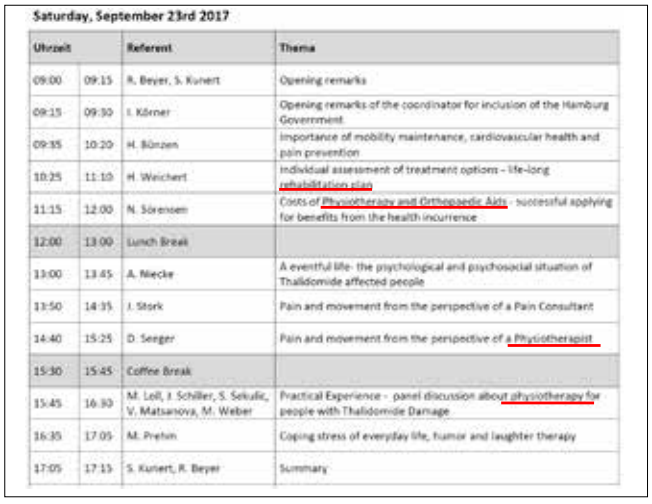
Fig. 3

All participants discussed their health problems. This was moderated by our rehabilitation specialist, Dr. Fujitani. The participants, after self-introductions, took turns presenting their recent problems with health and daily living. The moderator promoted a discussion on the participants' problems and their experiences of solving problems by referring to other participants' opinions. We then held individual interviews. Rehabilitation specialists had interviews with the participants who applied, and according to the complaints of the thalidomiders, we examined them and gave some advice. The total number of thalidomiders who applied for individual interviews was 36 in these five meetings. (Fig. 7)

The following shows health problems related to rehabilitation medicine. As for consulting a doctor, after the retirement of a doctor who had treated the thalidomider since childhood and had sufficient knowledge of TE, it was difficult to find another doctor. The thalidomiders cannot consult their family physicians about their pain or numbness. Thalidomiders feel stressed when the medical staff say that they have no knowledge of TE. (Fig. 8)

So, regarding pain and numbness, the thalidomiders cannot judge whether their symptoms are related to TE. Many thalidomiders complain of pain and stiffness in the shoulder and neck. Drug treatment and massage are common. Personalized exercise therapy was effective in some patients. There were opinions that the effects of chiropractic treatment and massage were temporary and not constant. Cervical spondylosis was detected in many of those who complained of numbness. Some of them were assumed to be affected by carpal or cubital tunnel syndrome. Some thalidomiders complained of chills in their forearms and hands.

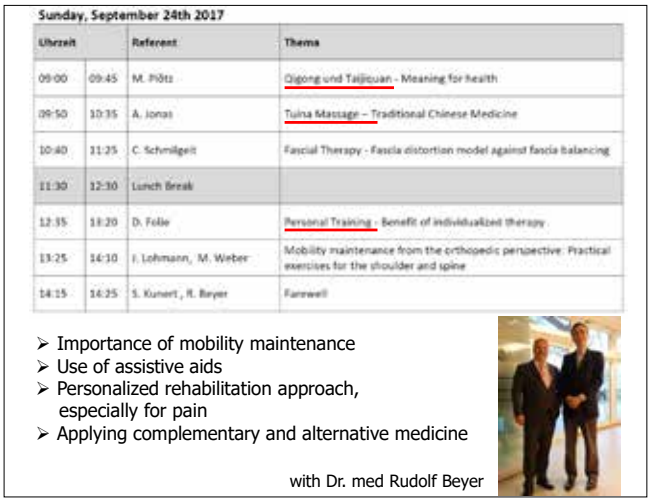
As for progressive physical dysfunction, some thalidomiders tended to drop objects when pinching with the fingers. Side pinching with fingers is common because of thumb hypoplasia. Some complained that their wrists often subluxated. Some who used their feet for many activities commented that they could not raise their legs as high as before, and that their balance decreased when standing on one leg and using another leg as a hand. Walking was common for the prevention of metabolic syndrome.



Saturday, September 23rd 2017

Uhrzeit		Referent	Thema
09:00	09:15	R. Beyer, S. Kunert	Opening remarks
09:15	09:30	I. Körner	Opening remarks of the coordinator for inclusion of the Hamburg Government
09:35	10:20	H. Bönzen	Importance of mobility maintenance, cardiovascular health and pain prevention
10:25	11:10	H. Weichert	Individual assessment of treatment options – life-long rehabilitation plan
11:15	12:00	N. Sörensen	Costs of Physiotherapy and Orthopaedic Aids - successful applying for benefits from the health incurrence
12:00	13:00	Lunch Break	
13:00	13:45	A. Niecke	A eventful life- the psychological and psychosocial situation of Thalidomide affected people
13:50	14:35	I. Stork	Pain and movement from the perspective of a Pain Consultant
14:40	15:25	D. Seeger	Pain and movement from the perspective of a Physiotherapist
15:30	15:45	Coffee Break	
15:45	16:30	M. Loll, I. Schiller, S. Sekulic, V. Matsanova, M. Weber	Practical Experience - panel discussion about physiotherapy for people with Thalidomide Damage
16:35	17:05	M. Prehn	Coping stress of everyday life, humor and laughter therapy
17:05	17:15	S. Kunert, R. Beyer	Summary

Fig. 4



Sunday, September 24th 2017

Uhrzeit		Referent	Thema
09:00	09:45	M. Plötz	Qigong und Taijiquan - Meaning for health
09:50	10:35	A. Jonas	Tuina Massage – Traditional Chinese Medicine
10:40	11:25	C. Schmilgeit	Fascial Therapy - Fascia distortion model against fascia balancing
11:30	12:30	Lunch Break	
12:35	13:20	D. Folle	Personal Training - Benefit of individualized therapy
13:25	14:10	I. Lohmann, M. Weber	Mobility maintenance from the orthopedic perspective: Practical exercises for the shoulder and spine
14:15	14:25	S. Kunert, R. Beyer	Farewell

- Importance of mobility maintenance
- Use of assistive aids
- Personalized rehabilitation approach, especially for pain
- Applying complementary and alternative medicine

with Dr. med Rudolf Beyer

Fig. 5



Fig. 6

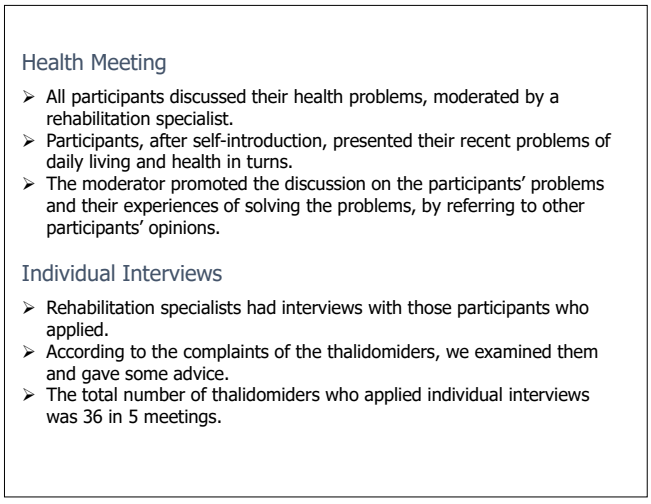


Fig. 7

As for inconveniences in work and life, though many workers complained of fatigue and shoulder stiffness, most hoped to continue their job. As for clothes, shoes, and bags, thalidomiders searched for products that were easy for them to use or modified them. They had difficulty in handling large objects, e.g., refrigerator doors, and in using small tools. Some used self-help tools. As for inconveniences in daily living, some thalidomiders positively sought support from others, some never bought products that were difficult to open, like vacuum-packed ham, and some abandoned what they could not do without support, like going outdoors with an umbrella on rainy days. (Fig. 9)

Last year, we visited Germany and the UK to meet experts like this. (Fig. 10)

In Heidelberg with Dr. Ding-Greiner, I learned that many thalidomiders were beginning to find difficulty in independent living because of pain and arthritis. To maintain independent living, they must change the height of various things in the kitchen, as well as the toilet, shower, and tables, and remodel their cars. No treatment methods for secondary impairments in thalidomiders have been established.

In Cologne, a German–Japanese symposium was held by Professor Peters. The outpatient center for thalidomiders is open 4 days a week, and provides examinations by medical doctors, physical and occupational therapists, and acupuncturists. They put a lot of effort into pain evaluation, partly because pain is influenced by psychological factors. (Fig. 11)

In London at The Thalidomide Trust, 93% of thalidomiders in the UK have musculoskeletal problems.

The Thalidomide Trust provides information advice on TE for general practitioners to foster good relationships between GPs and thalidomiders. In Hamburg, I again met Dr. Rudolf Beyer. The Thalidomide Clinic Hamburg provides initial medical examinations and admission for 4 or 5 days. Orthopedic surgeons, pain consultants, physical therapists, and psychologists join and conduct re-examinations in the outpatient clinic to control treatment. Though no new treatment exists for pain in TE, techniques focusing on fasciae, like physical manual therapy and osteopathy, are fundamental, he said.

Health Problems related to Rehabilitation Medicine

Consulting a Doctor
- After retirement of the doctor who has treated the thalidomider since childhood and has enough knowledge of TE, difficulty exists in finding another doctor.
- The thalidomiders cannot consult their family physicians about their pain or numbness.
- Thalidomiders feel stress when the medical staffs say that they have no knowledge of thalidomide embryopathy.

Pain and Numbness
- The thalidomider cannot judge whether the symptom is related with TE.
- Many thalidomiders complain of pain and stiffness in their shoulder and neck. Drug treatment and massage are common. Personalized exercise therapy was effective in 3. There were opinions that effects of chiropractics and massage were temporary or inconstant.
- Cervical spondylosis was detected in many of those who complain of numbness. Some of them were supposed to be affected by carpal or cubital tunnel syndrome.
- Some thalidomiders complained of chilliness in their forearms and hands.

Fig. 8

Progressive Physical Dysfunction
- Some thalidomiders tended to drop objects in pinching with fingers. (Side pinching with fingers is common due to thumb hypoplasia.)
- Some complained that their wrists often subluxate.
- Some who use their feet in many activities commented that they can not raise their legs so high as before, and the standing balance decreased when standing on one leg and using another leg as a hand.
- Walking was common for prevention of metabolic syndrome.

Inconvenience in Occupation and Life
- Though many workers complained of fatigue and shoulder stiffness, most of them hoped to continue their job.
- As for clothes, shoes, and bags, thalidomiders searched for products that are easy to use for them or modified them.
- They have difficulty in handling large objects (e.g. refrigerator doors), in addition to using small tools. Some used self-help tools.
- As for inconvenience in daily living, some thalidomiders positively sought for others' support, some never buy products difficult to use (e.g. vacuum packed ham), and some abandoned what they can not do without support (e.g. going outdoors with umbrellas on rainy days).

Fig. 9

Visiting Germany and UK to Meet Experts in 2018

Heidelberg:	Dr. Christina Ding-Greiner
Cologne:	German-Japanese Symposium with Prof. Dr. med. Peters (Dr. Becker Rhein-Sieg-Klinik)
London:	Dr. Dee Morrison (The Thalidomide Trust)
Hamburg:	Dr. med. Rudolf Beyer (Schön Klinik Hamburg Eilbek)



German Pharmacy Museum in Heidelberg

Fig. 10

Heidelberg: Dr. Christina Ding-Greiner



- Many thalidomiders are beginning to find difficulty in independent living due to pain and arthritis.
- For keeping independent living, they must change the height of kitchen, toilet, shower, and tables and remodel their cars.
- Treatment methods of secondary impairments in thalidomiders are not established.

Cologne: German-Japanese Symposium with Prof. Dr. med. Peters (Dr. Becker Rhein-Sieg-Klinik)

- The Outpatient Center for Thalidomiders provide 4-days clinic including examinations by MDs, physical and occupational therapists, and acupuncturists.
- They put a lot of effort into pain evaluation, because pain is influenced by psychological factors.



Fig. 11

As disabilities and secondary impairments in TE are complicated and varied, the standardization of managing secondary impairments is impossible. (Fig. 12)

How can we properly manage musculoskeletal impairments in TE? These X-rays are from the same patient with TE. (Fig. 13)

These are photos from Professor Kayamori's literature. The characteristics of Japanese thalidomiders show that lower limb malformations are rare. So, I will focus on only upper limb malformations and secondary impairments in TE. (Fig. 14)

When patients with TE use mainly the upper limbs for ADL, aging and overuse or misuse leads to joint dysfunction, tendinitis, or peripheral neuropathy in the upper limbs. And in those who use the trunk and lower limbs for ADL, aging and overuse may lead to spinal dysfunction or dysfunction in the lower limbs. Congenital musculoskeletal abnormalities associated with TE may have a partial effect on these. (Fig. 15)

In those who use the upper limbs for ADL, there is a paper from Dr. Merkle that shoulder osteoarthritis due to glenohumeral dysmelia in thalidomiders can be successfully treated with joint replacement. So, in thalidomiders, shoulder dysplasia is one of the problems.

From this paper on radial deficiencies, active motion of the wrists and digits is reduced, and grip and key pinch strength are lower than normal. The reduced active motion of the elbow and digits relates to the decrease in hand function. This is also true for thalidomiders. (Fig. 16)

As for peripheral neuropathy in the upper limbs, I will introduce two papers from Japan. In this paper on radial deficiency including TE, the anterior–posterior diameter and cross-sectional area of the carpal tunnel are small, as measured by computed tomography. Endoscopic carpal tunnel release is effective to treat carpal tunnel syndrome in TE. (Fig. 17)

For those who use their trunk and lower limbs for ADL, there are two papers related to this topic.

This is about children. Disc and endplate abnormalities existed in 14 of 28 children thalidomiders and appeared to be progressive in some, leading to intervertebral fusion. This

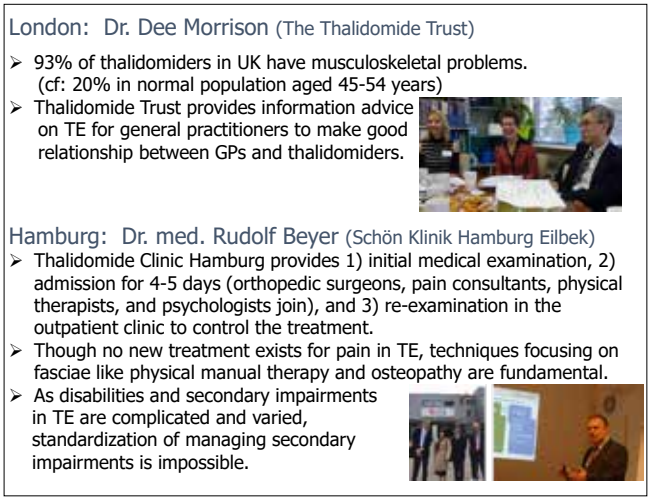


Fig. 12



Fig. 13

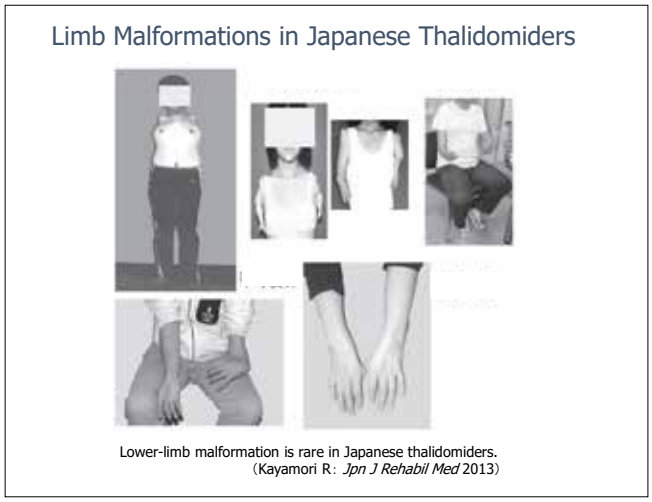


Fig. 14

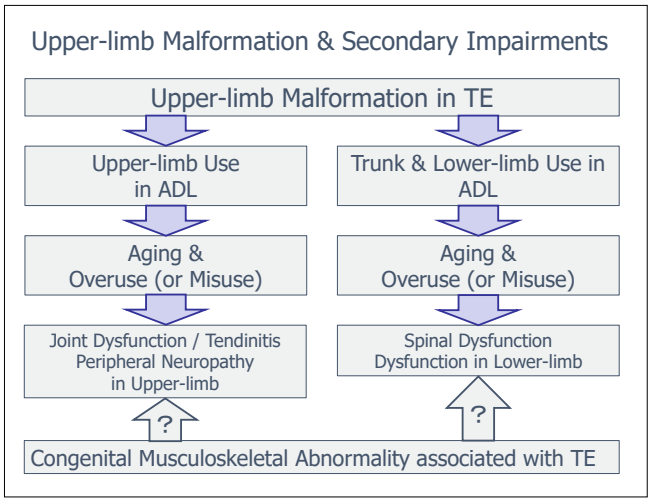


Fig. 15

is about the adults. Disc degeneration was detected on cervical spine MRIs in 24 of 27 middle-age thalidomiders. The degree of disc degeneration and foraminal narrowing was greater in thalidomiders than in controls. So, cervical disc degeneration is somewhat congenital, but affects age-related problems.

For those who use their trunk and lower limbs for ADL, there are two papers related to this topic.

This is about children. Disc and endplate abnormalities existed in 14 of 28 children thalidomiders and appeared to be progressive in some, leading to intervertebral fusion. This is about the adults. Disc degeneration was detected on cervical spine MRIs in 24 of 27 middle-age thalidomiders. The degree of disc degeneration and foraminal narrowing was greater in thalidomiders than in controls. So, cervical disc degeneration is somewhat congenital, but affects age-related problems. (Fig. 18)

This is a very old paper by a Japanese orthopedic surgeon about PFFD. This paper says that the degree of femoral hypoplasia is variable in TE, and accompanied by other lower limb abnormalities, including absent or defective tibia, absent patella, and inverted feet. So, these congenital abnormalities may affect the dysfunction in the lower limbs. (Fig. 19)

So, proper management of musculoskeletal impairments in TE needs, in my opinion, precise evaluation over the full body, including physical findings and imaging studies, to review congenital musculoskeletal abnormalities and the effects of overuse and/or misuse, investigation, and presentation of possible treatments, including surgical and conservative measures, repeated evaluations at regular intervals, advice on physical exercise habits, advice on accessibility to medical institutions, and support teams. Fostering TE specialists and providing education to medical professionals on TE is also necessary, I think. (Fig. 20)

Now, I will proceed to the next topic, sharing information on TE with the next generation. In 2013, to provide a multidisciplinary approach for patients with various limb malformations, we established a limb malformation clinic in a hospital. This is the University of Tokyo Hospital. Physiatrists, PTs, OTs, and prosthetists/orthotists joined together in

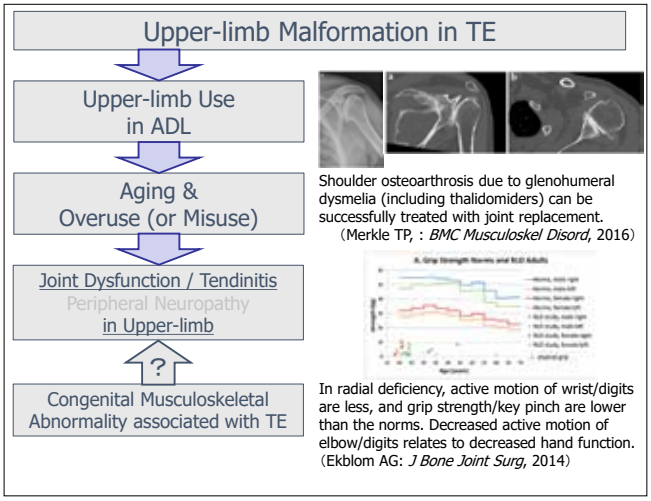


Fig. 16

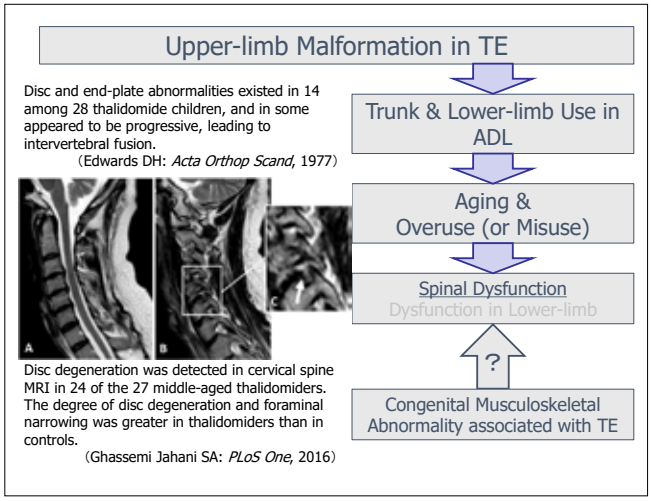


Fig. 18

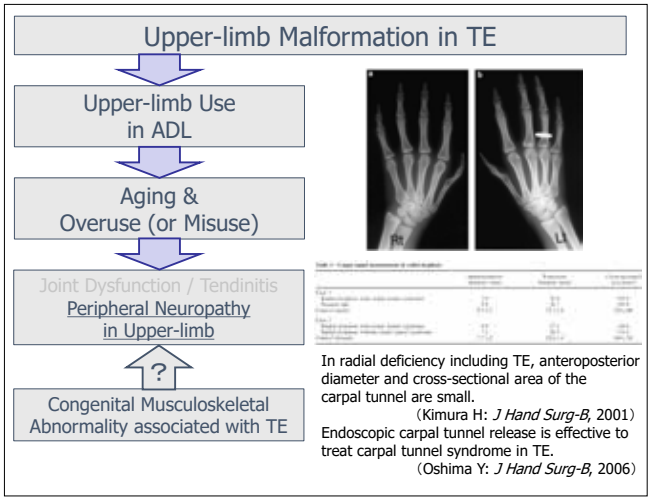


Fig. 17

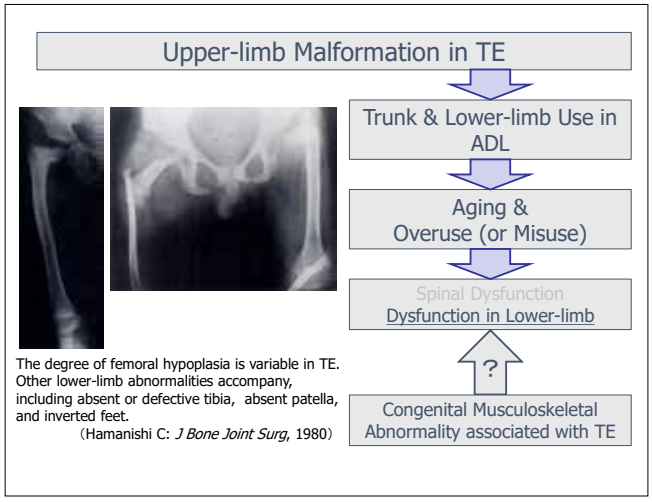


Fig. 19

this clinic.

We are also related to another department in the hospital, and for orthopedic surgery and long-term inpatient rehabilitation, we connect to another national rehabilitation center for children. As for genetic counselling and genetic tests, we work together with another university hospital. (Fig. 21)

We also recently performed an epidemiological study of congenital malformations in Japan. According to these data, the estimated prevalence of congenital limb deficiencies in Japan was 4.15 per 10,000 live births. Overall, 67% affected only the upper limbs, 20% only the lower limbs, and 15% both the upper and lower limbs. From these figures, there were 3.39 affected upper limbs per 10,000 live births. This means that last year, about 300 babies were born with upper limb malformations. (Fig. 22)

Now I will introduce two very old Japanese papers. This is a paper on ADL in mainly acquired upper limb amputations. So, most ADL are independent in persons with unilateral upper limb malformations or amputation, though their motion may be slow and they may need self-help support or changes in their motion patterns. But for bilateral upper limb amputations, only 23% can perform ADL by herself or himself.

This is about the school lives of children. There are many activities, and these are the situations regarding limb malformation. Among school activities, even children with unilateral forearm deficiencies have difficulty in art, home economics, and music. Those with higher level deficiencies have difficulty in arithmetic and physical education, like this. And those with bilateral upper arm deficiencies have severely limited school activities. (Fig. 23)

This patient is not a thalidomider. He had a bilateral radial deficiency with severe forearm shortening. There is only a small portion of forearm and bilateral fibular deficiencies with deformed feet. We only performed the correction of his deformed feet. This is a photo from when he was in elementary school. He is now 21 years old, a university student, and nearly all of his ADLs are independent. One reason why he grew up like this is partly because I think his father was also affected. His father had a similar but milder phenotype

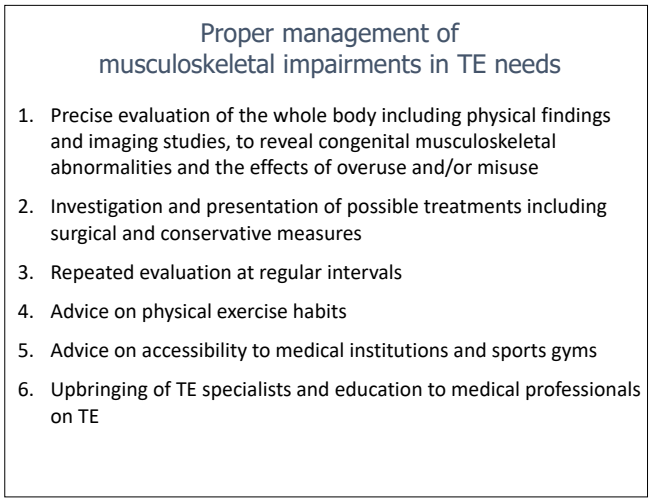


Fig. 20

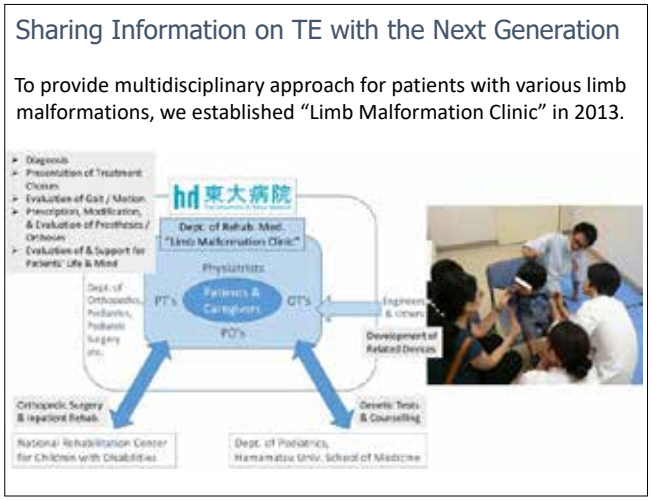


Fig. 21

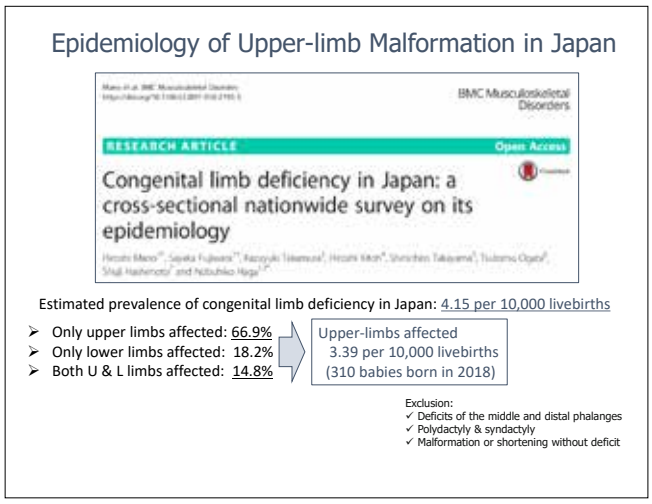


Fig. 22

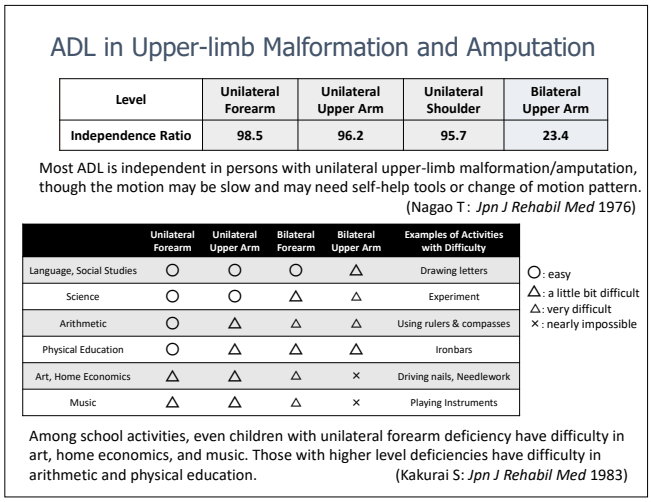


Fig. 23

with mild shortening of the forearm and mild shortening of the lower leg with fibular deficiency. (Fig. 24)

This is another patient. This is a 5-year-old boy with bilateral upper limb complete deficiency with scoliotic deformity. Although he received occupational therapy in another clinic to perform his ADL with his legs, his parents were eager to know how he would live his life in the future. (Fig. 25)

Thus, we conducted a small seminar on living with bilateral upper limb deficiencies to share knowledge and experience in March of last year.

Two Japanese thalidomiders from the Ishizue Foundation and two para-tae kwon do athletes participated in discussions with these children with bilateral upper limb deficiencies. (Fig. 26)

After that, my colleague joined a bilateral upper limb loss workshop held in October in Houston. There were many multiple amputees, including those with purpura fulminans. Because it was a very good seminar, a very good workshop, we held a similar seminar in Japan, Skills for Life Japan, in June of this year. Some upper limb deficiency patients participated, including very old persons. They showed how they lived their lives for a long time. (Fig. 27)

We are now in a research group of thalidomiders, but I think the lessons from TE can be shared with the next generation. Thank you for your attention. (Fig. 28)

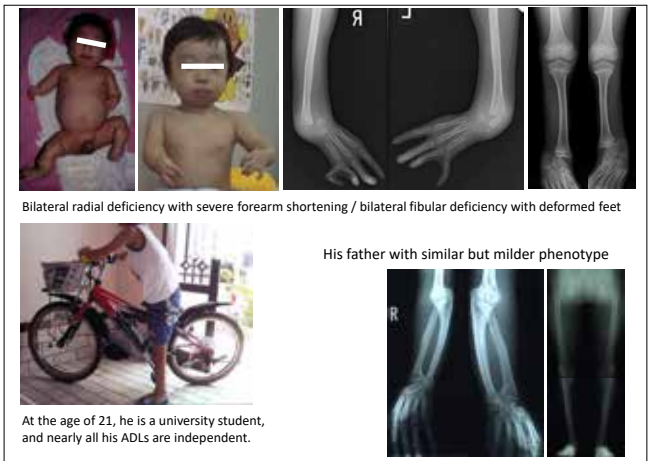


Fig. 24



Fig. 25

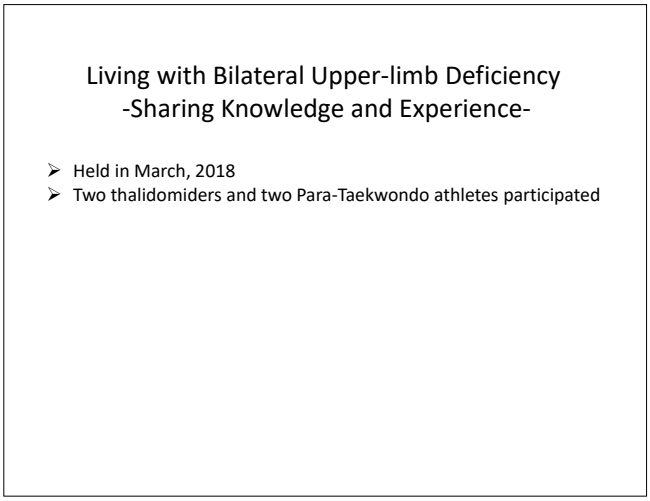


Fig. 26



Fig. 27

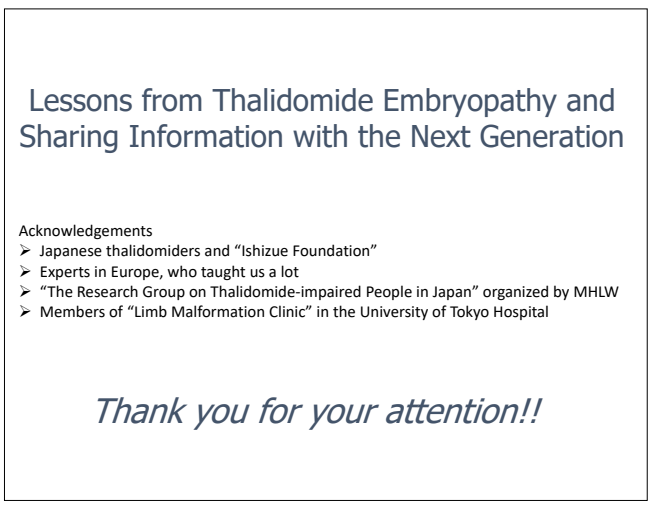


Fig. 28

Q&A

Ryoji Kayamori: So, are there any questions or comments? Okay. Yes, please.

Male Participant (Unknown Speaker with TE): Once again, thank you very much. Thalidomiders, age-wise, were born over a 5-year period beginning around 1961 or 1962. Recently, we have been talking about the reason for our existence. For example, sometimes, the upper arms can be donated to hospitals for the purpose of research, some patients have said. The Ishizue Foundation, which is an existing public corporation, is mainly for thalidomiders. But as you mentioned, we also have to think about the significance of our being. We are very creative about living our lives, playing sports, and other things that we can do based on our creativity. That's something we can communicate or hand down to those who have upper limb deficiencies. Also, together with people around the world, we would like to share our experiences, and having such an opportunity would be good for us. Sorry, this is only a comment. Thank you very much.

Nobuhiko Haga: Thank you so much for such a wonderful comment. I really appreciate it. Especially when it comes to deformities of the upper limbs, I mentioned that there are about 300 such children in Japan. For example, some of the finger defects are unilateral, that is, they are also included when we say upper limb deficiencies. So the children that I showed in pictures toward the end, we probably find just one or no such patients or children every year. They really want to have information. But even though we can give them medical information, we cannot give them sufficient lifestyle-related information.

Therefore, as I showed toward the end regarding the opportunities and meetings, it would be great if you get cooperation from thalidomiders. Thank you very much for your comment.

Ryoji Kayamori: The time is just now over. So, thank you.

Thalidomide Embryopathy: Orthopedic Aspects, Degenerative Changes and Quality of Life at Age 45

Shadi-Afarin Ghassemi

Unversity of Gothenburg, Gothenburg, Sweden

Nobuhiko Haga (Moderator)

The next speaker is Dr. Shadi-Afarin Ghassemi. She is now a medical doctor and PhD, and a senior consultant in orthopedic surgery. She graduated from the medical faculty of Gothenburg University, Sweden, and in 2006, she was licensed as an orthopedic surgeon.

In 2016, she obtained her PhD in orthopedic surgery. Since last year, she has been a senior consultant for the Osteointegration Unit, Orthopedics Department, at Sahlgrenska University Hospital.

Please start your lecture.

Thank you very much. Thank you for having me here today. I am going to talk about two studies involving my thesis. I will actually start with the third one, and once I tell you why, you will understand that more. None of the authors have any financial relationship to disclose. I need to say that. (Fig. 1)

The name of the, let's see, the name of my thesis is "Thalidomide Embryopathy (TE): Orthopedic Aspects, Degenerative Changes, and Quality of Life at Age 45." It seems like, well, it's quite old, but it's the time when we started gathering all the data. This was at the Department of Orthopedics, Institute of Clinical Sciences, at Sahlgrenska Academy, University of Gothenburg. (Fig. 2)

There are four papers. In 2015, I talked about my first paper, where we found a much higher risk of osteoarthritis in both the knees and the hips compared with the national population in Sweden. I am going to talk about papers 2 and 3. Paper 4 was, I mean, it's about orthopedic needs, both the surgeries and orthotic needs and so on. (Fig. 3)

I don't need to tell you more about thalidomide. You already know. We know that it's a potent substance, a very, very highly potent substance that was used in pregnant women in Sweden, especially between 1959 and 1962. When we started our study, we had, there were 108 individuals

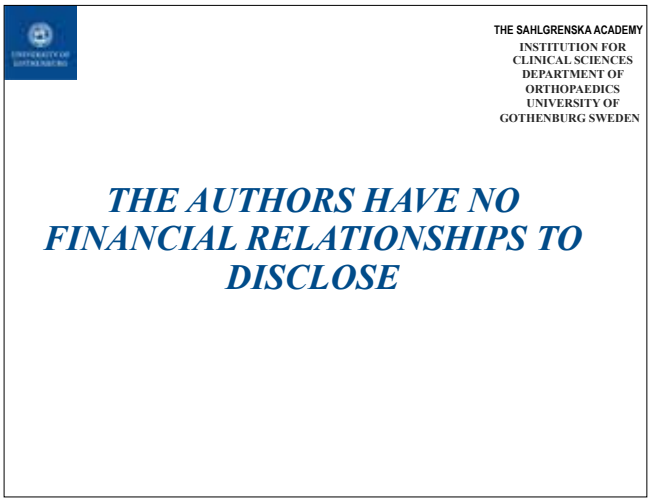


Fig. 1

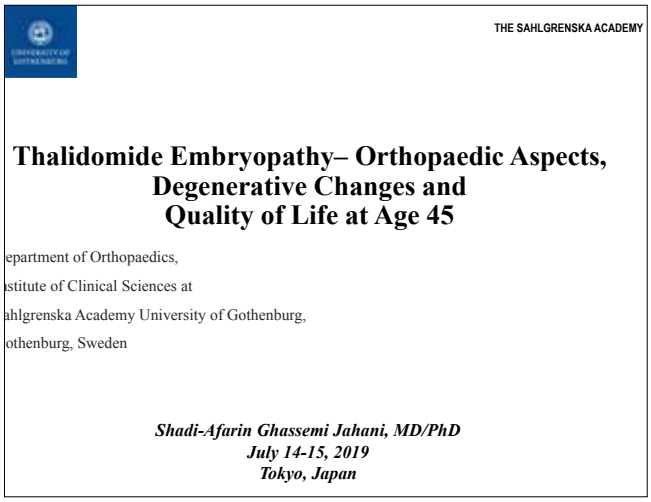


Fig. 2

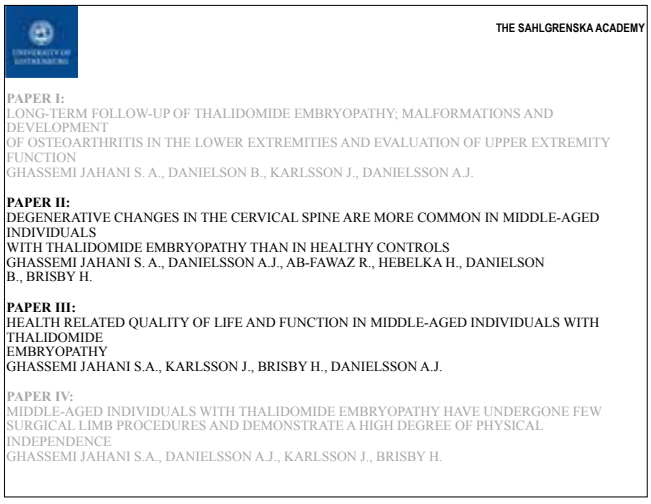


Fig. 3

registered in the Swedish Association of Individuals with TE. (Fig. 4)

And this is, I think this slide tells us a lot. My question to you, Dr. Hinoshita, is how come you didn't reach out to everybody? This was our main concern because out of 108 members, we were not allowed to send invitations to 24 because I mean, the association of TE in Sweden is very, very enclosed. So, if they say they don't want any invitation for any investigation, then you are not allowed to send anything. That's it. You don't even get their addresses.

So, 84 were invited and 33 didn't even answer. And also, a new law, I mean, it's the new, I mean, not new, but it's also another case of the rules that you are not allowed to send a new reminder.

Overall, 33 were accepted, and of those, one had recently suffered a stroke and one had a severe mental problem and was institutionalized. (Fig. 5)

So we had 31 participants: 18 males and 13 females. At that time, the mean age was almost 46 years. They came from different parts of Sweden. One was living in the US, and at the time, was actually visiting Sweden. One was living in Norway, and she came. The study was multidisciplinary, and conducted together with Professor Kerstin Strömland and Professor Christopher Gillberg.

Another problem was that many of the attendants who didn't want to come to this multidisciplinary study actually agreed to come to just the orthopedic part. But we couldn't do that. (Fig. 6)

As an orthopedic surgeon, I examined everybody, all 31 persons. We found that 25 individuals had malformation of the hand and 27 had poor grip function. We also found five individuals with a proximal femoral focal deficiency with a short limb, and they needed a wheelchair or orthosis. Regarding other conditions, we found diseases such as asthma, hypertension, sleep apnea, and migraines. These are the general diseases, but some others necessitated operations for carpal tunnel syndrome, total hip joint replacement, and so on. (Fig. 7)

This is a view of a proximal femoral focal deficiency, which is a deficiency of the femur and sometimes the hip joint. Depending on the extent of the malformation, it results in shortening of the leg, and in most cases, there is neither a

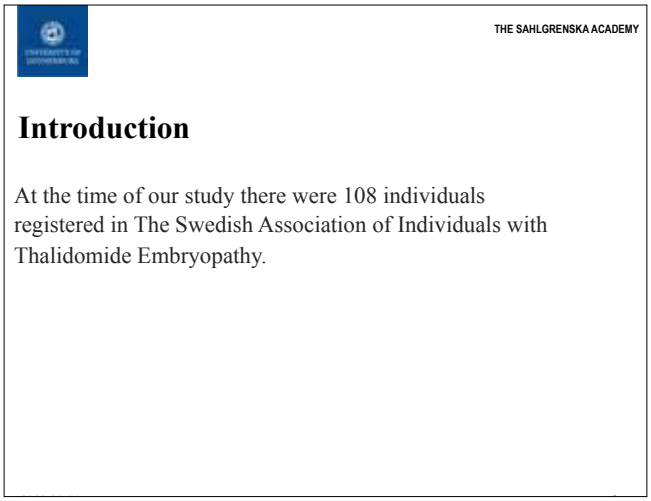


Fig. 4

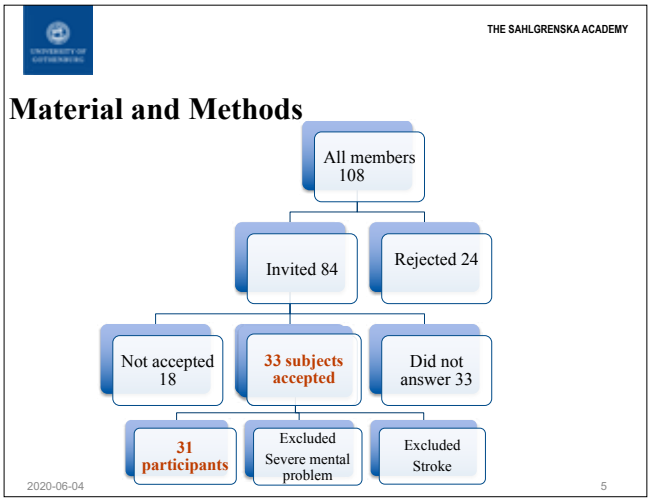


Fig. 5

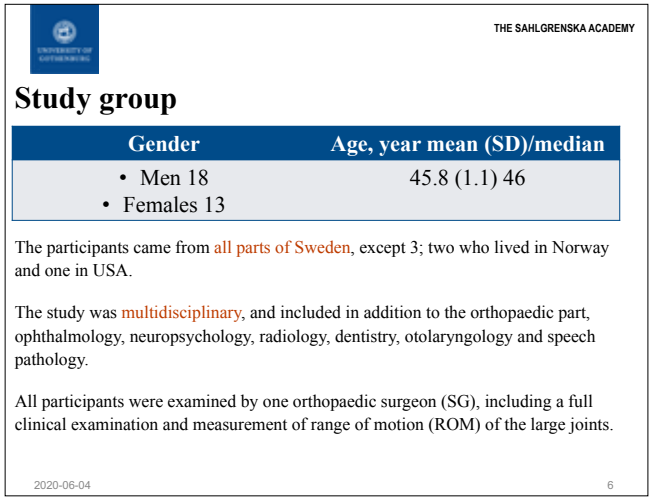


Fig. 6

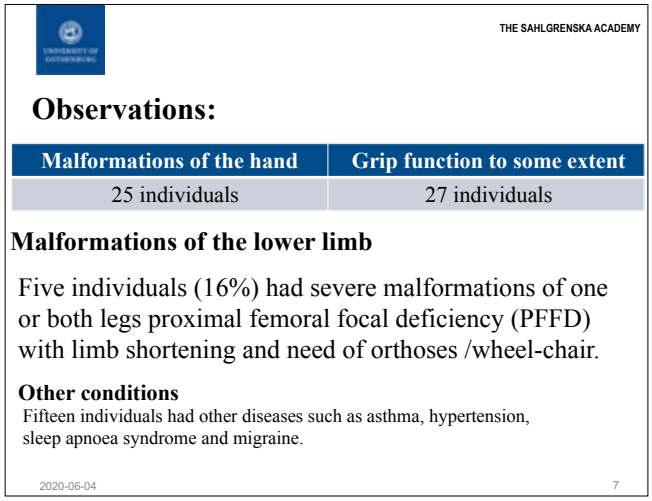


Fig. 7

thigh nor a hip joint. It causes the leg to grow from the groin, and foot to be at the level of the knee. (Fig. 8)

Other two patients of these five. The study is on health-related quality of life and sociodemographic characteristics of middle-age individuals with TE. (Fig. 9,10)

Knowledge about the function and health-related quality of life for the TE group is sparse. With aging, parts that were working quite well experience problems, and we need to address that as well. (Fig. 11)

The aims of the study were to assess whether the health-related control of quality of life is equal to that of the general population, to what extent limb malformation affects health-related quality of life, and whether the function of the upper and lower limbs, as measured by a validated questionnaire, is correlated with more general health-related quality of life. (Fig. 12)

We mainly used computer tomography (CT) for our previous study, but we also used the results for this one. We evaluated all musculoskeletal manifestations. We used validated questionnaires to assess disability in the arms, shoulders, and hands. We also used the Short Form-36 and EuroQuol-5 Dimension to evaluate upper extremity function. (Fig. 13)

The participants were totally divided in two different groups according to malformations, those with PF50 and those without PF50, according to how many limbs were affected. Thus, we had 15 individuals with more than one

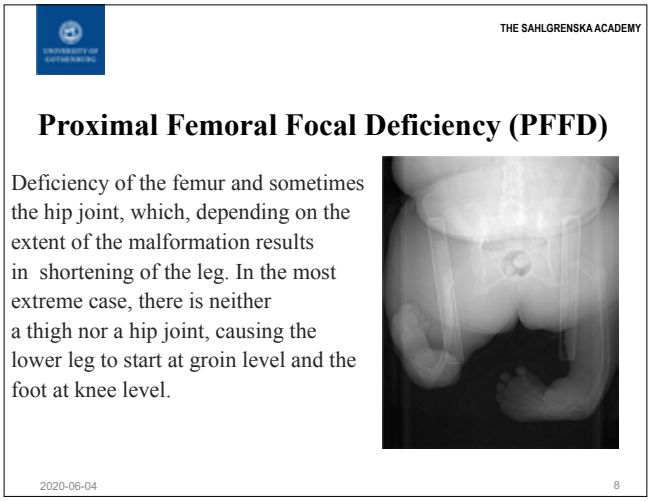


Fig. 8

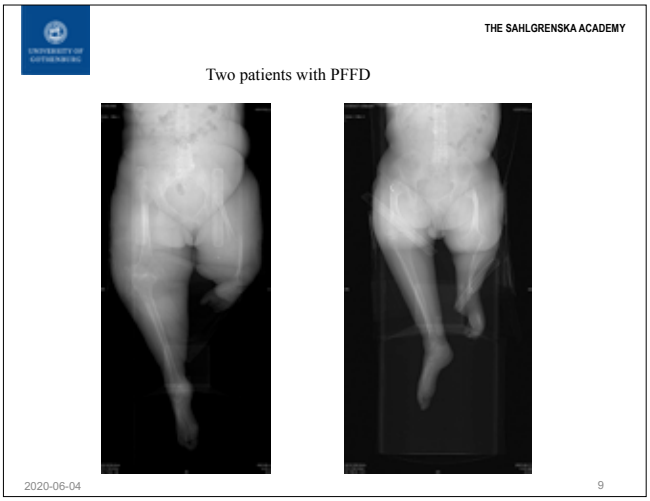


Fig. 9

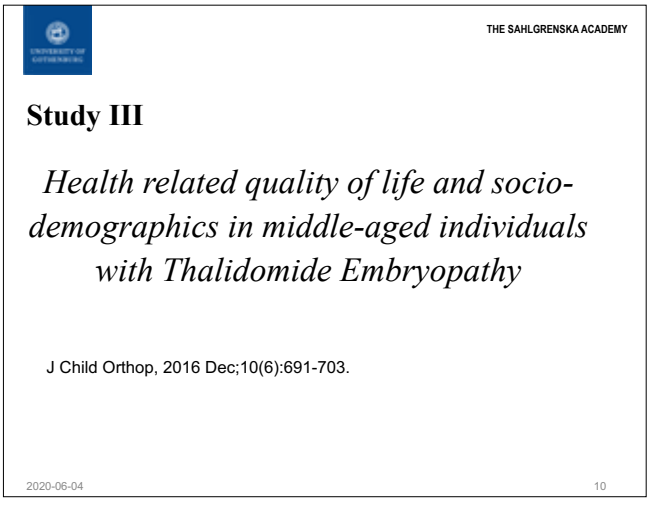


Fig. 10

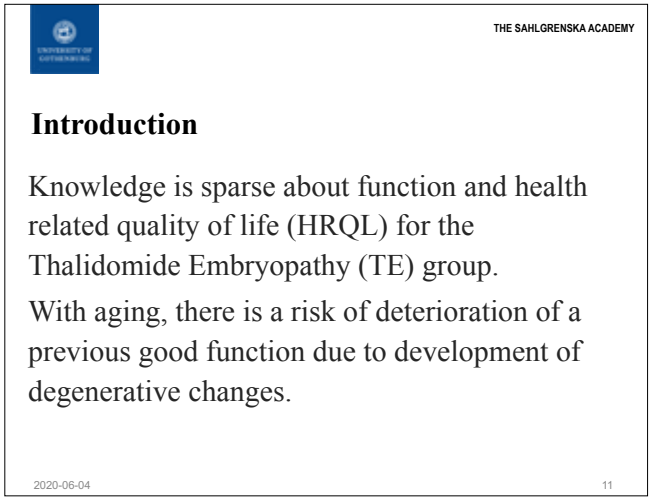


Fig. 11

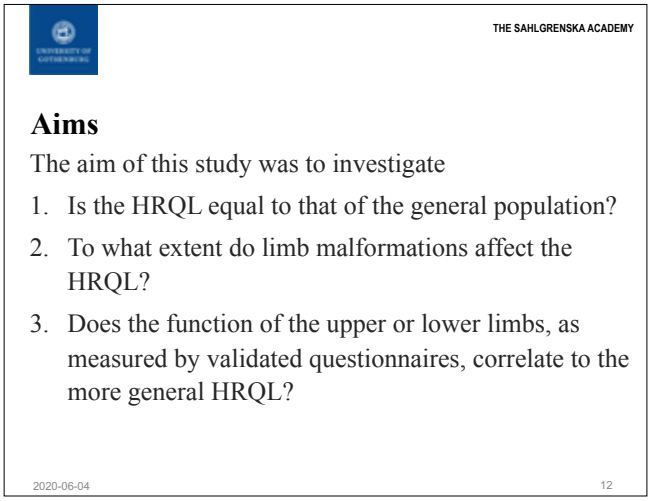


Fig. 12

limb with a major malformation and 16 with no limbs with a major malformation. We don't mean only thumb affection. We are talking about major malformations, shortening and so on. (Fig. 14)

Regarding sociodemographic status, 80% were married or cohabitating, and 77% were working. We also used the WHO questionnaire on stress during the day. The majority had some minor stress and only one had heavy stress. (Fig. 15)

I would like you to see here the results regarding upper extremity function. The lower the score, the better the function. Scores range from 0 to 100. (Fig. 16)

All individuals had very good function. Those with no major malformations in the limbs were even better. Those with major malformations in more than one limb had worse outcomes for the upper extremities, and this difference was statistically significant. The results don't say if it was the upper or lower extremity. It's just the amount. (Fig. 17)

Those with PF50 actually had diverse outcomes for DASH. (Fig. 18)

Regarding the SF-36, these are the normal mental and physical composite summary scores for the general population. The ones in color indicate those with no extremity with a major malformation, and next more than one major malformation in the extremities for PF50, and the total group. (Fig. 19)

You can see that physical quality of life is lower than that for the normal general population for all groups, including

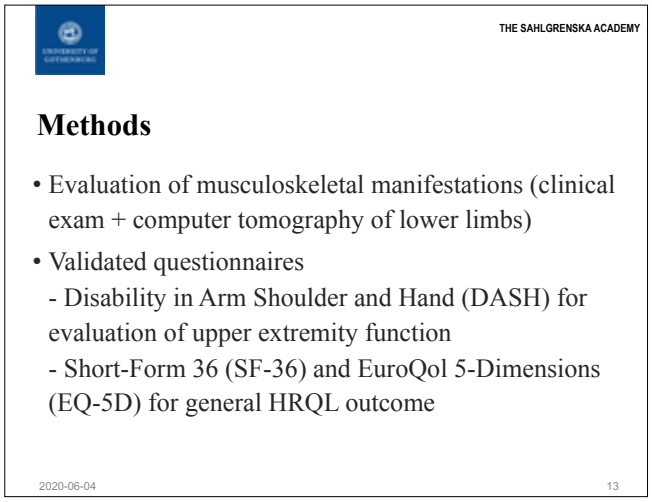


Fig. 13

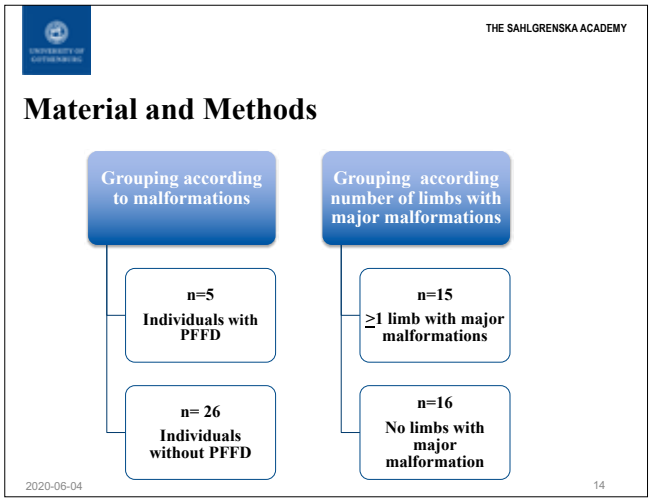


Fig. 14

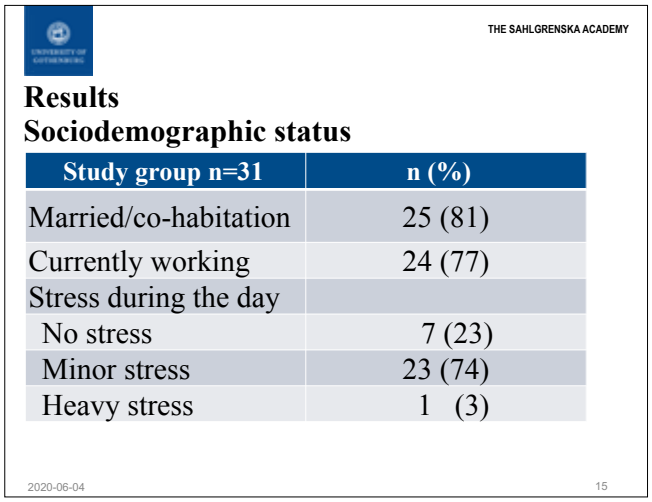


Fig. 15

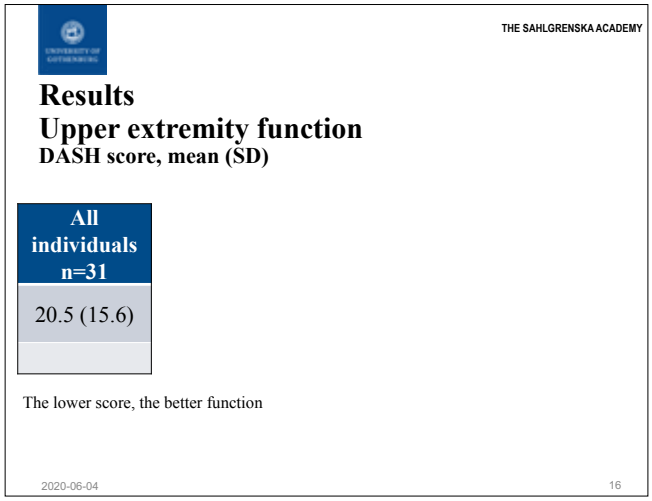


Fig. 16

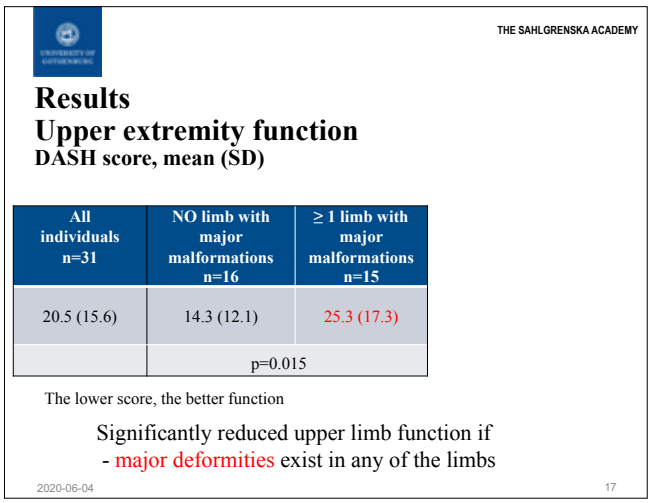


Fig. 17

the whole and subgroups. (Fig. 20)

Mental quality of life is actually the same, a little higher than the normal level which I think coordinates with most of the studies, both also showed the same. (Fig. 21)

If you look at the sub-scores, this is physical function bodily pain and general health, role physical vitality. This is the mental part and this is the sub-score for the physical part. The dotted line is the total study group, while the other one is the normal general population.

We also can see even here with those with more than one limb with malformation or a major malformation, it actually coordinates quite well. The most affected are the ones with PF50, of course, who have poor physical quality of life, even in the sub-scores, subgroups I mean, sorry. (Fig. 22)

We also looked at the EQ-5 Dimension and all from the whole group, the whole study group compared with the reference population. You can see that they have worse outcomes for mobility and self-care, and discomfort from pain is usual. But anxiety and depression is almost equal to that of the reference population of the same age. This can actually indirectly show the Western quality of life. (Fig. 23)

So, in conclusion, physical health-related quality of life is significantly reduced in many individuals and correlates well with existence of major limb deformities or with reduced function of the upper as well as the lower extremities, which I think is quite interesting. The mental aspects of quality of life are not affected, and the majority of the study

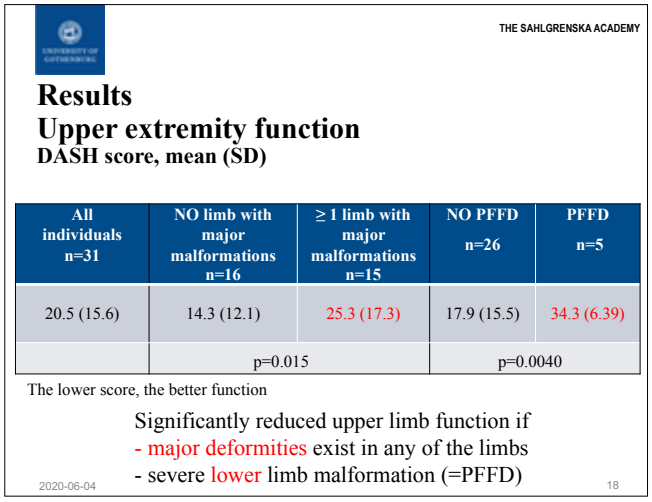


Fig. 18

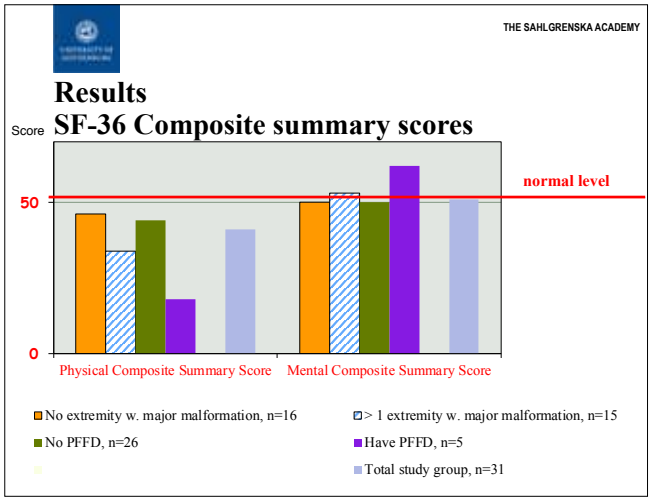


Fig. 19

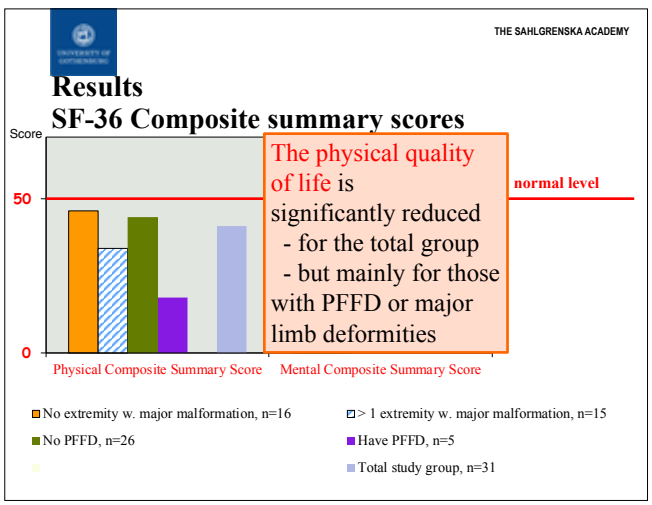


Fig. 20

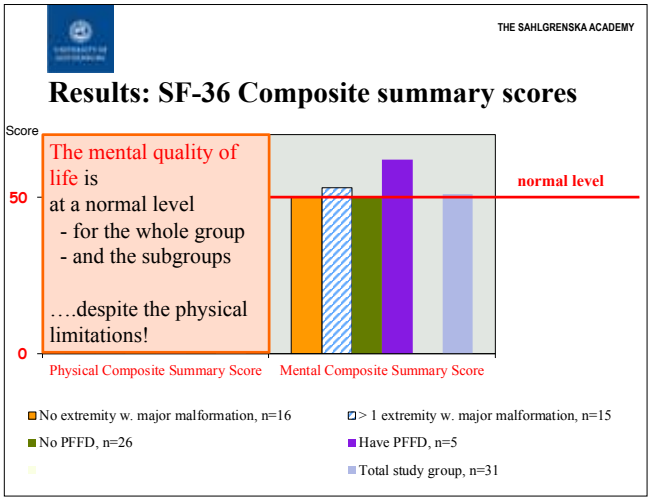


Fig. 21

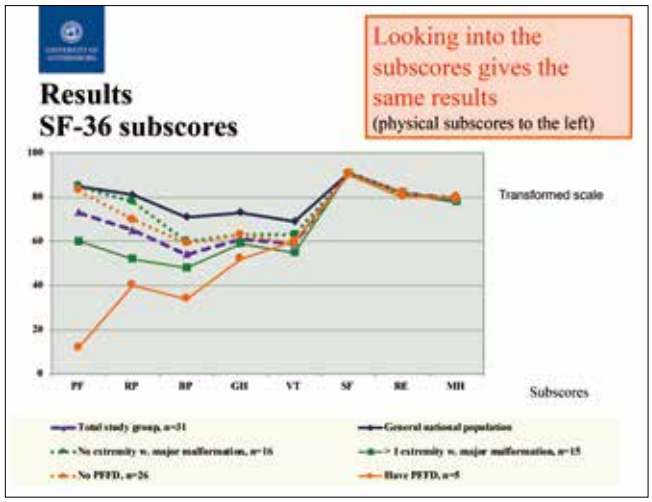


Fig. 22

group was working, had a family, and did not live under heavy stress. (Fig. 24)

I now turn to study 2 because we actually used the same 31 subjects, but not everybody underwent cervical spine MRI. Degenerative changes in the cervical spine are more common in middle-age patients with TE than in healthy individuals. (Fig. 25)

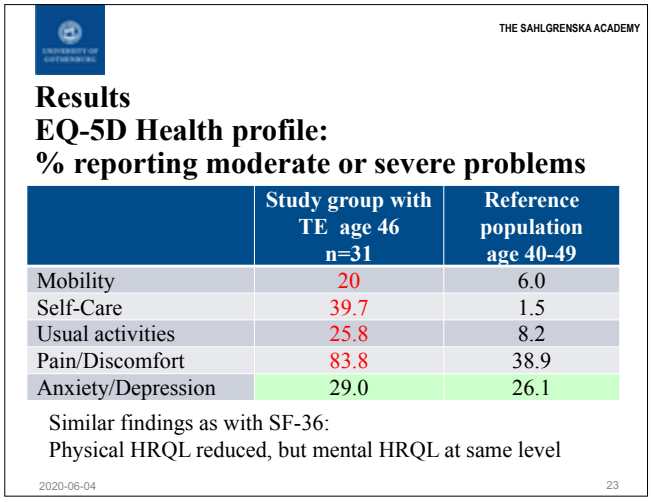


Fig. 23

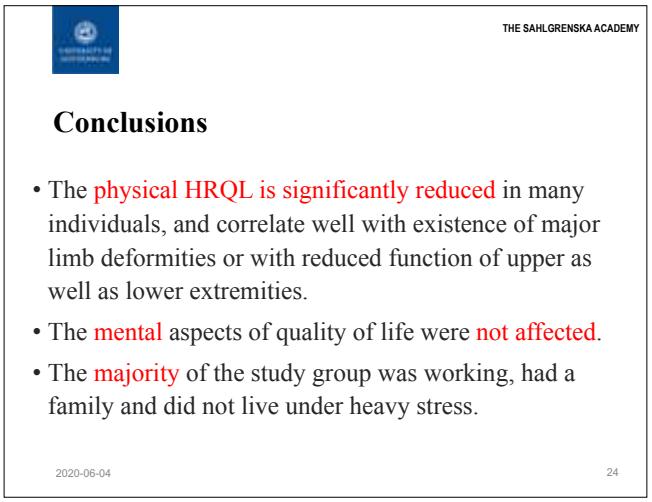


Fig. 24

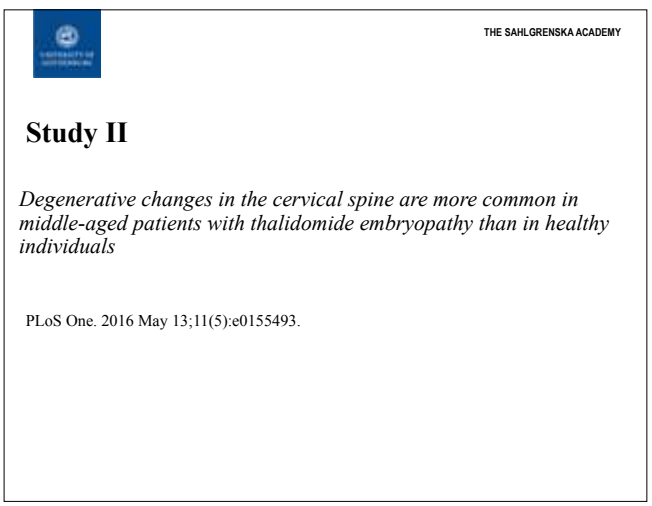


Fig. 25

Professor Haga just showed one figure that we had in that article. The aim of that study was to investigate persons with malformations and subsequent disc degeneration of the cervical spine in a group of middle-age individuals with TE and to compare these with a healthy group of controls. (Fig. 26)

We asked all 31 attendees if they could participate and invited them to undergo an MRI. One wanted to, but he was not allowed to because he had metal chips in his head, and two had claustrophobia. Actually, one of them went through with it, but they had to stop the examination, whereas the other one just refused.

Thus, the 27 remaining from the whole group underwent MRI. We compared them with 27 age- and sex-matched healthy controls. As earlier, we found that 85% had some degree of hand anomalies, so we evaluated disc signals according to the Pfirrmann grading system, which is grade 1 to 5 depending on how degenerate, which kind of degeneration they have in the discs. (Fig. 27)

Overall, 56% of patients had a deformity of one to four of the extremities, which we already knew. All had some function of the upper limbs, despite some individuals having

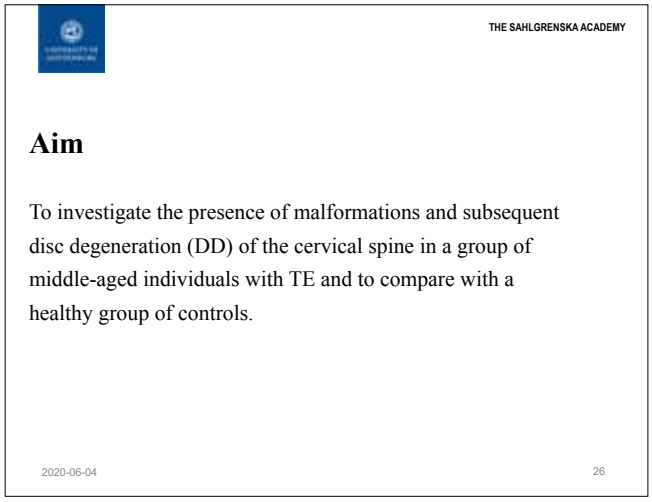


Fig. 26

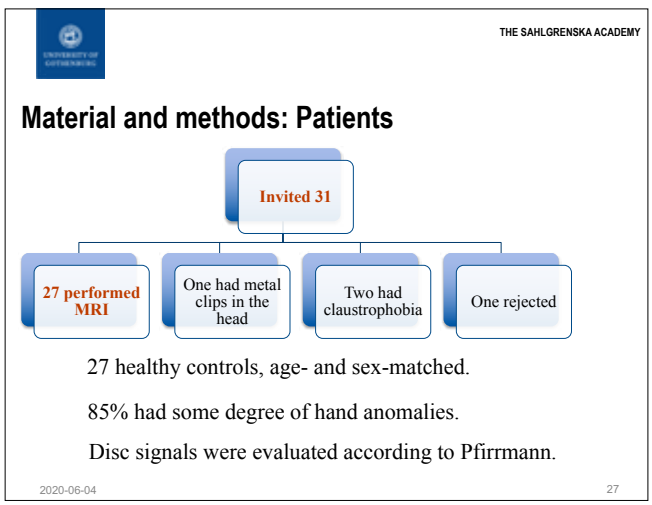


Fig. 27

short arms. Almost 80% had some degree of hand anomaly, and 30% patients had bilateral pincer grasp. (Fig. 28)

These are the Pfirrmann grades 1 to 5. This is the TE group compared with the control group. Every segment shows statistical significance in comparison. For TE, we already had grade 5 in the higher segments, which is quite unusual. We can find it only here in the C5–C6 segment and the C6–C7 segment in the control group, indicating a higher degree of disc degeneration in the cervical spine; thus, much earlier in the TE group and even in higher segments, which is quite unusual. (Fig. 29)

Therefore, 90% of the TE and 70% of the control group had disc degeneration of more than one level. Ten TE patients had more than four segments affected, which is also unusual. No one in the control group had more than three segments affected. And in both groups, the majority was still C5–C6, but the TE group had disc degeneration in upper segments C3–C4 and C4–C5. (Fig. 30)

Our findings support the earlier developmental course of disc degeneration in the TE group. This could be because we found more disc degeneration in the cervical spine in the TE group. We also found an increased number of affected segments in the TE group. But mostly they still come in the slower segments as it is in the control.

If the result is because of the drug itself, we don't know that yet. If it's because of the unusual loading on the neck, we also still don't know. Of course, we would like to have

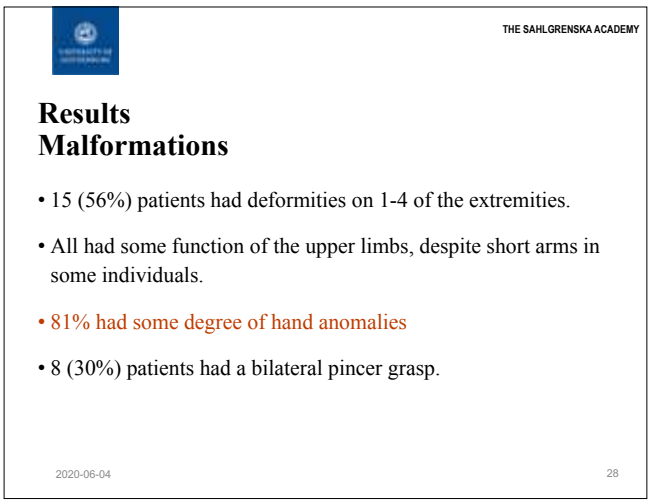


Fig. 28

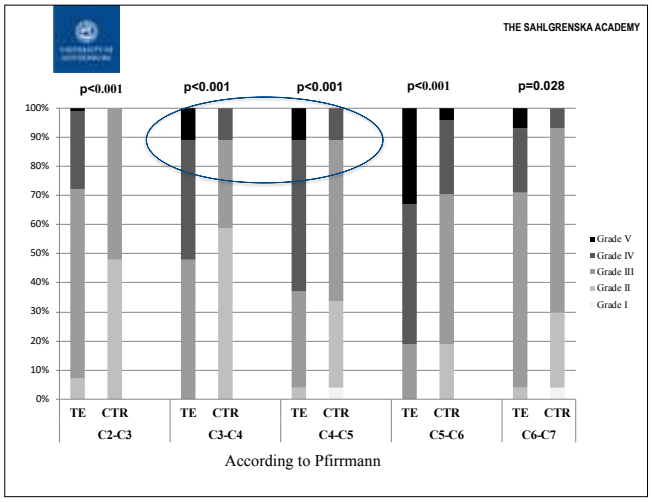


Fig. 29

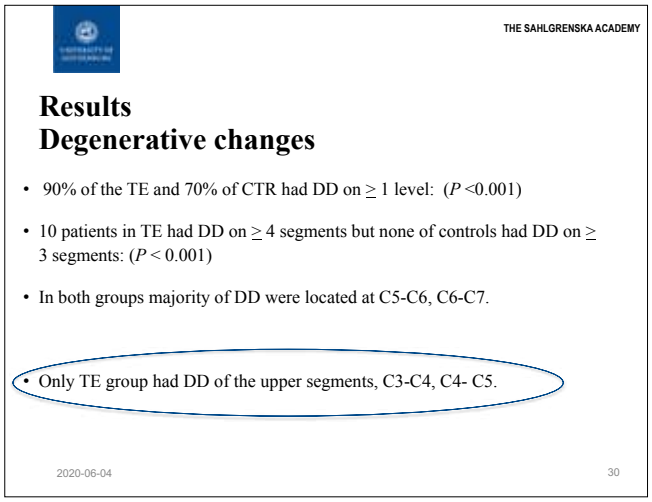


Fig. 30

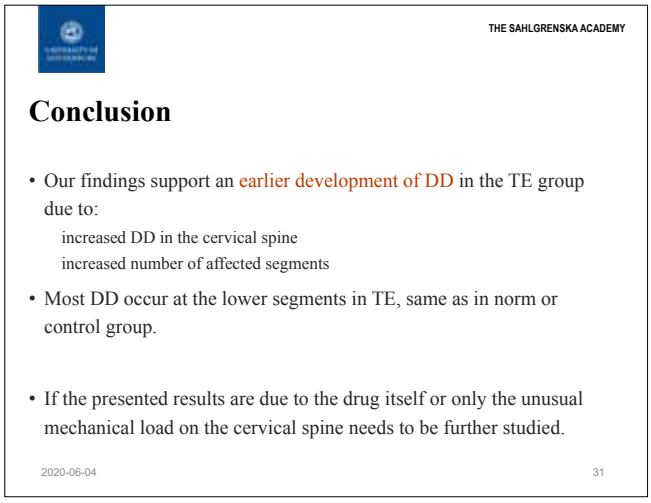


Fig. 31



Fig. 32

more studies on that, but I don't know if that's possible in Sweden. As I told you in the beginning, it's quite difficult. The group has been very enclosed, and we actually don't have, as I hear, any new claimers. It could also depend on, in Sweden, everybody has a personal number. I mean you cannot do anything if you don't have a personal number. So, it's very, very difficult to be somewhere in society and not be seen before. You cannot just come and say, "Okay, I have this and that problem, and it must be somewhat due to thalidomide." We will see if there is any possibility to do a new health-related quality of life survey, and then send it to these persons and compare the results with those regularly seen at 45 years of age. (Fig. 31)

I just wanted to show you this, so thank you very much, especially Dr. Hinoshita and the rest of the group who were in Sweden on August 3 years ago. I remember that it might have been cold, so I wanted to show you the very nice weather we have in April this year. Welcome back. Thank you. (Fig. 32)

Q&A

Nobuhiko Haga: Thank you. We are open for discussion. Okay.

Klaus M. Peters: Thanks a lot for the excellent data. I think that the high amount of disc degeneration in the cervical spine is due to the fact that they do more with the cervical spine. For example, some of them carry a water bucket with their mouth, their teeth. They carry weights with it, and therefore, I think it's a higher load for the cervical spine; therefore, I think degeneration is higher.

Shadi-Afarin Ghassemi: Of course, it could be that, but at the same time, we also noticed a lot of block segments, which makes it even more difficult to use the neck as a tool. But of course, we also believe it's more possible to believe that, yeah.

Nobuhiko Haga: Okay, please.

Elizabeth Newbronner: Thank you very much, Shadi. It was very interesting to hear your presentation. I was just interested because one of the things we have observed in the UK is that people have experienced a big change in their function, their pain levels, and their ability to work probably in the last 10 years. And knowing that your group, because of when you could collect your data, was sort of 45 at that time, do you have any sense of how things have changed in Sweden since then around things like pain, function, and capacity to work?

Shadi-Afarin Ghassemi: Thank you very much. It actually reminds me to say something I wanted to say, but forgot.
I definitively think that they have more problems with pain because they already had it, and that is why they were more keen to come and be part of the orthopedic part. They wanted, they didn't want to be part of the psychological part. They were not interested in that. But I actually called Ex-Center. I called Marie Wikström at Ex-Center before I came here because I just wanted to ask her what she wanted me to bring to that meeting and what she wanted me to say. She didn't mention the pain or the lack of money. She didn't even mention, but she did say that we have had some problems with the main, I mean, the vessel malformations. So we are interested to see if there are anymore.
Actually, I will talk to her about the Japanese study. We had also a patient with total hip replacement with iliac malformation. He actually, after the surgery, he was simply dying because they didn't know that he had that malformation. So, the only concern for her was that it would be nice to know to perform a body scan before we go through with any surgery. But it was completely normal. I mean, they knew that the hip might have been replaced. They might have a problem with the knees, and many others.
Since there is quite good economic management in Sweden, especially for the TE group, they are not much concerned about if they need to retire early. Actually, they don't need to work after some years because they have their retirement, yeah.

Elizabeth Newbronner: Thank you.

Shadi-Afarin Ghassemi: Thank you.

Nobuhiko Haga: Okay, do you have any other questions? I want to ask one question.

Shadi-Afarin Ghassemi: Sure.

Nobuhiko Haga: Do you know of any thalidomider who underwent surgery in their cervical spine in your country?

Shadi-Afarin Ghassemi: No.

Nobuhiko Haga: No, okay.

Shadi-Afarin Ghassemi: No, actually, they are very, very cautious. I mean the surgery should be very much needed. It's nothing that they just they have pain. It must be very much needed. And unfortunately, since the majority were not attending any of these studies, it's very difficult to know what problems they have, which is what I asked the Ex-Center about.

Nobuhiko Haga: Okay. No other questions? Thank you for your presentation.

Shadi-Afarin Ghassemi: Thank you very much. Thank you.

Outpatient Centre for Thalidomiders in Germany: Treatment Strategies and First Results

Klaus M. Peters

Dr. Becker Rhein-Sieg-Klinik, Nümbrecht,Germany

Nobuhiko Haga (Moderator)

So, the next speaker is Dr. Klaus Peters. He was born in Dusseldorf, Germany, and graduated from the University of Cologne and Basel. Since 1995, he has been a senior consultant in the Orthopedics and Osteologic Department at the Dr. Becker Rhein-Sieg-Klinik, Nümbrecht. Since 2011, he has been in the orthopedic and trauma surgery unit at Bergisch Gladbach. Since 2017, he has been the head of the medical center for thalidomide-damaged people in North Rhine-Westphalia. Okay, please start your lecture.

Thanks a lot for the introduction. I am pleased to introduce our results and data from our outpatient center for thalidomiders in Germany. (Fig. 1)

What's the background to establish such a center? The problem is increasing consequential damage in thalidomiders, and we have no real sufficient regular medical care to offer to thalidomiders in Germany. That's a problem. Therefore, the goal of the center is to improve the medical care situation for thalidomiders in Germany.

And what is the center? The structure of the center is as a medical institute for adults with multiple handicaps. The center is also part of a cooperation network with medical specialists and the Interessenverband Contergangeschädigter in North Rhine-Westphalia, an organization for thalidomiders like you have in Japan. We have very close cooperation with them. (Fig. 2)

As a medical expert center, the focus is on thalidomide-damaged people. They come from all over Germany, not only from North Rhine-Westphalia. It's important that thalidomide damage is accepted and recognized. Then, the cost of the statutory health insurance funds is guaranteed to be covered. Other people have a status of self-payer, especially those people for whom thalidomide damage has not been accepted up to now.

We have a so-called thalidomide competence team in the clinic consisting of physicians, physiotherapists, ergotherapists, and massage therapists. The competence team for thalidomiders currently has 16 members, all of whom can provide treatment. We have two coordinators for the center; these are very important persons who do the daily organizing. (Fig. 3)

The so-called MZEB is a special German organization construct. It's a medical center for adults with multiple handicaps. It can also be established for other diseases in Germany. It's an outpatient center that is important for thalidomiders because they don't want to stay in clinics. It is



Fig. 1

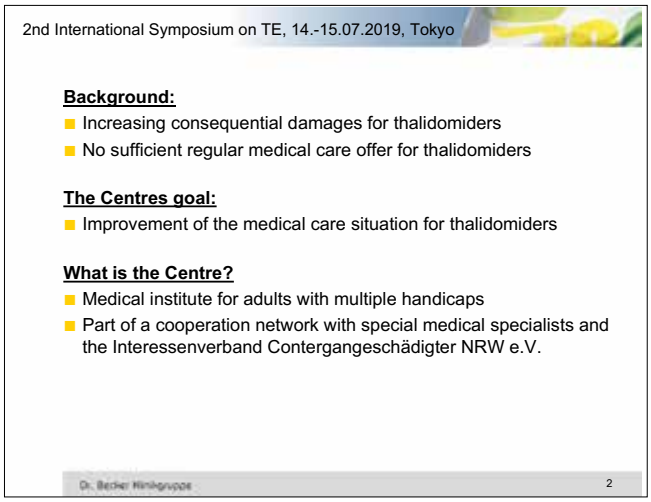


Fig. 2

licensed and contracted by health insurance companies in Germany. It's an expert center and contact point for thalidomiders. We offer medical and non-medical services. (Fig. 4)

What's the range of the services? Medical diagnostics, counseling, expertise, therapeutic assessments, training, and trial treatments. It also involves cooperating specialized doctors, mainly in Cologne, psychotherapeutic counseling, and explanations of treatment, often together with the University of Cologne. It also provides advice on aid, rehabilitation, retirement, care, assistance, individual living accommodations, applications, and much more.

As a concept for elaboration, further treatment accompanying the prescription of necessary therapeutic re-treatments, remedies, and aid is provided, as is the initiation of close-to-home care. As a final service, follow-up visits are made at intervals of several months, mainly 3 to 6 months, to check and adapt to the causes for therapy. (Fig. 5)

What are the key points of thalidomider visits to the center? These are mainly 3-day visits to the outpatient center. If desired, the thalidomider can visit cooperating specialized doctors, resulting in a duration of 4 days. All treatments are covered by German statutory health insurance. Deaf thalidomiders are accompanied by a sign language interpreter the whole time.

An overnight stay in a pension hotel is at the expense of the patients. They organize visits on their own, but it is possible to arrange transportation from us. (Fig. 6)

How do they prepare for a visit? It starts when the thalidomider contacts the center and the coordinators. The coordinators send a questionnaire to the thalidomider who wants to come. The questionnaire is filled out and sent back to the center. With that questionnaire, we hold a treatment conference and make a treatment proposal for the thalidomider. This treatment proposal is then sent back to the thalidomider, and during that time, we contact the cooperating specialist doctors or consultants of the Interessenverband of the thalidomiders. If necessary, we use a sign language interpreter. There is a lot of work to do before the patient comes.

Then, we make a definite treatment plan. That treatment plan is sent in advance to the thalidomider. If it's okay, they get the date for the visit. We normally have a duration of 3 to 4 weeks until they can come. If it's urgent, they can come

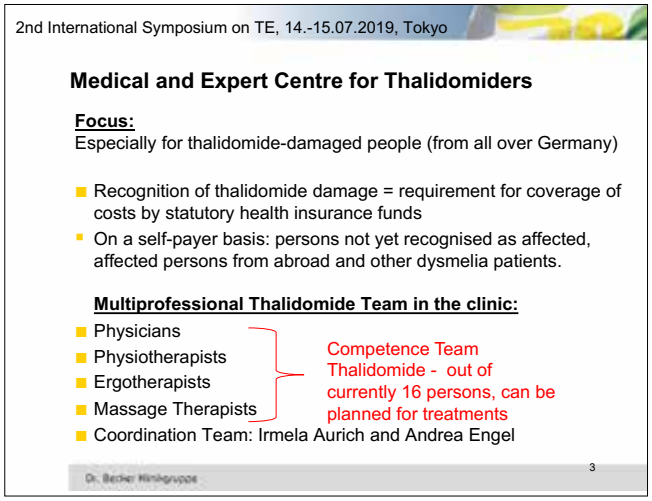


Fig. 3

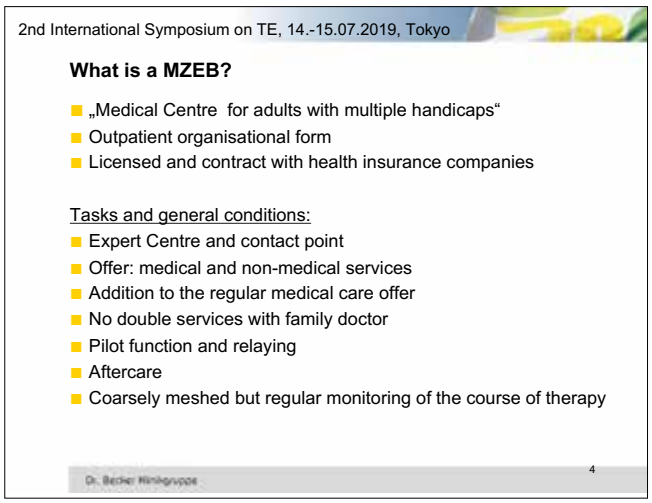


Fig. 4

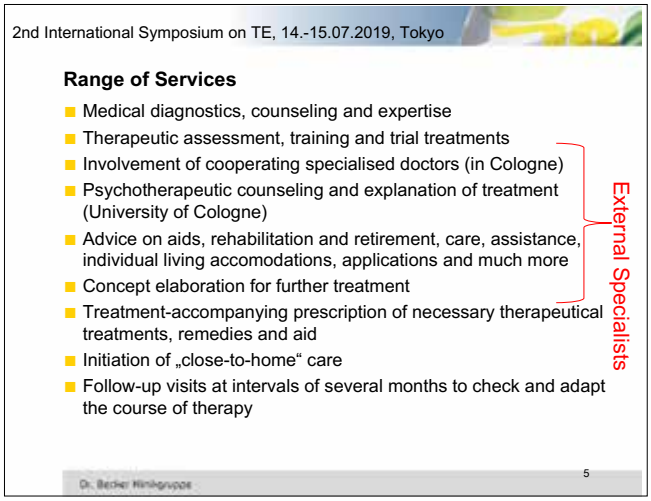


Fig. 5

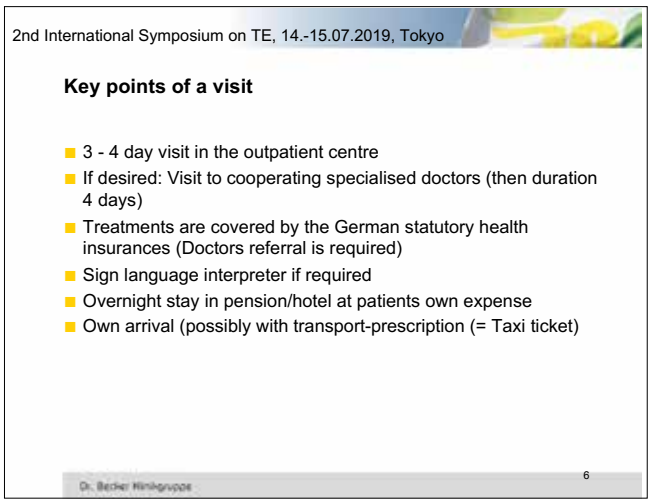


Fig. 6

earlier. We offer further support, including a doctor's referral, medical referral, transportation, prescriptions, accommodations, arrivals, taxi reservations, required aids for a visit, and incapacity certificates. You see, there is a lots of work that has to be done for thalidomiders. We have recognized that every applicant requires about 13 to 15 hours to prepare for a visit. That is a lot. (Fig. 7)

Where does the visit take place? The center is located at the Dr. Becker Rhein-Sieg-Klinik, Nümbrecht, which is about 50 km east of Cologne. (Fig. 8)

Here is an example of a treatment plan for a patient in our center for 4 days. The third day is the so-called specialist day. In this case, it was a psychotherapeutic consultation at the University of Cologne. (Fig. 9)

The visit in the center starts with a physical checkup. It includes examinations such as diagnostic findings, maybe X-rays, and bone density measurements, because many thalidomiders seem to have osteoporosis already. Blood pressure measurements are done for every patient. Acupuncture is provided for pain therapy if desired.

What are the therapeutic treatments? Physiotherapy with mobilization, a sling table, special exercises or physiological movements, physical therapy with craniosacral therapy, foot reflexology, connective tissue massage, ultrasound, ergotherapy with mobilization of hands, arms, and shoulders, and individual aid counseling. At the end of the stay, the physician speaks to the patient and suggests further therapies and prescriptions.

If they come again after 3 or 6 months, they come for 1 or 2 days and get another exercise pool. (Fig. 10)

What are our initial results? We started the center in September 2017, and have results up to June 2019. By that time, we had treated 59 thalidomiders: 35 females and 24 males. At that time, the number of visits was one to four, and the frequency of visits was 3 to 6 months. (Fig. 11)

What is involved in the visits? Cooperating doctors were appointed in 48 cases. Psychotherapeutic consultations were provided in 10 of these 48 cases. Consultation with the Interessenverband was provided in 29 cases, and a sign language interpreter in 11. (Fig. 12)

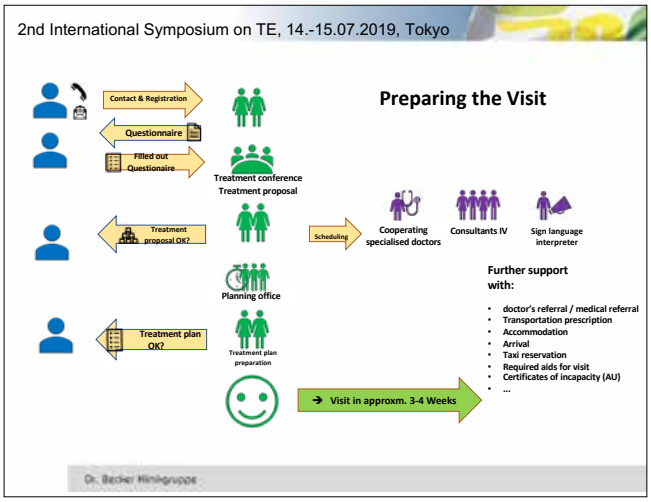


Fig. 7

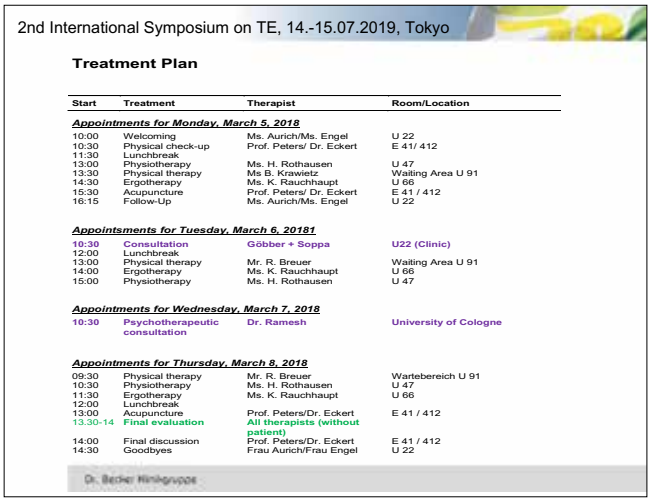


Fig. 9

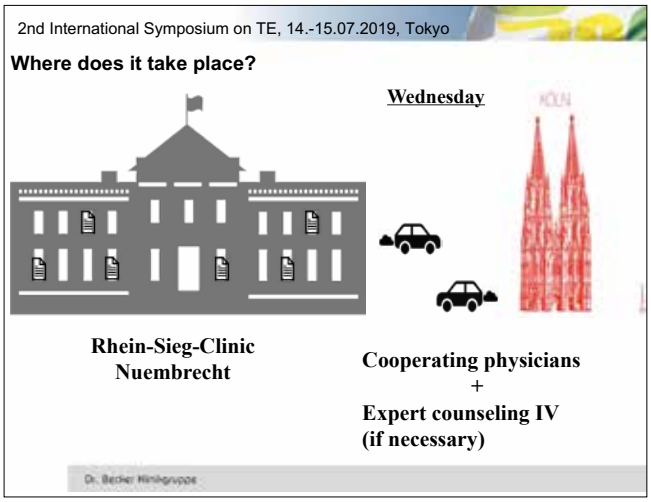


Fig. 8

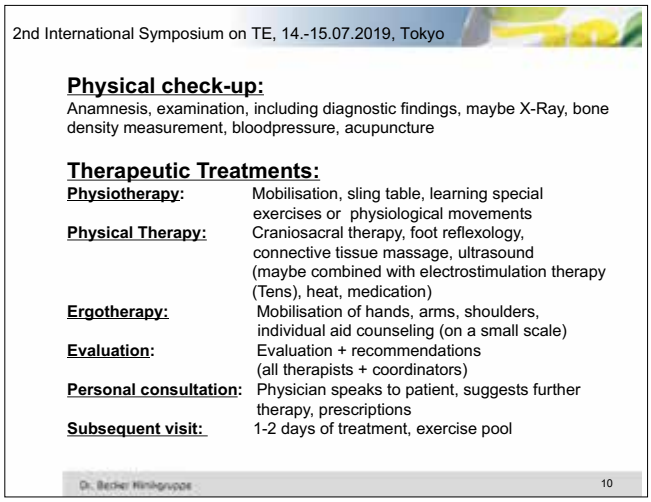


Fig. 10

Why do patients want to visit our center? The main reason is pain, chronic pain. About one-third of the users have chronic unspecific back pain. Another portion (16 cases) has cervical spine problems, pain in the thoracic and lumbar spine. They can have several regions of pain at the same time. Shoulder and neck pain were seen in 44 cases. Problems and pain in the arms, hands, and fingers were seen in 30 cases, with the hips in 16, and with the knees in 17. In addition, problems with the legs and feet were seen in 15 cases, and with the ears, eyes, and jaws in 11. (Fig. 13)

Here are more data from another schedule. (Fig. 14)

What about treatments? What did we do within this time? Acupuncture was provided in 88 treatments. Physiotherapy and massages were given to nearly every thalidomider, and ergotherapy to a large percentage. Diagnostic X-rays were given in 25 cases. There must be special risks for this, otherwise we don't do it. (Fig. 15)

We did evaluated patient feedback because this is very important for us. We asked, "Are you content with your visit?" In total, 98% answered content or very content. We also asked, "Would you visit us again?", and 98% also answered yes. "Would you recommend the center?": 100%. I think it's very good feedback for us because it's very important to have high affinity with thalidomiders. (Fig. 16)

Finally, that's our address and that's our clinic. Thanks a lot for your interest. (Fig. 17, 18)

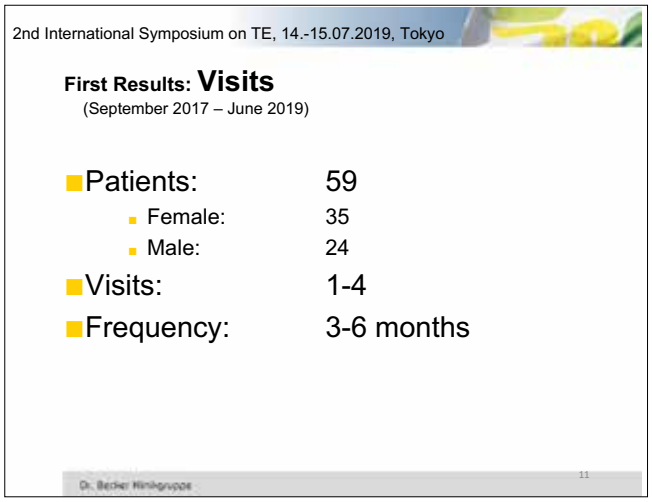


Fig. 11

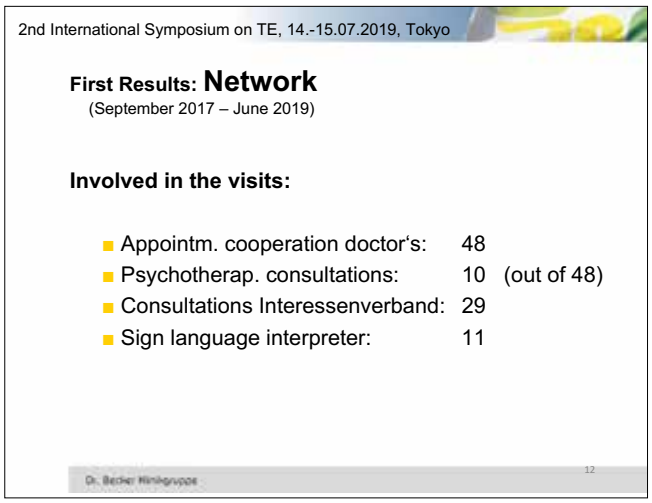


Fig. 12



Fig. 13

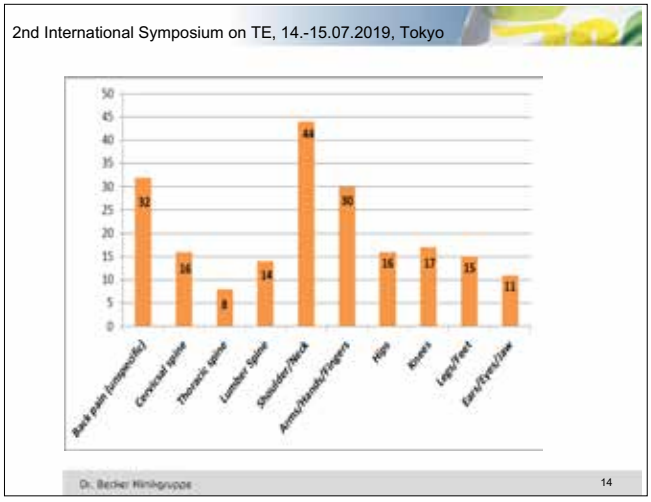


Fig. 14

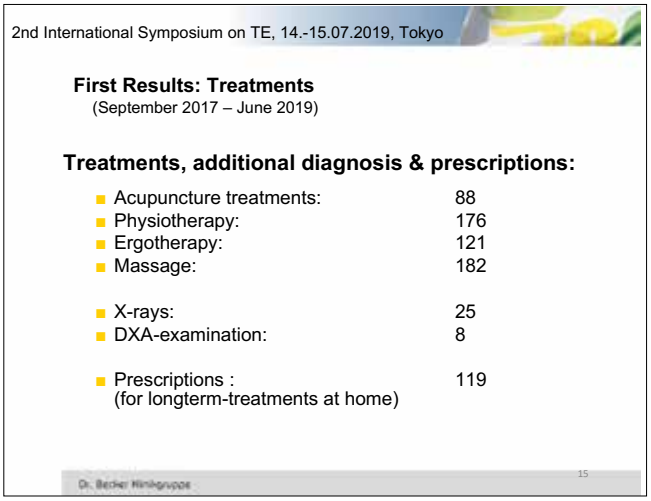


Fig. 15

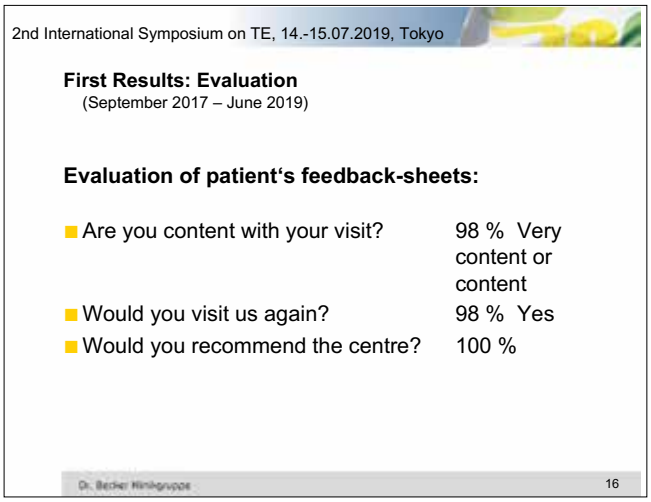


Fig. 16

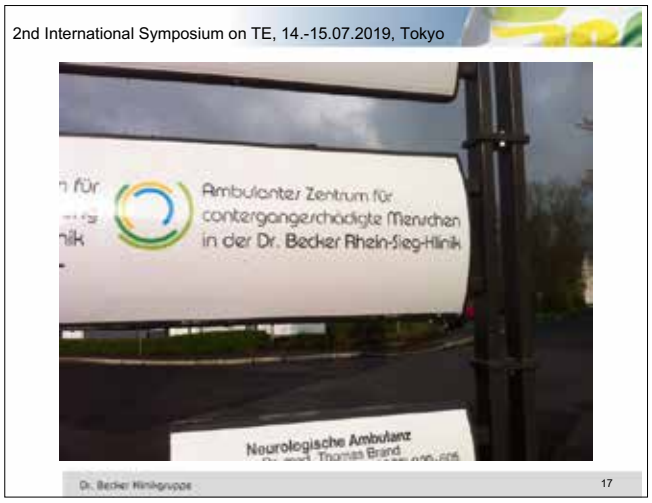


Fig. 17



Fig. 18

Q&A

Nobuhiko Haga: Thank you very much. Does anyone have any questions or comments? Okay, Dr. Peters, would you please explain the difference between physiotherapy and ergotherapy, because ergotherapy is not a standard concept in Japan.

Klaus M. Peters: In Germany, ergotherapists deal more with the upper extremities. It's divided. Physiotherapy is for the whole body, whereas ergotherapy is especially for the upper extremities, like the shoulders, elbows, and hands.

Nobuhiko Haga: So, is there a special category for ergotherapists in your country?

Klaus M. Peters: Yes, there is.

Nobuhiko Haga: Okay, thank you.

Junko Fujitani: Can your project provide pain relief for patients? Many patients have chronic pain, so what is the percentage of pain relief?

Klaus M. Peters: We measure it with an analog scale, and we have several possibilities to treat pain. One very common treatment is acupuncture because they are willing to do that. A lot of the thalidomiders don't want drugs for pain therapy. That's often a problem. They are undertreated with drugs because they don't want them. Therefore, we use acupuncture. We also use physiotherapy and massage for pain relief.

Junko Fujitani: In your project, patients stay in the clinic for several days, so do you expect to provide relatively focused, high-volume treatment during that time? After that, what treatments can patients receive?

Klaus M. Peters: Yes, they can. We give long-term prescriptions for people, mainly 3 to 4 units every week. And I think that will be a good thing for in between visits. After 3 to 6 months, they come back, and we check and control the results.

Junko Fujitani: Oh, so you recommend three or four sessions in a week?

Klaus M. Peters: Yes.

Junko Fujitani: Thank you very much.

Nobuhiko Haga: Okay.

Elizabeth Newbronner: Thank you very much, Dr. Peters. I found that really interesting. Can you also give people advice about adaptations to their homes and equipment that

they could use to reduce the strain on their bodies? Is that something that's available through the clinic?

Klaus M. Peters: Yes, we have expert employees from the Interessenverband who are looking to improve the circumstances at home, yes.

Female Participant (Unknown Speaker): Thank you very much. Very interesting. I just want to know if the cost of this investigation is covered by the government, or by the thalidomide foundation in Germany?

Klaus M. Peters: It's paid by only insurance, not the Conterganstiftung.

Female Participant (Unknown Speaker): It's from the government?

Klaus M. Peters: It's all from the government.

Female Participant (Unknown Speaker): Okay.

Nobuhiko Haga: Dr. Peters, do you have any experience that after a 3- or 4-day visit, you recommend some surgical intervention to the patients?

Klaus M. Peters: Yes, in some of the patients, surgical interventions are necessary. For example, hip or shoulder joint replacement. We also have another center in Bergisch Gladbach, Evangelisches Krankenhaus, where we can perform such operations. If they want to, they can also use other clinics.

Nobuhiko Haga: Okay. There are no other questions. Thank you, Dr. Peters. I will close the morning session at this time.

Growing Older with Thalidomide Embryopathy: Research and Support in the UK

Dee Morrison
The Thalidomide Trust, St Neots, UK

Elizabeth Newbronner
The University of York, York, UK

Christina Ding-Greiner (Moderator)

The doors are closing. I think everybody is back. I hope you had a good lunch and interesting conversations. Again, an interesting subject is waiting for us, "Growing Older with Thalidomide Embryopathy: Research and Support in the UK".

Dee Morrison is a general practitioner. For the last 7 years, she has worked for 3 days a week at The Thalidomide Trust. Her issues are varied. They include advising new claimers and research. But her main focus is assisting thalidomide survivors in health issues.

Liz Newbronner is a research fellow, PhD, and doctoral student at The University of York. She has cooperated with the Thalidomide Trust for 10 years. Her research involves the investigation of age-related issues and their impacts on prenatal and secondary damage. Now, we are very curious to see what you will tell us.

Dee Morrison:

Thank you, Dr. Ding-Greiner, and thank you, Dr. Hinoshita. It's very kind of you to invite us here. It's a fantastic learning opportunity for us, and I am sure it will greatly influence our work when we return home. For those of you who don't know the Trust, just a very quick recap. (Fig. 1)

The Thalidomide Trust was established in 1973. It was set up to provide support and assistance for those with TE. We have now 464 beneficiaries. (I think Professor Skinner said that we have 468, so I am not quite sure what has happened to the missing four). We basically have two aims at the Trust:

- To provide financial assistance. There are two grants we distribute annually. The first one is the main one from Diageo, from the original distributors of thalidomide in the UK, and the second one is a small one, more recent, from the UK Government.
- We also try and help with the thalidomide survivors' health and well-being. We are constantly improving our knowledge and resources, and we currently have a much improved website that we continue to try to improve upon.

We wanted to focus on the second area today. We undertake research with the University of York, so Liz Newbronner is going to present the research that we use to build the knowledge to develop our resources, and I will present the resources. Then, I will present three case studies to show how we use the resources, followed by a short video. The three areas we wish to focus on are mental health, lifestyle, and musculoskeletal issues. Now, I hand it over to Liz to present the research. (Fig. 2)



Fig. 1

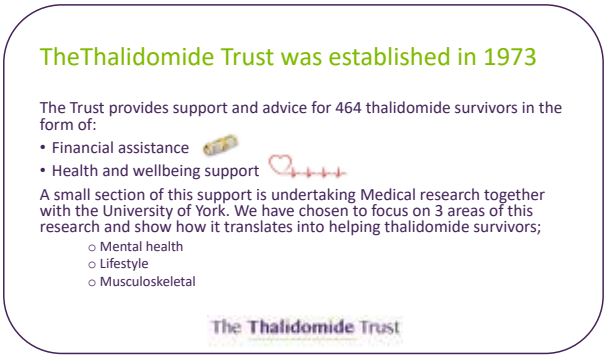


Fig. 2

Elizabeth Newbronner:

Thank you very much, Dee, and thank you to Dr. Hinoshita for inviting me to this important gathering. As Dee has said, what I'd like to do today is just give you a brief overview of some of the recent research in the UK around growing older with thalidomide embryopathy (TE). The research evidence comes from the studies that we've done jointly between the University of York and The Thalidomide Trust, and from my PhD research, which I am in the last few months of now. I've also included some data from The Thalidomide Trust routine processes from their needs assessments. So that's not really research evidence, but I think it adds to what we, you know, the picture that I'd like to present today.

So, just turning first to mental health. In the UK, mental health problems, common mental health problems, are the second-most common health issue experienced by thalidomide survivors. In 2015, we did a health and well-being survey of all UK thalidomide survivors, and almost half reported that they had recently or currently experienced depression and/or anxiety. And in the health needs assessment that The Thalidomide Trust conducts, it has also emerged as a common area of concern alongside broader issues such as loneliness and social isolation. (Fig. 3)

So last year, The Thalidomide Trust asked the University of York to conduct a mood survey. We called it a mood survey to make it seem a little bit friendlier to thalidomide survivors, but basically, it was a survey of common mental health problems. It went to all the thalidomide survivors in the UK via the Trust. We had 182 responses, which is about 40%, so it's a slightly disappointing response rate because in the previous health and well-being survey, we'd achieved a 75% response rate. But I think it perhaps reflects the sensitivity of the issue and concerns that people had about reporting on their mental health.

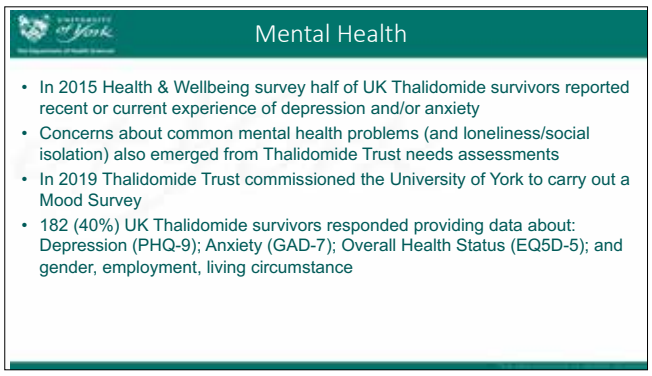


Fig. 3

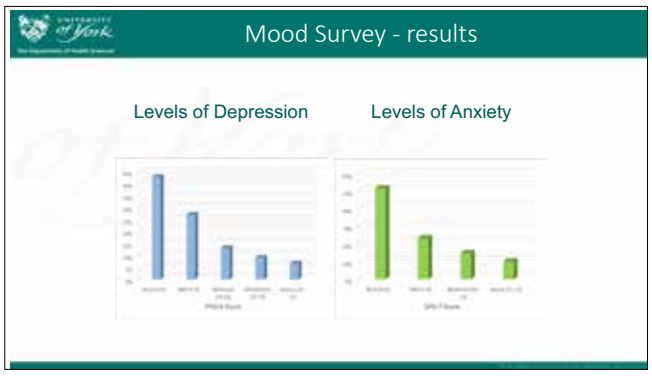


Fig. 4

And so, in that survey, we kept it quite short and simple, but in the survey, we explored symptoms of low mood and depression using the PHQ-9, a standard questionnaire. We also looked at anxiety, again using a standard measure, the General Anxiety Disorder 7 questionnaire. We also looked at overall health status using the EQ-5D-5. Alongside that, we collected some brief information about gender, employment status, and living circumstances. (Fig. 4)

I just want to sort of very, very briefly present some of the highlighted results and conclusions. Just looking at depression and anxiety, first, for depression, we found that over half of the survey respondents reported some symptoms of depression, ranging from very mild to severe depression. But around 30% were experiencing moderate to severe symptoms.

For anxiety, slightly under half of the respondents reported some symptoms. But again, a quarter were experiencing moderate to severe symptoms. I think those are very significant levels, really. (Fig. 5)

So, what conclusions have we been drawing from the mood survey? I think the first thing to say is that the prevalence of self-reported depression is much higher at all levels for thalidomide survivors than it is for the UK population of a similar age. And I think those findings echo the work in Germany and Brazil. So I think a picture is developing internationally.

However, the levels of depression and anxiety experienced by thalidomide survivors were not dissimilar to other people with early acquired disability, so, for example, peo-

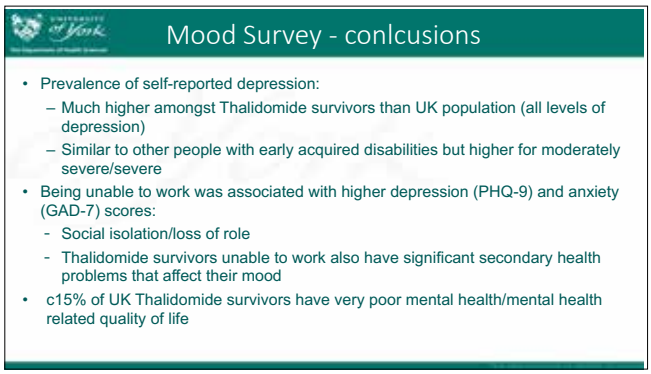


Fig. 5

ple with cerebral palsy or spina bifida, but the thalidomide survivors generally had higher levels of symptoms. So, although the overall picture was the same, thalidomide survivors were experiencing higher levels.

One of the things that we were interested in is that in the UK, almost two-thirds of the thalidomide survivors are no longer in paid work, and a very high proportion of them have given up work because they feel unable to work, not because they are choosing to, but because they simply feel unable to because of their physical problems or pain and so on. (Fig. 6)

Thus, we wanted to look at whether there was an association between being unable to work and having higher levels of depression and anxiety. We did indeed find that, and it was statistically significant. So, I suppose one thing that we've speculated on is why that might be the case. We think it might be partly due to do the fact that giving up work means that people perhaps lose their role, and that there is an increased level of social isolation, but also that thalidomide survivors who are unable to work are perhaps experiencing more significant secondary health problems, which is then also affecting their mood. So, it's sort of not a simple picture, really.

The other thing I wanted to just mention was that over the last few years, in the various smaller and larger studies that we've done, we seem to find that consistently, around 15% of thalidomide survivors have very poor mental health, whether we've looked at the measures that I've just described or mental health-related quality of life. I think, interestingly, in comparison with the quality of life study in Sweden, what we found was that people with lower levels of damage were more likely to have poor mental health-related quality of life, so it was the opposite of physical health, you see what I mean.

We think that might be because many thalidomide survivors have led very active lives, and now in later life, are experiencing new levels of disability, which is causing the problem. So, that's an interesting issue, I think. I've also sort of been thinking in my doctoral research about why thalidomide survivors' mental health might be so vulnerable.

I'd be interested in your thoughts, but my feeling is that there is a mixture of things going on. I think on one level, it's the accumulative effects of living with disability, particularly a rare disability, for many years, and the thalidomide survivors in the UK that I talked to described the effort of coping with daily life, year after year, and constantly having to sort of plan ahead and so on. But also, that sense of being different, and perhaps sometimes, sadly, unwanted attention, ranging from just people staring to actually having people being mugged or having discrimination at work and so on. So, I think that's a difficult issue. But more generally, I think there's an issue around the emotional impact of pain and loss of function. Particularly, that leads to difficulties with daily living, of activities of daily living, which are brought about by the secondary health problems.

However, I think what we found in the UK, and this is not surprising, I guess, is that there is a big influence in terms of people's individual circumstances, their family attitudes, and their life events, perhaps earlier in their lives, but also in sort of a wider social context; so, how much support and care they have, and whether they have a good social network and good financial resources. These things are all very important in determining how people respond to the pressures that they are coping with. And certainly in the UK, we found that the improved financial position of thalidomide survivors in the last 10 years has made a huge difference because people have much more choices and options in how they live their lives.

Dr. Morrison is going to talk a little bit more about how the Trust supports thalidomide survivors with common mental health problems, but one of the things that we are testing at the moment at the University of York is a short six-session behavioral activation program to help thalidomide survivors with low mood and depression. I have some

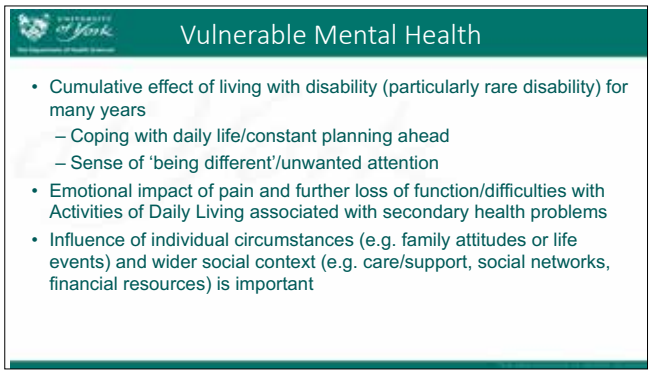


Fig. 6

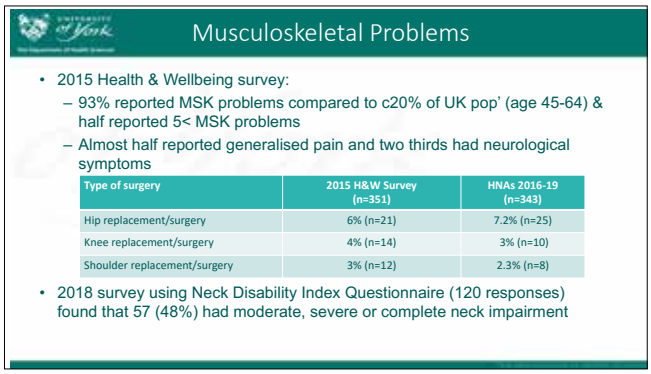


Fig. 7

copies of the booklet that we are using if anyone would like a copy toward the end of the session. (Fig. 7)

Now, turning to musculoskeletal problems, it seems to me that listening to all the speakers today and from looking at the literature that musculoskeletal problems are probably the most commonly reported health issue for thalidomide survivors. As I described when I came to the symposium 4 years ago, that certainly was the case in the UK. Around 93% of the thalidomide survivors who responded to our health and well-being survey said that they had some, one or more musculoskeletal problems. That compares with about 20% of the UK population of a broadly similar age, so a much, much higher proportion. (Fig. 8)

Interestingly, we found that many thalidomide survivors, over half, had five or more musculoskeletal problems, so they were dealing with a lot of different issues. More generally, people were reporting generalized pain and neurological symptoms. I have not gone into detail here because there's not really the time, but I just wanted to flag that.

I know from the panel questions that Dr. Hinoshita kindly sent us that there's some interest in joint replacement surgery. While our data aren't very solid, if you know what I mean, I thought it might be interesting to briefly present some of those figures. You see from the table that I've included the data that we have from the health and well-being survey, and from the holistic needs assessment, which the Trust staff carry out with individual beneficiaries. We estimate that around 6% to 7% of thalidomide survivors in the UK have had hip surgery or a hip replacement as an adult; this is not what happened to them as children, but as adults. That compares with I think around 1% of the general population of a similar age, although Professor Skinner might say more about that.

Similarly, for knee replacement surgery, it's around 3% to 4%, and again, this compares with about 1% of the general population. For shoulder replacement surgery, we think it's around 2% to 3%, but we don't have very good comparative data in the UK for that, so I am not quite sure how that compares with the general population, but we think it's higher. And just briefly, just to say, in terms of the other information that we have in the UK, last year, the Thalidomide Trust did a survey using the Neck Disability Index Questionnaire, and they had a good response, 120 responses. Of those 120 responses, 57 or nearly half had moderate, severe, or complete neck impairment.

I know Dr. Morrison is going to say a little bit more about how the Trust is helping thalidomide survivors with that specific problem, but more generally, with musculoskeletal problems.

I just wanted to sort of conclude talking about musculoskeletal problems by saying that it feels to me as though there is a real consensus internationally that consequential or secondary musculoskeletal damage is primarily caused by overuse and postural adaptations in very broad terms. But I think what I feel has emerged from my research is that often, injuries from falls and accidents, which are in some way linked to people's original damage, so for instance, mobility problems, balance problems, and sight problems, are a growing concern for a lot of thalidomide survivors.

Interestingly, I think a few thalidomide survivors in the UK have said to me that sometimes, surgical treatments are a mixed option for them, so that might reduce the pain they are experiencing, but they might then find some loss of movement or loss of flexibility, particularly in relation to shoulder treatments.

I think the other thing I just want briefly to say is that, it seems to me that musculoskeletal problems and the sort of issues that they cause, in terms of activities of daily living, pain, and a decreased ability to work, are completely intertwined with mental health issues, so it's really not possible to look at these things in isolation. (Fig. 9)

Turning briefly to lifestyle diseases, I would say that in the UK, our research information about lifestyle diseases is not very good and is a bit inconclusive, so I am cautious

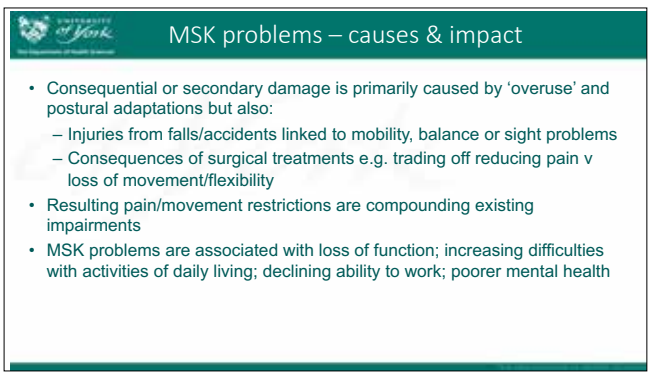


Fig. 8

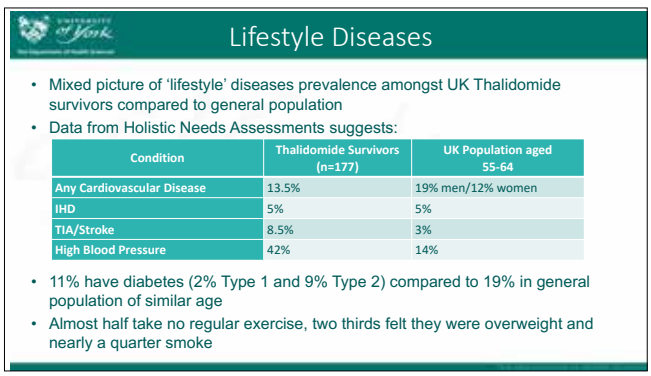


Fig. 9

about presenting some of the data here. But knowing that it is an area of interest, Dee and I just wanted to sort of show you some things. Most of the data actually come from the needs assessment that the Trust has done. So we can see by looking at the table here that for cardiovascular disease and ischemic heart disease, broadly speaking, the figures are very similar to the general population of a similar age. But for stroke and high blood pressure, the figures are much higher. The high blood pressure figure I think needs to be treated with some caution, because it's entirely self-reported, but it seems not dissimilar to all the data that have been reported, not so much in Japan, but in other European countries.

The data we have about diabetes, again, we are not too confident about it. But just to give you a broad picture, in the UK, it actually seems to be lower than that in the general population, so that's an interesting issue that perhaps needs to be explored further. But around the issues of risk factors for lifestyle diseases, certainly, almost half of the thalidomide survivors in the UK say that they take no regular exercise, two-thirds feel that they are overweight, and nearly one-quarter smoke. So again, as Dr. Morrison was saying this morning, I think that's higher than the national picture.

I think those things reinforce Dr. Shiga's work and the points that Dr. Schulte-Hillen was raising this morning about the need to be able to measure blood pressure and BMI accurately if people are going to be helped to live healthier lifestyles. (Fig. 10)

Before I close and hand things over to Dr. Morrison, I just wanted to say a little bit about multi-morbidity because I feel that it's something that perhaps isn't very explicitly discussed in the literature around aging with TE, but reading all of the work that has been produced here and listening to the presentations today and yesterday, it seems to me that it's a growing concern for thalidomide survivors as they grow older. I mean, it is a concern for populations at large, but certainly in the UK, the issue of multimorbidity is much more prevalent among thalidomide survivors than among the general population of a similar age. Almost half of the thalidomide survivors are reporting four or more separate health problems, which compares with about 10% of the UK population. So it's significantly higher.

I think the other point is that for thalidomide survivors, often, the morbidity burden is high. I think this presents difficulties for them in terms of the complexity of their needs and how the healthcare practitioners that are working with them provide support. But more generally, I think it presents issues for the thalidomiders themselves in terms of self-managing their health conditions, and that can be both practical and clinical, so people face a lot of practical difficulties, and also clinical issues.

To close, I'd like to just sort of draw some broader conclusions and perhaps try and set our research in the UK, in the context of the wider literature about aging with early acquired disabilities because I think there's much that we can learn from that broader field of research, and much that we can contribute, as Dr. Haga was saying earlier. (Fig. 11)

I think there's now clear evidence that the cumulative effects of living with a disability for many years contribute to a premature decline in health and social disadvantages, which of course, are interconnected. I think what we see is that the layering of secondary damage onto lifelong impairments creates new disabilities, but also a new sense of being disabled for some people, so the people who have previously led very active lives are now feeling disabled in a way that they perhaps didn't previously. Moreover, all of that is contributing to people's mental health problems.

Thus, I think for thalidomide survivors, like other people with early acquired disabilities, such as people with cerebral palsy, the sort of philosophy of "conserve it and preserve it" may be preferable to the old philosophy of "use it or lose it". I think in fact that thalidomide survivors themselves are making that choice; they are looking at ways to preserve their function while at the same time trying to keep as much

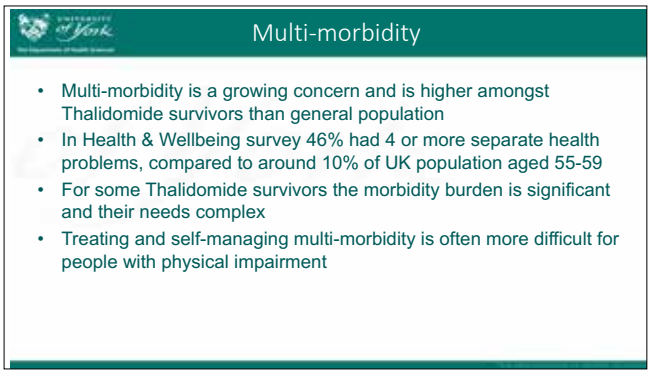


Fig. 10

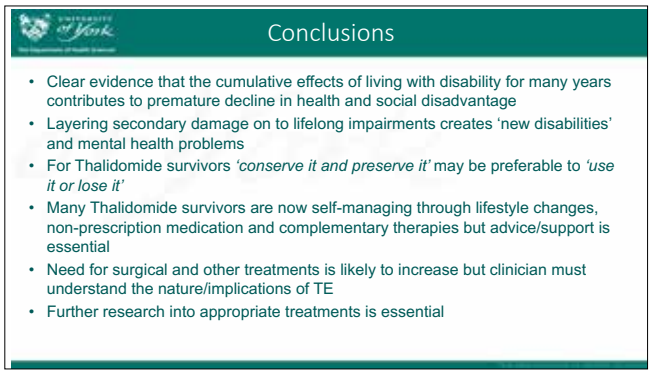


Fig. 11

independence as possible. So I am sure in all countries, they are making greater use of aids and adaptations, making lifestyle changes, and using complementary therapies as we were hearing about earlier.

But I think out of all of that, what sort of comes home to me is the importance of having really good access to advice and support, I think that's absolutely essential. But alongside those self-management options and choices about preserving function, it feels as though the need for surgical and other interventions or treatments is likely to increase in the coming years, and I think the work that's going on in Japan to educate doctors and other healthcare practitioners about TE is really wonderful because I think that's something that is so needed. If thalidomide survivors are going to be given good care and good treatment, they need doctors and other healthcare practitioners who really understand their condition and how it's affected them.

So with that, I'd like to pass things over to Dee, who's going to talk more about how The Thalidomide Trust supports beneficiaries.

Dee Morrison:

Thank you, Liz. So you've heard now some of the research we've been doing, and I am just going to try to explain how we use the research to help build our knowledge and put resources in place to try and help the individual. (Fig. 12)

I'll start with mental health support. I'll just briefly run through the resources we can pull in to help the individual. We can offer telephone support call from the Trust staff. This can be on a weekly basis or a bit more regularly. We can also offer an assessment from a medical advisor (I say medical advisor because I have a fellow GP, Dr. Susan Brennan, who joined the Trust last year, so now there are two of us). We look at the local services that are already being offered, what's happening with their GP, and what's happening with counselors, medication, etc., locally.

Then we can decide whether to pull in a bit more support to try and help further. We can call on volunteers, and we have two ways of doing this. So, the volunteer is actually a thalidomide survivor or a thalidomider, as some of you call them, and they can either visit them informally or call them. Or we have a more formal project called Talk Together. This is where the volunteers have actually received training in a project and have support. They usually call at a set time during the week.

We have a low mood improvement research project that Liz is involved in, which she mentioned briefly, for which, I held the booklet up earlier (Fig. 13)

I'll share a little bit more about the case study later. We recently involved a psychotherapist. This is quite an important resource for us. He is very experienced; he has provided care for doctors, for the army, for people who return from war very burnt, and for the fire service. He can use a wide range of therapies. He Skypes, which allows us to access all beneficiaries who are situated all over the UK. He can treat anxiety and depression, as well as addiction problems; we do have a higher incidence of alcohol use. The other area that we had no therapy for was social phobia, the psychological issues from a very visible physical deformity. He is trained in existing psychological therapies, but he also offers a new therapy called metacognitive therapy. This targets overthinking and allows them to control their attention to thoughts and behavior. So, basically, when people start to get anxious or depressed, they ruminate, they look at what's happened in the past, and their thoughts go over and over, or they worry about the future, and they can't shut the thoughts off, and then they can't sleep. He teaches them to control this and control their behavior so they don't turn to alcohol, which allows them to focus their thoughts elsewhere.

We also have Trust events where we remind them to look after their mental health and well-being. (Fig. 14)

If I quickly go on to the next topic of lifestyle, there's a lot of information in the public domain about lifestyle. What we try and do is tailor the information and make it more



Fig. 12



Fig. 13

specific to those with TE, explaining the why and how. We can do this with either websites or talks and seminars. For example, I recently wrote "How healthy is your heart?", a blog pulling in research from Germany and Japan, as well as from Dr. Beyer's recent paper saying that we thought there was a slightly increased risk of cardiovascular disease. But I was able to reassure them that currently, there's no specific evidence to say it's due to thalidomide per se, but that we were taking steps to learn more about it. I explained what they themselves could do about it.

So that was the "why and how" regarding lifestyle. Then again, for the "how," we try and offer test sessions, either for the individual or for the group. Sweden did a very good project some time ago where they pulled in nutritionists and personal trainers over the course of a year. We learned from this and devised our own project, called Fit for the Future, where we did it over a weekend, so we had personal trainers, physios, nutritionists, and a group of beneficiaries. It was very successful. We followed up with the group over Facebook and we repeated this a couple of years later, for different beneficiaries, again over a weekend. One very important way that we try and help with lifestyle is to inspire them with stories from other beneficiaries. We got Simone on our website, logging her food. She lost 4-1/2 stone (1st = kg * 0.15747) in 2-1/2 years and we have also got Kath trying to improve her balance and prevent falls through exercise.

We designated 2020 as the year of health and well-being. So we're going to do events across the whole of the year. Underpinning this is the "One Small Change" campaign, where we are going to ask them to make one small change in say, about 6 weeks, and we're hoping then that they will follow up with other changes. That change could be eating a piece of fruit or going for a walk for 10 minutes three times a week. (Fig. 15)

Lastly, the third area is musculoskeletal problems, a really important area. Again, tailored information is very important. The work with our specialists has allowed us to build up our knowledge so we can tell them a little bit about what's causing their hip, shoulder, and neck pain, why they are getting more of it, and also about balance and falls, which I think is going to be a big issue as they age, and what they can do about it.

Backing this up are our beneficiary stories, and again, peer-to-peer support; so, stories about the hip, the shoulder, the neck, how they had their surgery, what implications there were, how it was organized, what the rehab was like, what they needed to order in terms of extra carers, and also working with physiotherapists or massage therapists.

We've also developed a professional network. This has been quite informal over the last few years, but with the new website, we have a special page, and we are building up there specialists and therapists who are known to the Trust or who've actually helped thalidomide survivors.

Individual support with the helpline is obviously an area that I care very much about. We liaise with the GP regarding medication, advice about massage, physio, and exercise programs, put them in touch with local therapists, and follow them through. But again, a major part of this work is the help with specialists, where we have a small budget in the Trust. We can facilitate a private referral to a specialist who is familiar with thalidomide issues and who is a complex surgery specialist, such as Professor Skinner. This allows us to speed up greatly the referral, and enables a really good conversation for the individual with a specialist familiar with their issues to explain what the issue is and what can be done to help them.

Lastly, the Trust staff go to a lot of events and can also help with ergonomics, personal assistance, wheelchairs, gadgets, etc.

So, those are the resources we have put in place. I'll just quite quickly take you through several case studies to show how we pull in the resources in individual cases.

These cases are not for publication, and have been omit-



Fig. 14



Fig. 15

ted from the written summary of the seminar. However, one case study showed the use of psychological help with the LIFT study, another case study showed how another individual was helped with depression, pain, and alcohol, and the last case study showed how one individual with neck and referred pain was helped by successful cervical spine surgery.

The video I am going to show you now is on David. This followed inspiration from attending Dr. Beyer's seminar on physio and exercise in Germany. It also followed a weekend seminar, called "Fit for the Future," that I mentioned earlier, and an expert from Loughborough University talking about exercise and how to create an established pattern. He said it needs to be fun, it needs to be sociable, and it needs to be easy to do. So we took this learning and ensured that the physiotherapy was followed up by exercise and the development of an established exercise routine. And this is what happened.

[Video begins]

The conversation between David and Fraser is shown below.

David: For a long time and in my late 40s and early 50s, I started having trouble in my back, and I just thought it was arthritis. I struggled a lot with my balance and going up and down stairs, and I didn't feel very secure when getting on and off buses. I spoke to Dee from The Thalidomide Trust, who suggested I contact Fraser, who is a physiotherapist.

Fraser (physiotherapist): From David's initial assessment, one of the biggest things that we found was that David has got a slightly shorter leg than the other one, and because of that shortening over a long period of time, it's put an awful lot of stress on David's back. So, what we've done is initially refer David to an orthotist, who has taken a mold of David's foot and provided a custom-made insole. And what that has done is just support the shorter leg, making it a little bit longer and evening out his posture, which will actually help David walk better.

David: The reason I got in touch with The Thalidomide Trust is because I went to a weekend Trust event called "Fit for the Future," and it was just about keeping your body in good shape, dietary help, what can help pain, etc. But the thing I was the most interested in and have never done before was Pilates. They encouraged me because I had never seen Pilates before, and now myself and my wife are looking into joining a Pilates class. But we intend to get a little bit more fitter before taking this further.

I've never done exercises before, I never really knew about it until Fraser told me, and then it all kind of made sense.

Fraser (physiotherapist): The ultimate aim of physiotherapy is to give David his independence back and to really get David to take ownership of his own health. So we are going to look at David going along to a local Pilates class after probably about 4 or 5 months of treatment.

David: Fingers crossed.

David (months later): In general, my back is 100% better, even walking is all better. I am more confident when I am out and about. I am walking a lot more, and I am not putting as much strain on my back, so obviously, the pain is not going to be as severe. I can reach things, and I can bend over a bit to get things from the cupboards, which is a lot easier.

Fraser (physiotherapist): One of the big things that David was wanting to be able to do is to be a bit more active regularly, so The Thalidomide Trust has put him in touch with a local Pilates instructor, and Pilates itself is quite a nice exercise program because it keeps you strengthened and stretched in the right way.

David: Yeah, the first two (Pilates) classes went really well, and she's quite surprised how good my balance is. But I would not have been able to do it without physiotherapy. I would have never ever dreamed of going to physiotherapy. I was too embarrassed, but I find that once you get started and get more involved with physio or Pilates, your confidence grows. I just took things for granted because of the shortness of my leg. This was the way I walked, and that was it, and there was nothing could be done. I honestly should have done it years ago (referring to physiotherapy).

[Video ends]



Dee Morrison: I hope you can now see how we have taken the knowledge learnt from the research, not just from the UK, but from the work you have all been doing, the specific projects in the UK and abroad, and the work with specialists such as Professor Skinner and symposiums like this, to

build knowledge within the Trust and put in place resources to help thalidomide survivors, as shown in these individual case studies. Thank you.

Q&A

Christina Ding-Greiner: Thank you very much for this very beautiful presentation. Are there any comments or questions?

Fumihiko Hinoshita: I have a question for Liz. You showed us the incidence of cardiovascular diseases and IHD, ischemic heart diseases, and then TIA and stroke, between the general population and thalidomide beneficiaries. Interestingly, the incidence of cardiovascular problems or diseases was almost at the same level in thalidomiders and the general population. But as for TIA and stroke, there is a large gap between the thalidomiders and the general cohort. What do you think is the cause? I mean, from hypertension or other problems, for example, some anatomical problems of the cerebral vessels or so. What do you think?

Elizabeth Newbronner: Dee can probably answer this better.

Fumihiko Hinoshita: Yeah, Okay.

Dee Morrison: We don't know. I think I asked my question poorly yesterday, but what I was trying to say was that we know there are lots of abnormal vessels, but we don't know whether the disease processes as they grow older might be more detrimental in certain areas than in others. But there isn't any evidence at the moment to say that for those who are affected by thalidomide in the room, so we really just don't know. We can really just monitor what's happening and keep a close eye on everything.

Fumihiko Hinoshita: Okay. I would like to know the further results of your survey, and then consider the cause, please. Basically, in your country, you have more cardiovascular events than we do, so I was very much interested in the gap. Interestingly, more thalidomiders are suffering from TIA or stroke in your country. That's it.

Elizabeth Newbronner: Just to say as well that I think we hope that The Thalidomide Trust is intending to repeat the health and well-being survey in 2020. I think we've learned from the past survey, so we're hoping that we'll be able to get much more accurate data about both the lifestyles and diseases in older age and risk factors, so hopefully, if we ever meet again, we'd be able to present some more accurate data.

Christina Ding-Greiner: Are there any more questions or comments? Nobody? Then, thank you.

Ageing with Thalidomide Damage: Evaluation 2019–Special Needs

Christina Ding-Greiner

Institute of Gerontology, University of Heidelberg, Heidelberg, Germany

Klaus M. Peters (Moderator)

Today, I am happy to introduce my German colleague, Dr. Christina Ding-Greiner. She studied medicine at the University of Heidelberg and Vienna, specializing in internal medicine. Afterwards, she got another specialization in gerontology. Nowadays, she is still a member of the Institute of Gerontology at Heidelberg. I think she's been dealing with thalidomide-affected people for several years. Her topic today is "Aging with Thalidomide Damage: Evaluation 2019". The focus is on special needs.

Thank you very much for your introduction. Thank you, Dr. Hinoshita, for inviting me. (Fig. 1)

As a result of our studies, which I presented 4 years ago, in 2015, we had two amendments to the Law of the Contergan Foundation for Disabled People, in 2013 and 2017. In 2013, rents for thalidomide embryopathy (TE)-affected people were raised sevenfold, and in addition, they got a sum of 30 million euros per year for special needs. This amount was budgeted in 2017, and they get now, in addition to rent, a yearly budget of between 5000 to 15,000 euros, depending on the degree of their damage. (Fig. 2)

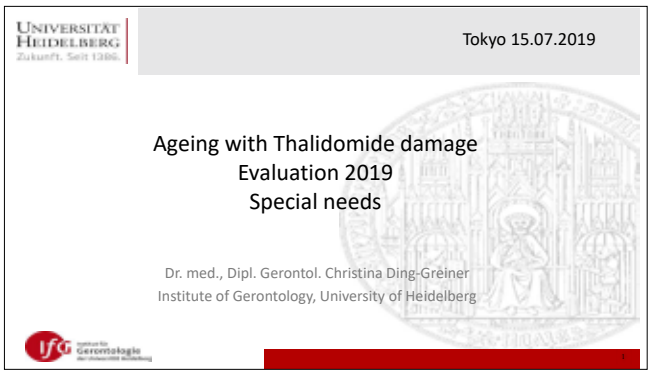


Fig. 1

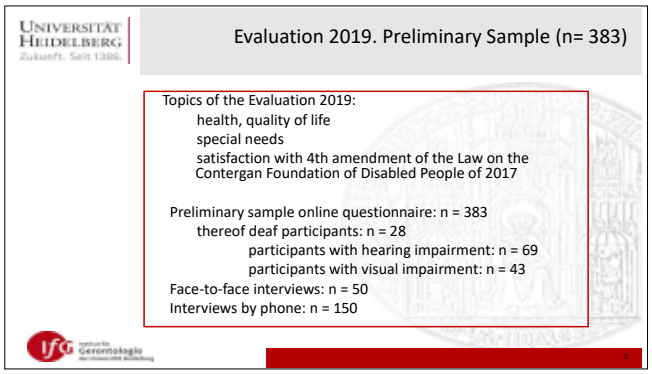


Fig. 2

The Institute of Gerontology was assigned to evaluate the outcome of the Fourth Amendment of the Law of the Contergan Foundation for Disabled People in 2017. We have not yet finished our survey; therefore, the data we present are only preliminary.

Our tools were: 1) an online questionnaire and video produced for deaf affected people with a sign language interpreter translating the online questionnaire; 2) face-to-face interviews with a mean duration of about 2 hours, which were analyzed with qualitative methods; and 3) interviews by phone calls lasting about 30 to 60 minutes, which were evaluated qualitatively and quantitatively with SPSS. (Fig. 3)

Overall, 40% of our sample were still employed; 54% had a full-time job and 46% part-time. Also, 40% of the TE-affected people in our sample who left employment since 1978 retired during the last 6 years. They benefitted from improved financial conditions and are now able to care better for themselves. (Fig. 4)

But why did they leave? It was not an easy decision for all. Almost 90% told us about a reduction in physical capacity. A second reason referred to was pain and reduced resil-

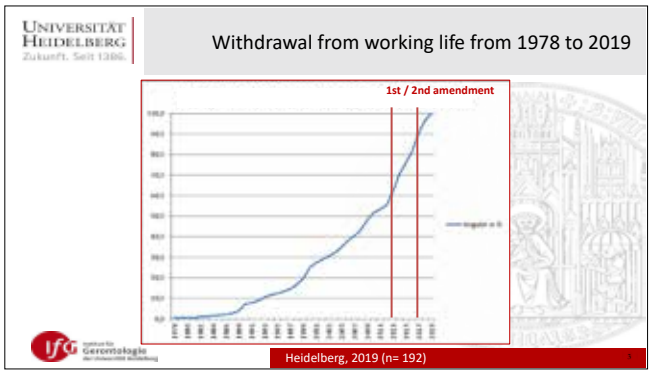


Fig. 3

ience; only 7% mentioned that they had no job offers.

The reduction in physical capacity is a problem in all TE-affected people. They describe it as a slow and constant process lasting more or less for 10 to 20 years. This process has accelerated during the last 3 to 5 years. There are acute episodes where affected people lose capacities in a short period of time. They often manage to restitute the prior condition to some extent, not entirely, but mostly. The trend leads step-wise downwards and implies a loss of strength, a loss of skills, and the stabilization of a lower level of physical capacity.

TE-affected people never know when it will happen or to what extent they may lose capacities or will be able to restore them. Especially those who are single are concerned and fear an acute event because they don't know whether they may be able to cope with it.

This is one reason why they rate the current situation concerning health as moderate to poor. Only one person told me in the interview she had a good healthy condition. (Fig. 5)

The prevalence of pain in our preliminary sample was high, with 82.5% declaring that they suffer from pain. We divided the sample into four groups depending on the damage points they had: up to 25, 25 to 50, 50 to 75, and 75 to 100 points.

As you can see, there were very small differences between the different groups concerning the prevalence of pain. Even those affected persons who have only a small amount of damage points, as they have few prenatal damages, show a high prevalence of pain, too.

Affected people with only slight damage lived a more or less normal life with stress and burden as if they had no damage. But obviously, there is a higher physical vulnerability in this group, too. Their physical health condition today shows an accelerated aging process, as we can see in all thalidomide-affected persons. Considering their condition, they are in a similar situation as other TE-affected persons with a higher amount of prenatal damage, and who therefore have higher benefits. The group with lower damage points and lower benefits are endangered, as their benefits don't meet their current needs.

Since 2010, an increasing number of participants in our surveys have told us about remarkable pain episodes, which can occur without any apparent reason in any part of the body at any time. There is a sudden, short, and very violent pain, like a bee sting. If they happen to carry something in their hands, they may drop it, or they may even fall if the pain occurs in the feet or legs. The origin of these symptoms is not known.

No doctor could tell them until now what the cause of the symptoms might be. It would be interesting for me to hear from you about whether your patients tell you about similar symptoms. (Fig. 6)

We asked the participants about the intensity of their perceived pain, considering a scale from 0 to 10, with 10 being the highest level of pain. For all four groups, we calculated the mean value for 2009, 2016, and 2019. The differences between the mean values of the years 2009, 2016, and 2019 were statistically significant, and this process goes on. The pain level was increasing over the years in spite of retirement or more physical therapy; some people have physiotherapy three times a week, they have massages, they go swimming, they have more rest, and they adapt their environment to their needs.

We had the impression in our interviews that some affect-

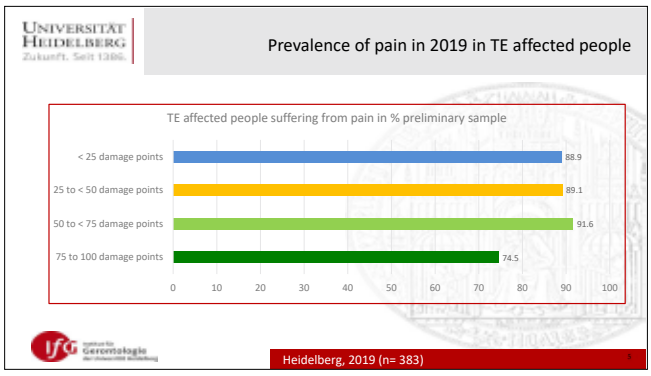


Fig. 5

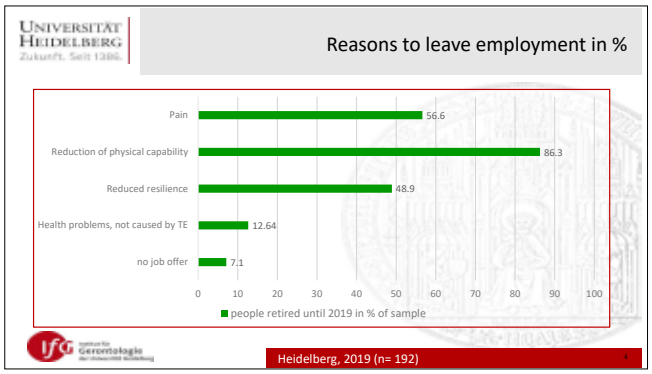


Fig. 4

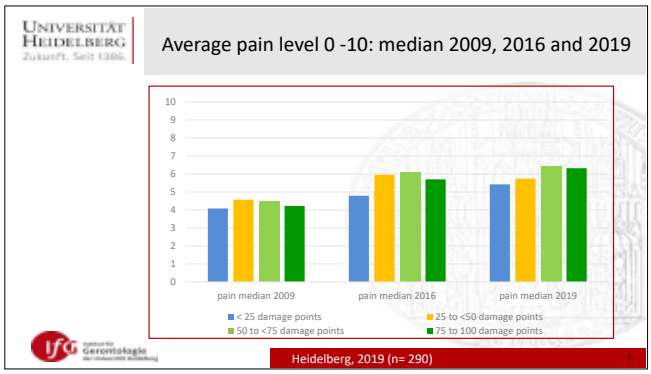


Fig. 6

ed persons showed no further increase of discomfort, as they had changed their way of life since they left employment. But all of them know that this will not last for a long time, that the aging process is in progression. (Fig. 7)

The pain disability index measures how much chronic pain prevents people from performing different aspects of everyday life. For different items such as family and home responsibilities, recreation, social activities, occupation, sexual behavior, self-care, and life support activities, we calculated the median index points for the sample. The higher the index, the greater the person's disability due to pain. We see as well that the differences between 2016 and 2019 in all items were statistically significant. There were severe and progressive restrictions due to pain in essential life activities.

TE-affected people try to palliate the situation with all kinds of physical therapies and sports, with good results. They get support from friends and family. But if the restrictions grow, the demand for assistance will grow, too. We learned in our interviews that first, they cut down activities that give support through participation in social life. Thus, they might become endangered in regard to mental health. (Fig. 8)

Overall, 43% of the participants in our survey had a regular need for assistance; the higher the degree of disability, the higher the need. Also, 30% and 35% of the participants with fewer than 25 or with 25 to 50 damage points showed a need for assistance, respectively. The collected data for hours per day of needed assistance, independent of who was assisting, showed a statistically significant increase from 2016 to 2019, and this trend continued. It was linked to higher expenses, which affected people will not be able to afford privately in the long run. In addition, more professional assistance includes lesser privacy, and quite a different individual orientation in everyday life; these problems are severe mainly for people living independently. (Fig. 9)

The participants were asked whether they had a regular need for assistance or care at present, or whether they thought they would need assistance or care in 2022. The actual needs were quite high, almost 50%. The estimated growth rate was 1.3 for future needs in 3years. TE-affected people in Germany live at the moment in quite a good condition. They are able to provide for almost everything they need, but as this trend proceeds, a distinct change in the general situation can be expected. There will be difficulties in funding and in finding adequate assistance to preserve personal autonomy. (Fig. 10)

The focus of required demands is on mobility, new cars with adapted equipment, and adaptations to the living environment, including the actual loss of strength and skills needed to remodel bathrooms and kitchens for more independence. Electronic devices provide better relief in everyday life activities. It is now possible for TE-affected people to cover their demands and care for the future. They adapt their homes for wheelchairs, even though they do not yet

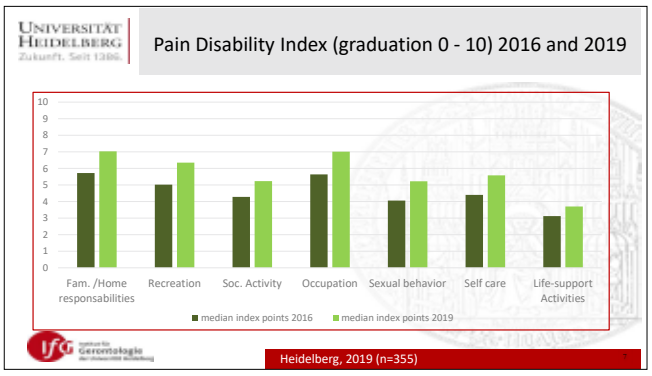


Fig. 7

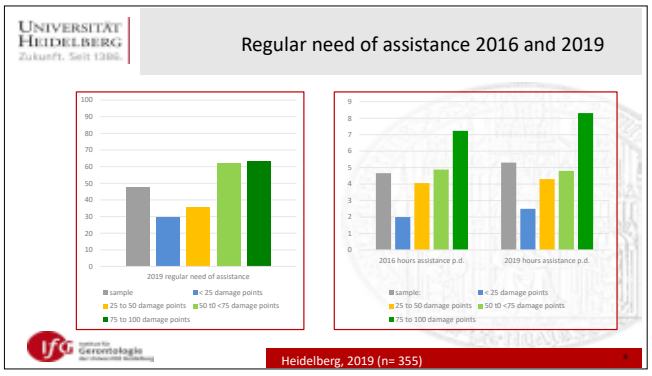


Fig. 8

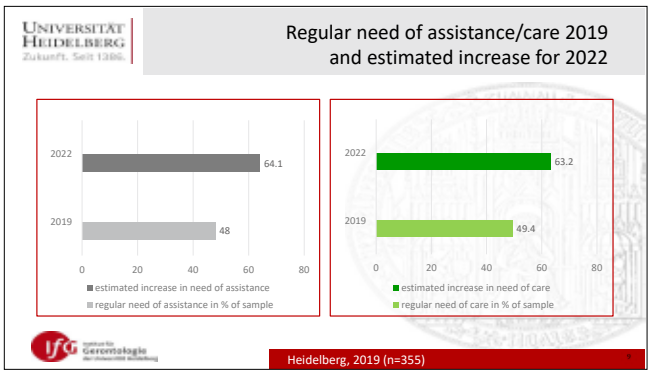
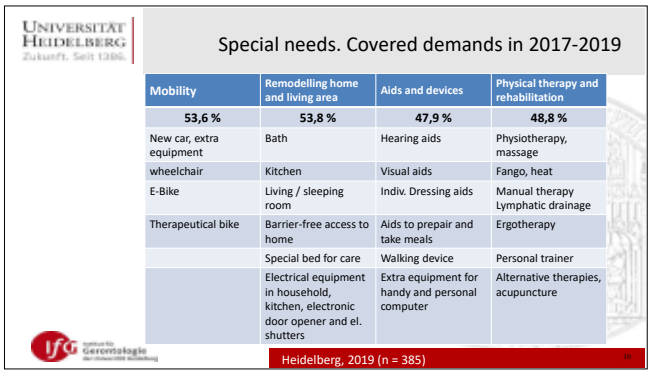


Fig. 9



Mobility	Remodelling home and living area	Aids and devices	Physical therapy and rehabilitation
53,6 %	53,8 %	47,9 %	48,8 %
New car, extra equipment	Bath	Hearing aids	Physiotherapy, massage
wheelchair	Kitchen	Visual aids	Fango, heat
E-Bike	Living / sleeping room	Indiv. Dressing aids	Manual therapy Lymphatic drainage
Therapeutical bike	Barrier-free access to home	Aids to prepair and take meals	Ergotherapy
	Special bed for care	Walking device	Personal trainer
	Electrical equipment in household, kitchen, electronic door opener and el. shutters	Extra equipment for handy and personal computer	Alternative therapies, acupuncture

Fig. 10

need one. They install an elevator in spite of not actually needing one. They try to anticipate future needs to be ready for old age with a high level of autonomy.

Concerning aids and devices, they have high demand for hearing and visual aids because they age as everybody else does. Physical therapy helps them palliate pain and physical decline.

These kinds of needs can be purchased, they can be paid for, but there are needs you can't pay for. We have been looking at thalidomiders from the outside, and I think it's important to let them speak for themselves. We only perceive their demands and problems from the outside since we are not affected. We have no idea what it feels like to be a TE-affected person and to live a whole life with congenital damages and impairments. Every thalidomider is unique, as their damage is never the same; thus, everybody has their own story. Last year, I had the opportunity to collect stories from thalidomiders and their parents, siblings, and children. I got about 80 stories.

I would like to read you the story of Antje Goebelsman, a thalidomider born in Germany who later lived in America. Antje wrote to me from America and wanted to have her story told because she wanted order in her life. She was first in quite a bad condition, and told me to publish her story anonymously.

A couple of weeks ago, I called her and I asked her whether I could read her story here in Tokyo. She told me, "You may read my story and you can say my name, I am much better now." I have shortened this story. The title she gave to her story is "Becoming Whole."

This is the original version.

Antje Goebelsman: Becoming Whole

Currently, I'm living in America with my son and husband, but Germany will always be my home. My friends and pets bring me much joy, and my son is the light of my life. I love designing and creating beautiful things. It is important to me to be a kind person, and to leave the world as a better place than it was when I entered it in 1960. I want everyone's life to have equal value, and I believe that we all deserve an equal chance at well-being and love.

Contergan determined much of my fate, but it is impossible for me to untangle the person that I might have become from the person I am. Now and then, I wonder which aspects of my personality are innate, and which are just adaptations to a life with deformities and disabilities. Would I have accomplished more if Contergan had been as safe as promised by the manufacturer? Sometimes I think about the many dreams, talents, and capabilities that were denied to the Contergan victims.

One thing I'm sure of is that there need not have been so much sadness in my life. My physical disabilities posed serious challenges and made many things impossible for me. I've endured much physical pain, and my body disappoints me every day by not being able to keep up with my ambitions. However, the rejection and hatred I encountered were much worse than any physical issues. I'm still shocked by how cruel people were to me. Perhaps children have a primal urge to eliminate the unfit. As an adult, I understand that the abuse had more to do with the abusers than it did with me, and I'm doing my best to let go of bitterness.

An Unpleasant Surprise

My mother never fully recovered from the trauma of bearing a child with deformities and serious disabilities. My mother loved me dearly, but wasn't ready to parent a child like me. She was still drugged from the anesthesia when the doctors told her that I had no ears and would never hear or talk. My mother insisted that she didn't want the baby if there was something wrong with it. My great-grandmother pointed out that Hitler would have had the authorities take me away. The midwife made it clear to everybody that I should be treated like any other baby, that I should be loved and talked to even if I couldn't hear. In 1960, the cause of my birth defects was unknown.

Surgeries

In my early twenties, I chose to undergo a series of five surgeries to construct facsimiles of outer ears using rib cartilage and skin grafts. The resulting ears were somewhat rough and lacking in detail, but I wasn't disappointed because I had known what to expect. My mother believed that I could now keep my most serious birth defect secret from a future husband. However, these new ears would in no way fool anybody who saw them clearly. However, this surgery improved my life tremendously. My embarrassing stumps were gone, and I no longer worried about strangers discovering my secret.

My blood-red left eye could not be hidden. Apparently, my ears were too awful to talk about, but everybody asked me what happened to my eye. I had my final day of being pretty when I was 8 years old. I had delicate features, shiny brown hair usually concealed my ears, and I was still skinny. My brown eyes were clear, albeit crossed and malfunctioning. I needed a "final" surgery for strabismus.

After several days of the usual post-surgery vomiting,

the bandage was peeled off my left eye. Later, when I was alone in my room, I checked the mirror to see if there were any noticeable improvements. The sclera, which is supposed to be white, was blood-red, and my eye was still immobile, but staring quite far to my left. I went into a sort of numb shock as I looked at myself. I wondered why the nurses hadn't removed the mirror to shield me from having to acknowledge my bloody eye. I was defined first and foremost by my red left eye, and few people looked beyond that.

Southern California

My father moved his family to the United States, to Southern California, to advance his career.

We were transplanted into a newly-built, pseudo-glamorous suburb in Southern California, where we had to adjust to new social rules. Here, it was important to be good-looking, fair-haired, tanned, and financially privileged. This move happened immediately after my life-disrupting eye surgery, and right before adolescence, when children are at their cruelest.

In the United States, nobody except for doctors knew about Contergan. My mother worked hard to help me hide my ears and my hearing aid. At that time, I had a bulky, body-worn hearing aid, which was concealed under my blouse. A wire snaked through my clothing to a bone-conductor. My mother sewed a blue hairband to cover the metal headband that kept the bone-conductor pressed to my skull. I walked with my shoulders hunched up to help hide my ears and the strange-looking hardware. I dreaded stormy days, when the wind would lift my hair up to expose my ear stumps. More than anything, I wanted to change myself so I could be exactly like everyone else.

Beauty, Shame, and Envy

My sister was a winner in the genetic lottery for beauty. Sylvia was born blond, with large, greenish eyes, high cheekbones, pleasing facial proportions, and a lovely smile. I resembled my father, but Contergan had interfered with my face. In addition to causing my face to be oddly asymmetrical, Contergan paralyzed much of it, leaving me with a grim, serious expression, which many people find off-putting.

My mother often accused me of being jealous of her and my sister's beauty, but she was wrong. I was jealous of the many unfair advantages that beauty provided for her—the main advantage being our mother's love. It seemed that everyone believed Sylvia deserved the best the world had to offer, and that I deserved nothing. I was furious that nobody would admit that this was an immoral system.

My being a kind, well-behaved good girl did not make people like me. My never making demands of anyone did not make people like me. My careful hiding of my ear stumps did not make people like me. My resentment of Sylvia made our relationship tense, and we argued and fought. This was very difficult for my mother, and I was often punished.

As if my life wasn't difficult enough already, I made it worse by pulling my hair out. I first pulled my eyelashes out after a difficult hospital stay in Germany, but I do not remember this. When I was 6 years old, I had the first episode of pulling out hair from my scalp. The day we arrived in Southern California, I created a large bald patch. Over the next year, my stress and anxiety levels became unmanageable, and I had to wear an ugly kerchief to hide the bald patches, hearing aid, and disgusting ear stumps. Despite my best juvenile efforts, I could not resist the urge to pull my hair out.

I'm dismayed by how much time we wasted with my family's pointless beauty drama. Of course, even I will admit that beauty can bestow many advantages, but I still maintain that the people who value it too much are shallow and not worth chasing after.

Boy Trouble

When my body became curvaceous, some boys became interested in me. It took a few years for me to realize that these boys would not give me the love and kindness I longed for. One young man told me that he could never love me because of my deformities. It seemed that I had become alluring enough to have sexual relations with, but wasn't beautiful enough to be loved and cherished. By the time I turned 20, I decided to avoid the boy–men and focus on my education. In my early 30s, when it seemed that I was the only unmarried woman I knew, I began to worry about running out of time, whereupon I made some more mistakes.

Feminism was good for me. After all, I couldn't achieve the vitally important task of being attractive to men. Not only was I disfigured, but I couldn't even camouflage myself with cosmetics. I was restricted to an unflattering hairstyle because my ears had to be concealed. My eyes were too dry for contact lenses, so I had to wear actual eyeglasses. My father laughed at the feminists, but the idea that my worth as a female human was not dependent upon my allure to men was liberating. This concept became a crucial factor in the construction of my self-esteem.

Design and Art Being Appreciated

It was in college that being good at art and design turned my life around. People in the art world were relatively tolerant of personal differences and idiosyncrasies. Being part of this world helped cure me of my intense desire to be just like everyone else. My peers admired me for my work and didn't publicly pass judgment on my looks. Also, the appearance of my left eye had been improved by surgery just in time for college. I was surprised to be invited to parties, and to make some very close friends at college. Somehow, my awful childhood was over.

Twisting the Hand of Fate

After my son was born, it took a long time for me to overcome the nagging feeling that I had grabbed onto something that was not intended for me. My life was suddenly much better than what I deserved, and I worried that fate would take my baby away from me. I was so happy to have a child, that I promised myself to never again be jealous of my sister.

It wasn't so easy for me to navigate relationships and marriage. My husband and I have the usual challenges, and my deafness frustrates him every day. But he has given me something other men wouldn't, which is that he was never bothered by my facial palsy, red eye, reconstructed ears, scars, and moth-eaten hair. When people ask me if my husband doesn't mind my deformities, I know that they have absolutely no idea of how hard I work, and how few demands I make of anyone.

However, my social network consists of nice people who don't need me to change myself. I am so grateful to have close friends whom I adore and love spending time with.

Mercifully, the Future is Concealed from Us

I don't want to elaborate on my physical issues because there are Contergan victims who have much more pain than I do. Bodies are fragile, and even minor issues can cause serious problems. We have had to use our bodies in ways they were not designed for. Death can sneak up on anybody, but it's disconcerting to worry about one's malformed internal organs failing prematurely. In addition to the typical health concerns of an older adult, I have constant musculoskeletal and nerve pain. My eyes seem to have everything wrong with them, and on some days, I just can't see clearly.

Hopefully I'll be able to recalibrate my desires as I age, so that I can find contentment even when my body prevents me from doing the things I want to do. I am grateful that I can still create artwork, and hope to have the chance to complete many projects. I would also love to do more to help and empower other people, to make the world a gentler place.

It would please me if my narrative could help convince people of the need for kindness and tolerance.

I thank you for your attention.

Klaus M. Peters: Yes, thank you, Christina, for the presentation of your data, and especially for the impressive story of a thalidomider. Any questions or remarks?

I think you've collected a lot of these stories. They are very interesting.

Christina Ding-Greiner: That's the inside story of a thalidomider. We can't know what is going on inside of them, but we may catch an idea about the meaning of life with such a terrible disability. I learned a lot from the conversations I had with the authors and their stories; therefore, I wanted to share this with you. Thank you.

Klaus M. Peters: Yes, and I think we as doctors can learn a lot from thalidomiders because of the management of their lives and their problems. I think it is also very helpful for other patients.

Total Hip Replacement in Thalidomide Embryopathy? What Are We Worried About?

John Skinner

Royal National Orthopaedic Hospital, Stanmore, UK

Dee Morrison (Moderator)

I'd like to introduce Professor John Skinner. He is a complex hip and knee orthopedic surgeon at The Royal National Orthopedic Hospital, the leading Hospital in the United Kingdom for orthopedics. He takes complex referrals from across the UK and occasionally internationally. He is a clinical leader for joint reconstruction and the Director of Research and Development. He told me he saw his first thalidomide survivor in 1999.

He's tremendously well thought of by thalidomide survivors, very helpful and supportive to The Thalidomide Trust, and some of the nurses have commented to our thalidomide survivors that they think he's the best.So, John.

Dee, thank you very much indeed, and thank you, Dr. Hinoshita, for the extremely kind invitation. I can't tell you what an honor it is to be here in this organized group to discuss such an important group of patients. I've called my talk "Total Hip Replacement in Thalidomide Embryopathy (TE): What Are We Worried About?" (Fig. 1)

Well, hip replacement, total hip replacement, is not yet 80 years old. This was the first total hip replacement performed in London by Sir Philip Wiles in a few patients. Until that time, the treatment was either to take the ball off the head and take the hip joint out, or to fuse the femur to the pelvis. (Fig. 2)

It matured through Charnley and various other people in the 60s to be described as the operation of the twentieth century. (Fig. 3)

And that was in no less a publication than the Lancet. So we know that with hip replacement, we've got happy patients, we can reproduce it, few complications, and people's function improves dramatically. It's cost effective, it sometimes seems expensive on day 1, but the cost of a hip replacement over the lifetime of its use is £7, or just under ¥1000 per week. That's incredibly good value healthcare when you consider what the drugs would cost to relieve the pain. (Fig. 4)

In the UK, we have the national joint register, which now has 2.5 million records. It's the largest registry in the world. Just over 100,000 patients a year have hip replacements. In the UK, two-thirds, or 60%, are in women, 90% for osteoar-

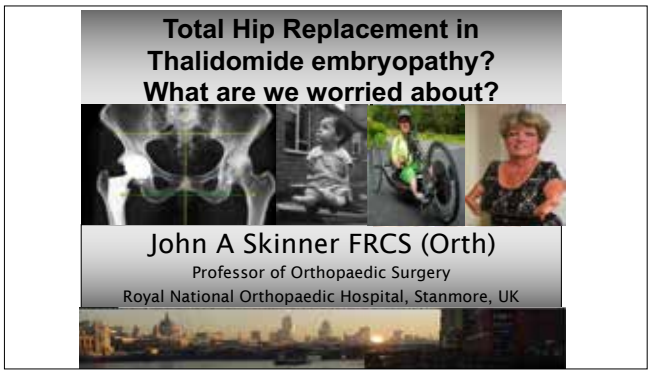


Fig. 1

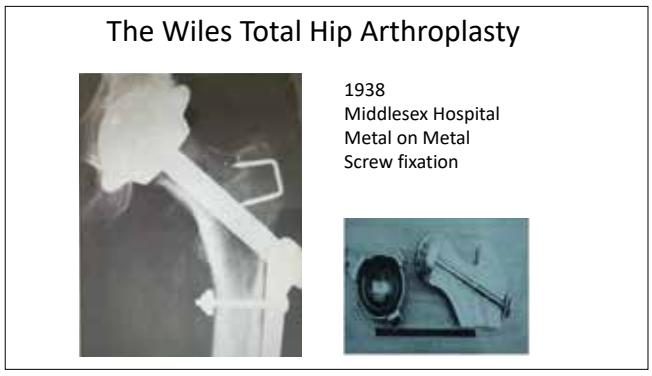


Fig. 2

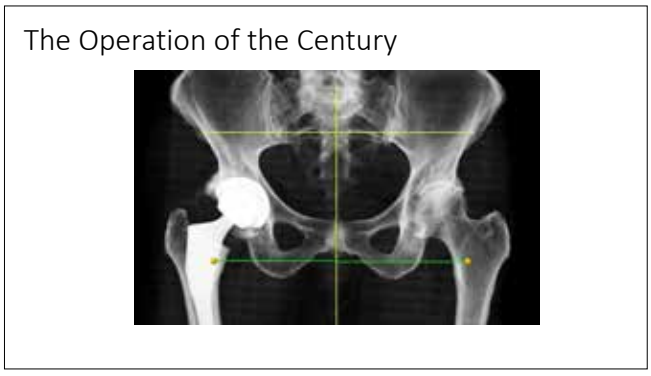


Fig. 3

thritis, and the BMI would be higher than that in the Japanese population, at 28. It's even higher for knee replacement patients, where it's over 30. (Fig. 5)

So, our challenge is to establish the role of hip replacement in TE. Is it worthwhile? Is it still effective in thalidomiders? Is it cost effective? Do we have any alternatives, or is this the best thing that we have, and can we adapt it to the wide spectrum of abilities and anatomies that we all see? (Fig. 6)

Hip replacement to an orthopedic surgeon is the best form of pain relief for arthritis of the hip. That's the prima facie reason to do a hip replacement. It does improve quality of life. It keeps people mobile. And I think keeping people moving is really important as they age, and that's for the whole population, not just thalidomiders.

And people do different things. The lady on the right is a farmer, and the lady on the left enjoys running, so we have to tailor what we do to patients' needs. (Fig. 7)

Arthritis, hip dysplasia, whatever it is, however you get there, the end game is arthritis, and it's painful and it's easy to dismiss; patients have a little bit of arthritis, and no one cares. If you say I've got cancer, everyone understands that and they care. You say you've got heart disease, you've had a stroke, people know what that means.

What we find is that patients feel a burden to their family, their friends, their GPs, their doctors; they feel that they are bothering them unnecessarily because it's just a bit of arthritis. (Fig. 8)

So we need to be aware of that. It's common. The UK has a population of 60 million people, 10 million of whom have arthritis of some form, so we lose 30 million working days a year. And almost one-third, certainly one-quarter to one-third, of all GP appointments have to do with musculoskeletal problems. (Fig. 9)

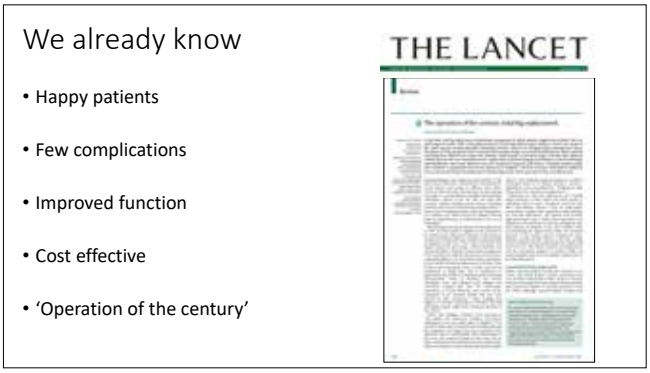


Fig. 4

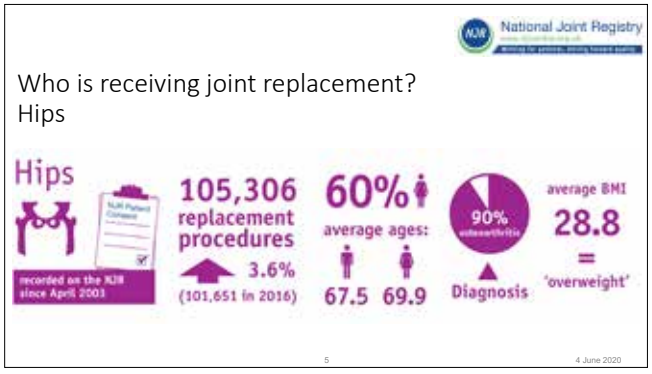


Fig. 5

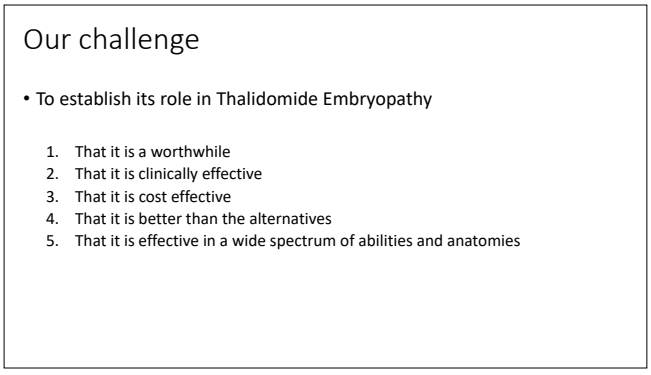


Fig. 6

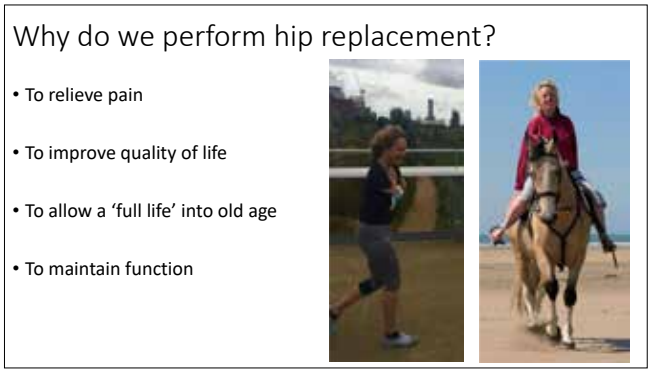


Fig. 7



Fig. 8

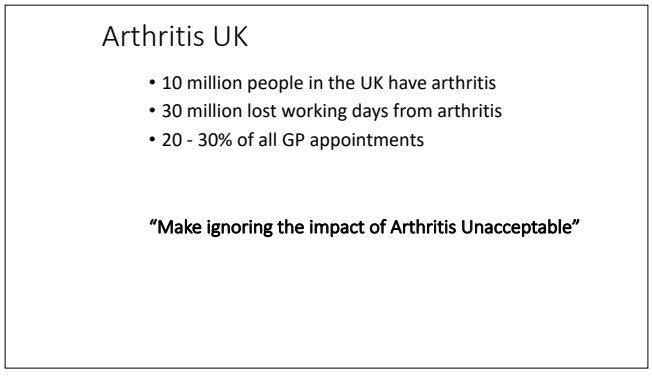


Fig. 9

What we've tried to do in the UK is to make ignoring the impact of arthritis unacceptable. I just wonder if we should look at the same in the thalidomide population because they are exactly the same. Is it acceptable to say that if you've got arthritis, you can't do things, you stop doing things? That's the bit we need to look at.

Patients waiting for hip replacement or patients in pain for whatever reason are miserable. It takes longer to do things. People adapt, humans adapt to whatever you put before them. If they are in pain, they stop doing things. Runners stop running, walkers stop walking, people stop going to shops, they avoid the stairs, they avoid driving in the end, and people just adapt. And we know that in the UK population, 32% of women and 25% of men in pain waiting for joint replacement have clinical depression. I think that's another principle that applies exactly to thalidomiders. (Fig. 10)

Does it matter? Well, it does. This is the Oxford Hip Score, which is validated, and goes from naught to 48. No matter where you are on the scale, if you have a hip replacement, your pain and quality of life gets dramatically better. But if we leave patients to get so disabled that they stop walking, they go off their feet, yes, they get better, but there's a ceiling effect, so we need to be cognizant of the fact that we don't want people to lose all muscle tone, become chair-shaped, become immobile, and lose cardiorespiratory fitness before we replace their joints. Because if we do it earlier, we can make them better. (Fig. 11)

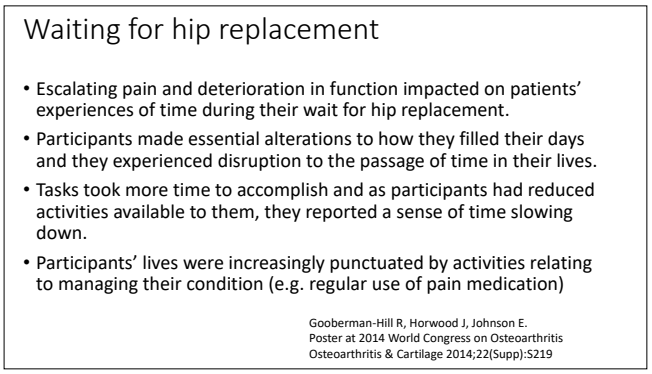


Fig. 10

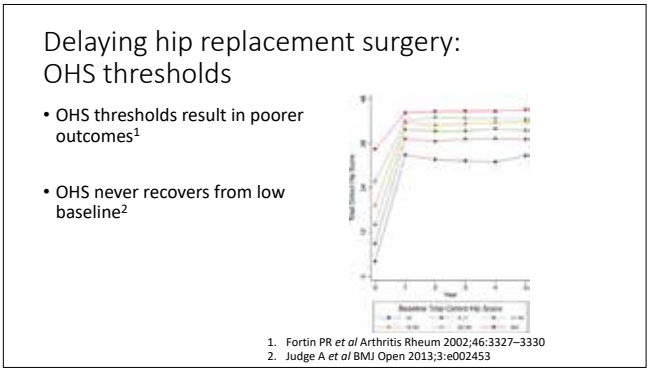


Fig. 11

But there's always a balance. We know that the quality of life improves, and it's maintained using any number of validated systems. (Fig. 12)

Most patients who are working will get back to work. Far fewer patients who've gone off work will get back to work. That's the same in anything, and is almost entirely understandable.

This graph shows leisure activities, the percentage of people finding it very difficult to engage in leisure activities, including sports, hobbies, social activities, and holidays. These are the fun things in life. After joint replacement, they get so much better.

We also know, Christina was the first person to mention it, that if you have a joint replacement, we hear from ISSA that 27% of patients have more sex, and 44% have better sex. It's difficult to have intercourse when you are in pain and disabled; therefore, it's an important part of the human existence to everybody. (Fig. 13)

Patients remain satisfied, 96% are still satisfied 13 years later. (Fig. 14)

This study involved half a million patients in the UK, which, for such a big operation, is a very low incidence of readmission to hospital within the first 60 days and reoperation. The people who have problems tend to be the extreme elderly, those with very low or very high BMI there's a bimodal distribution of BMI affecting outcomes and those living in poverty. We need to make sure that income does not

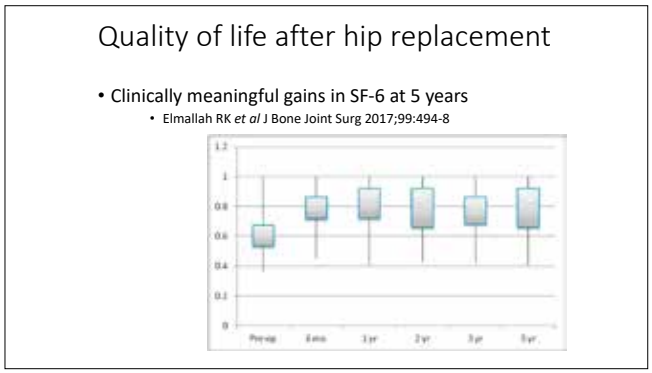


Fig. 12

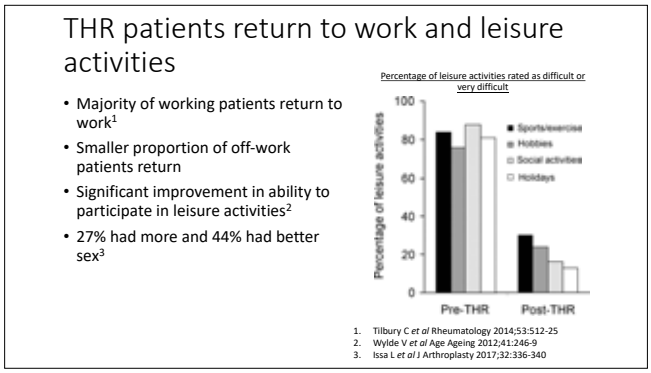


Fig. 13

predict and mandate outcomes.

Mental health issues, depression, as we have mentioned, dementia, and confusion, all of these things can lead to poor results. If you've been admitted to hospital, if you've got diabetes, let's control it. If you've got high blood pressure, let's control it. Uncontrolled, concomitant diseases affect outcomes, as do smoking and drug use. It's quite interesting that the patients who are now going on opioid medications worldwide have worse outcomes after joint replacement. When you get rid of the pain generator, they don't get off opioids; that's an important consideration as well. (Fig. 15)

Hip replacement is cost-effective. This is NICE (National Institute for Health and Care Excellence) data. It is £20,000 to £30,000, and this measures QALYs, or quality-adjusted life years. So, removing a brain tumor is £150,000 per quality adjusted life year. It's expensive, but if you've got a brain tumor, I'd put it that you'd want to have a go at it. Dialysis, it falls in this range, and no one will deny dialysis to a patient with renal failure. Coronary artery bypass when needed. Cataract surgery is very cost-effective to restore sight. But hip replacement is at the top of the list; per quality adjusted life year falls well within the NICE valuation. (Fig. 16)

Orthopedic surgeons know this, and we just need to make sure that other people realize how good hip replacement is as well. (Fig. 17)

Overall, 93% last 13 years, and 91% last 16 years. Even long-term, our patients we're talking about now are at that age, with 78% lasting 35 years, so it's got good durability already, and we believe it's getting better. (Fig. 18, 19)

One point I will just show in the NJR: survival. This is patients who are age 69–70. NICE expects 95% survival of the implant at 10 years. Among younger patients, thalidomiders are going to be about here, will have a higher revision rate. That's because if your joint is wearing out at a much young-



Fig. 14

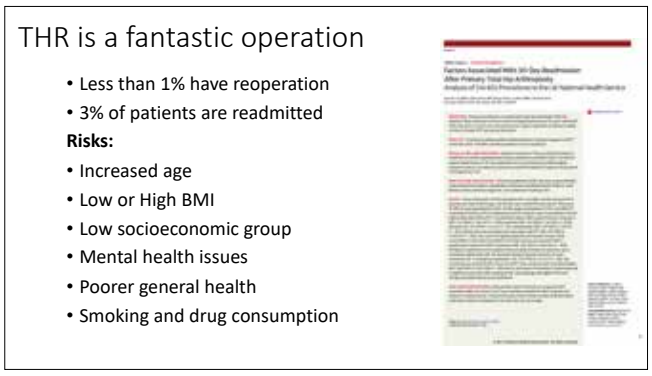


Fig. 15

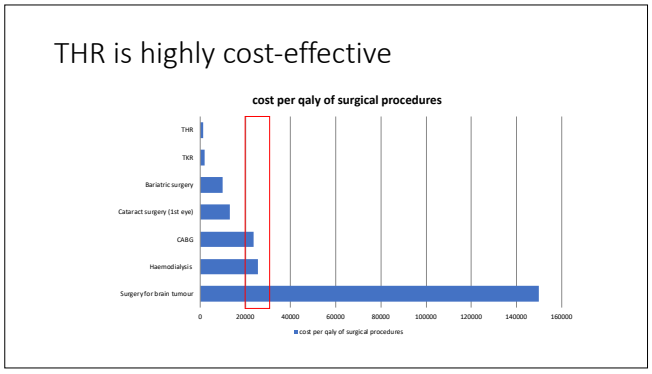


Fig. 16

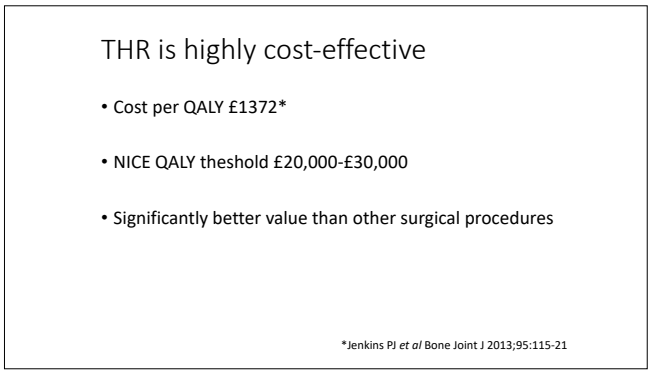


Fig. 17

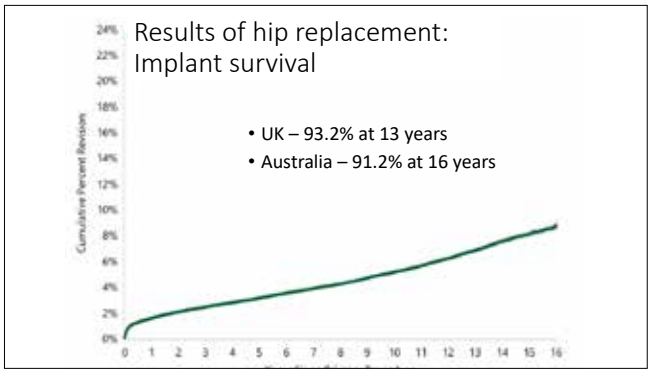


Fig. 18

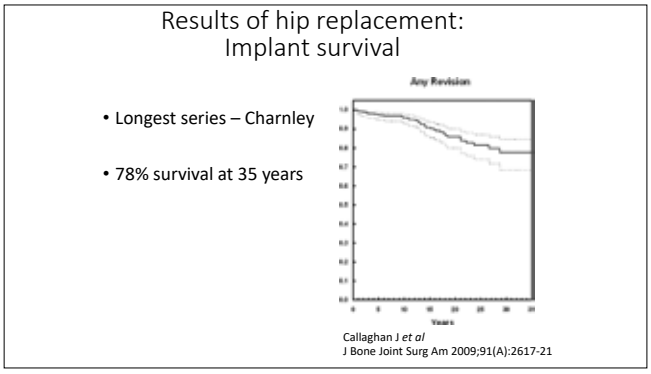


Fig. 19

er age, it's usually because the anatomy is not right. It's dysplastic or malformed, so the surgery is more complex and needs more thoughtfulness in planning to optimize fixation and the best possible result. (Fig. 20)

So, what affects function? We've got to fix to the skeleton, particularly with abnormal anatomy, we've got to make sure we can do that. We want the joint to stay in place. We've got to get a good range of movement; this is really important in thalidomiders, who use their lower limbs for much more functional things. (Fig. 21)

And that's important. Bearings we can work out, and we always need to consider pre-arthroplasty performance and what would we like to do after the hip replacement, so we can plan it. I said it's the best form of pain relief. It really can't be a good idea to resort to opiates and opioid drugs with addictive potential for a chronic condition with no obvious end. (Fig. 22)

So, in the UK, similar to everyone else, I think thalidomide was used from 1958 to 1961, and we think about 2000 babies were born from 1959 to 1962. We think half died in the first year, so there are 460, I am happy to take this figure of 464. Thus, our patients are now age 57 to 60. They are the new middle-age. (Fig. 23)

Regarding the patterns of deformity, everyone knows Henkel's work on the lower limbs, the full spectrum. But I would put it to you that for the patients I see and those I am operating on, this is the most common deformity: dysplasia. It's an almost normal joint that is weight-bearing, transmitting load, wears out, and presents a surgical opportunity to replace it and to relieve pain. (Fig. 24)

Thalidomide is still used in the UK; you know about myeloma. My dermatology colleagues tell me that it's still used for cutaneous lupus, and also recalcitrant itching or pruritus. But dermatologists are worried about it because of its potential to cause peripheral neuropathy. (Fig. 25, 26)

This is a video, I hope it'll play. I just want you to listen to this. Everyone is different, I think.

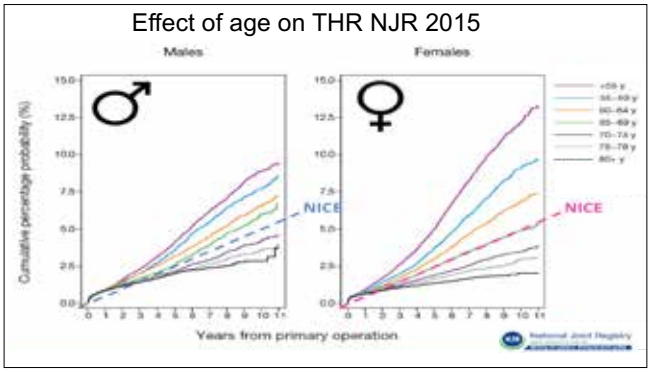


Fig. 20

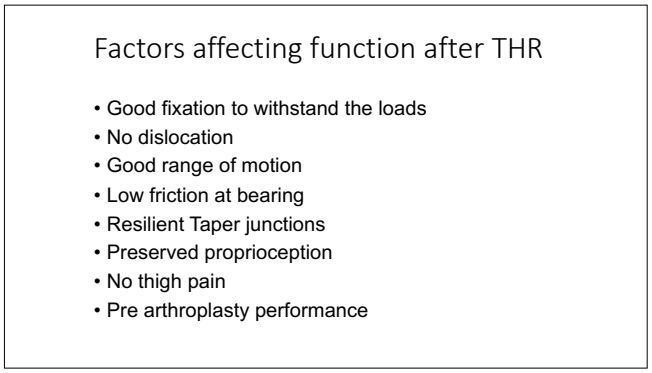


Fig. 21



Fig. 22



Fig. 23

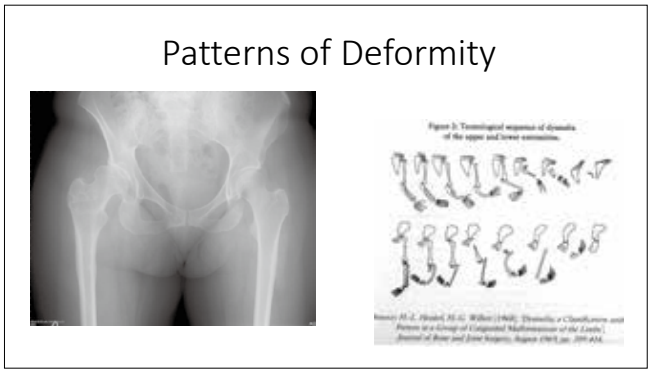


Fig. 24

[Video begins]

Some male thalidomider in this video

My life. I don't think thalidomide has affected my life in the sense that I was born like this. Therefore, I don't know anything else. I just get on and people think, oh, you can't do certain things, but you just adapt. You know, I've never seen it kind of getting in the way of anything I do, and that's been from an educational point of view or physical point of view, and I try and be active because I think it's extremely important, especially with my body as it is. I think the hardest thing about the challenge is that I've got to cycle 13 days consecutively in order to cover the 1000 miles, which on average work outs to about 80 miles a day.

People have asked me why am I doing this challenge. Well, I think one of the reasons personally is that if people tell you that you can't do it, then don't take that as your definitive answer because there's always a way around it. You might not be able to do it their way, but you can do it your way. I've got no right leg, I've got two short arms, and my hands look like this, but then again, limitations shouldn't stop you from doing anything in life.

[Video ends]

John Skinner: I think most of us would say he's a fairly elite athlete. I just feel sorry for the dog; I hope the dog is not going to do the whole 1000 miles. So dysplastic hips, again, it's a spectrum condition from mild, like I showed in the first X-ray, to this, which is a high dislocated hip, which is part of the same condition. (Fig. 27)

So, a little bit about how we classify these. What we're talking about is the percentage of subluxation of the femoral head from the acetabulum, so if it's within the acetabulum, it's type 1, type 3 is between 75% to 100% subluxated, and type 4 is completely dislocated. (Fig. 28, 29)

I think, from the surgical point of view, it is classified as dysplastic, it's still in the socket, low dislocation, and high dislocation. I think any classification certainly in surgery only needs three arms good, bad, and very bad and I think that works. (Fig. 30)

So dysplastic, low dislocation, and high dislocation with the sockets down here. (Fig. 31)

We have different ways to reconstruct them depending on where they are, and I think it's probably easier to show you that. So we can get, the natural acetabulum is here, we can

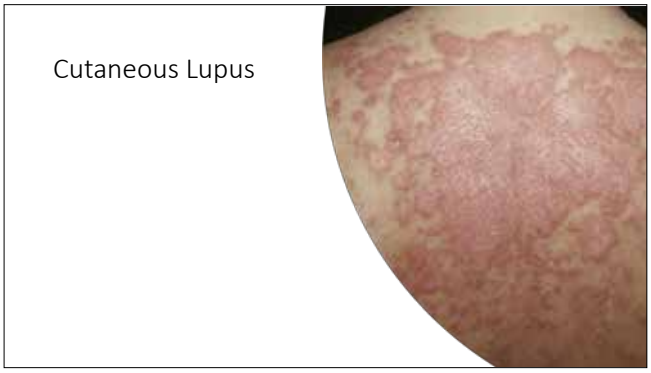


Fig. 25

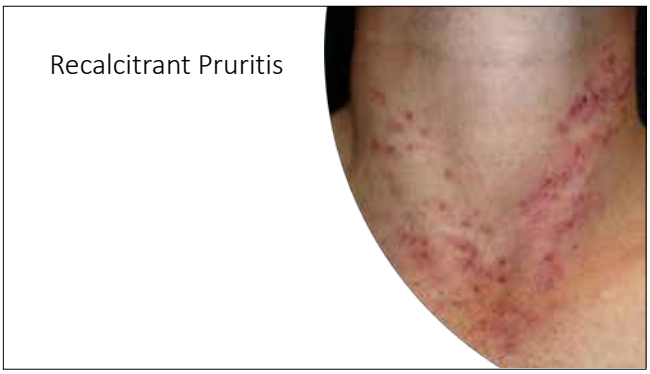


Fig. 26

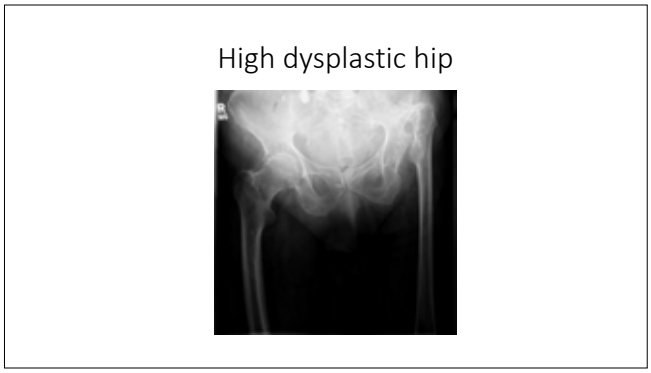


Fig. 27

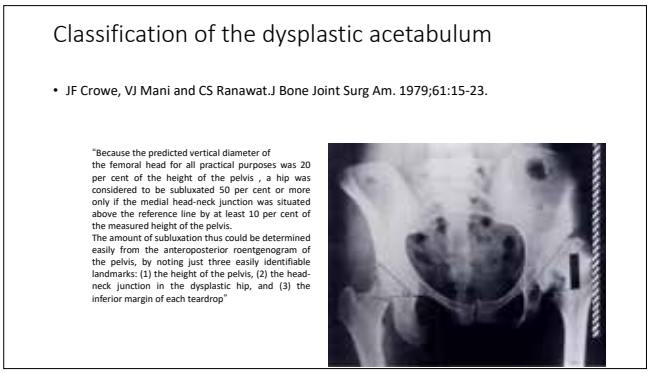


Fig. 28

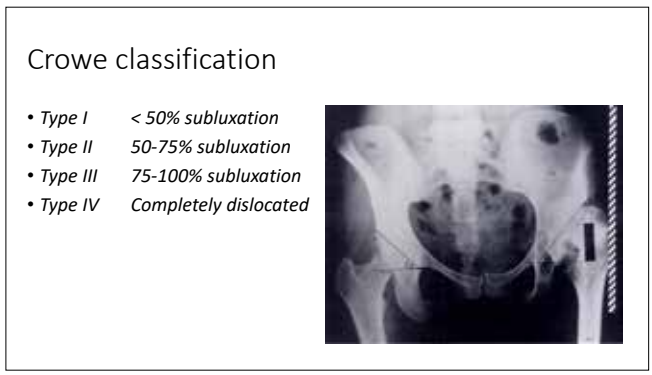


Fig. 29

go for a high hip center, put the femoral head, put the socket where the femoral head has always been. Technically, it's the easiest to do. Mechanically, it's disadvantaged because you don't get the muscles, the abductor muscle's moment arm. (Fig. 32)

If there's no roof, we're going to throw the femoral head away so we can use it as a bone graft and screw it back on, or we can build up the anterior wall and the floor with bone graft, so there are various things that we can do. (Fig. 33)

The femur, I think, the point is that the femoral neck, instead of pointing sideways, is anteverted and is pointing forward as part of the deformity, and the bones are small. Usually, it's a whole field defect in the limb, and the leg length also, the legs are maybe the same length, and dislocated or maybe short. I mean, usually, we can bring it down about 4 cm without getting too worried about the sciatic nerve. (Fig. 34)

Dysplasia and hip replacement are relatively straightforward because the socket is shallow, and there's a screw to increase fixation; that will work quite well. Low dislocation, the problem with this socket, it doesn't have a roof. [Unclear], it's got a roof where you could put a socket underneath, but this one doesn't. So this is the native femoral head here, and what we do is screw the femoral head back on, form a roof, put a socket in, and fix it. And this is a porous surface, which the bone on grows. (Fig. 35, 36)

We've got a high dislocation, so for both of these hips, the natural socket should be here and here. They are both up, and this femur is also angled and deformed, and this is what we see. This is where the femoral head has been articulating, and this is where it should have been. We can make that, shape it out with reamers to make it take a socket, and then put it down there. If you're an orthopedic surgeon, that is beautiful. (Fig. 37, 38)

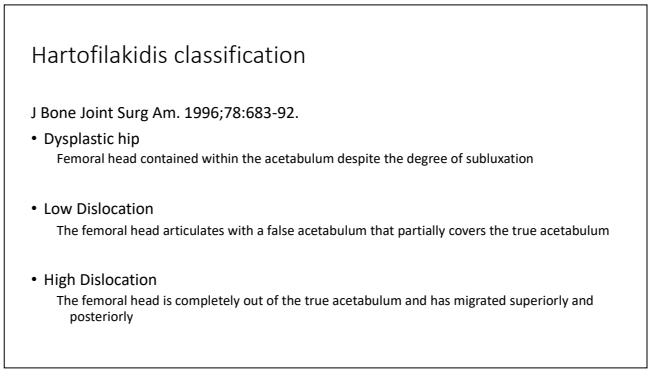


Fig. 30

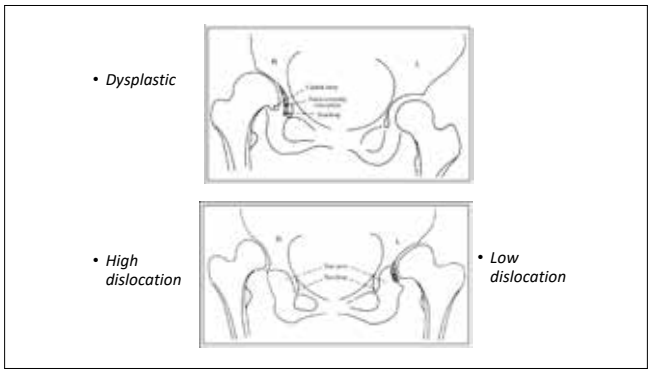


Fig. 31

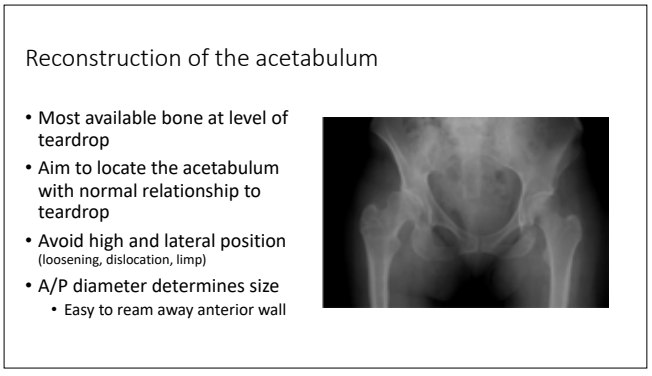


Fig. 32

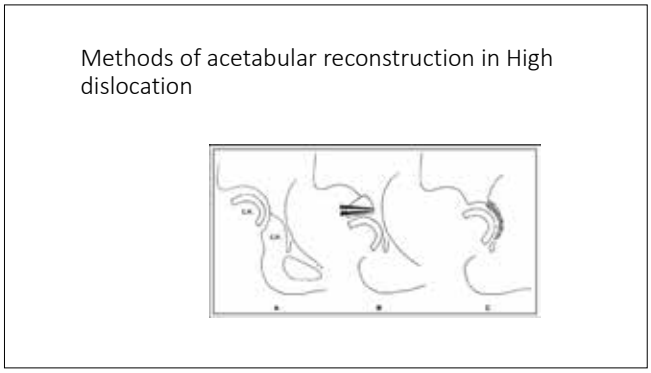


Fig. 33

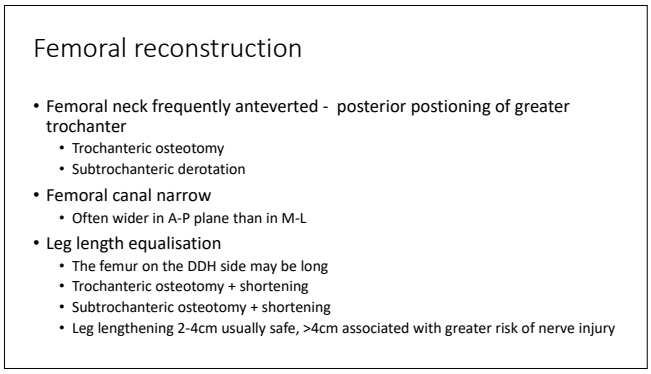


Fig. 34

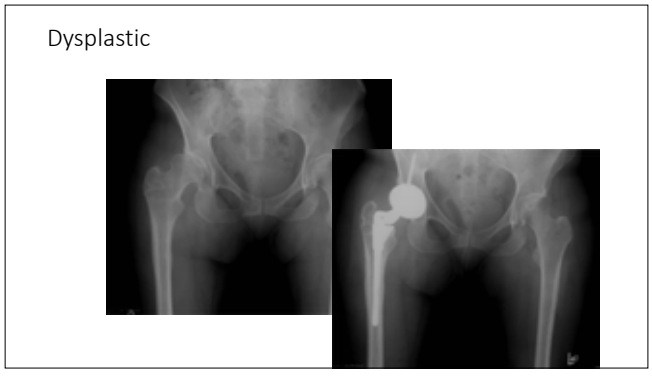


Fig. 35

As an orthopedic surgeon, an important part of the operation is to always admire the X-rays. So the hips have been brought down from there into here, that bend in the femur has been an osteotomy to straighten it as well, so we've restored good anatomy, it can be done. (Fig. 39)

This is a problem, so this socket is high dislocation and the leg lengths are equal. So, if I bring that down to here, I am going to lengthen the leg by 5 cm. Patients do notice if you do that to them, and they don't like it, and it hurts. (Fig. 40)

So, what we can do is, to plan it beforehand, to take out a disc of the femur of whatever we've measured, so the 5 cm, shorten it, and then use this as a bone graft around it. And you see, several years later, it's incorporated, and the patient is walking well. And because we've reconstructed the abductor arm, avoiding sciatic nerve palsy, the rehabilitation potential is great. It takes time, but it can be done. (Fig. 41)

The other one is when X-rays look like this. It's because the femoral necks are pointing towards you, they are very anteverted. This is a scan or an X-ray, very similar to one Dr. Kayamori showed yesterday, with really anteverted dysplastic hips. That's the epicondylar axis and the femur; that's almost 70 degrees of anteversion, whereas it should be 10 or 15. (Fig. 42, 43)

And with that, we can do a derotation osteotomy, twist it around, and reconstruct the anatomy again. So with planning, we can work out what we're doing. This is a patient who had some sort of operation in childhood with a metal plate, presumably some sort of osteotomy. Unfortunately, that's infected. (Fig. 44)

She has very little below here, and an extension prosthesis. She walks with a limp, and she manages. She has full employment, despite her upper limb defect. (Fig. 45)

This is the sinus, which is still there, so it's low volume. This is about a day's discharge. She manages it by changing

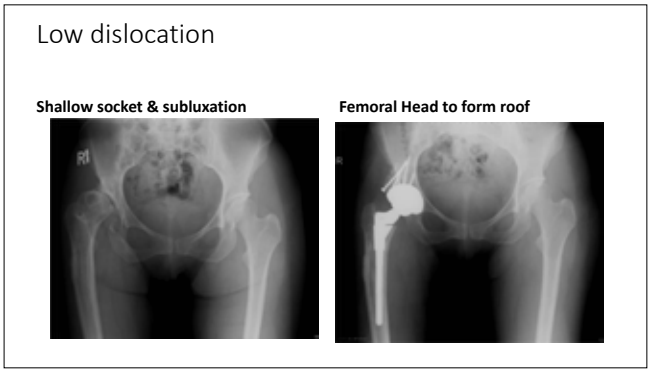


Fig. 36

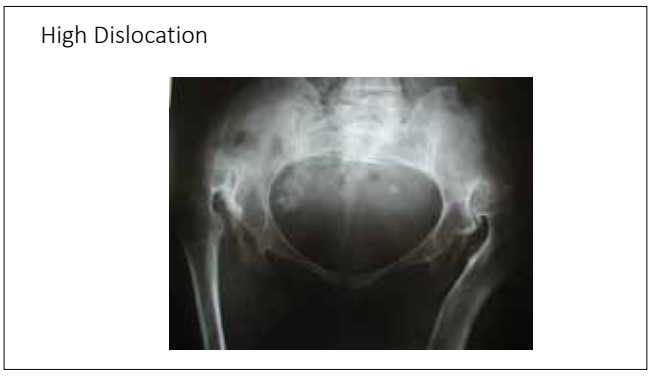


Fig. 37

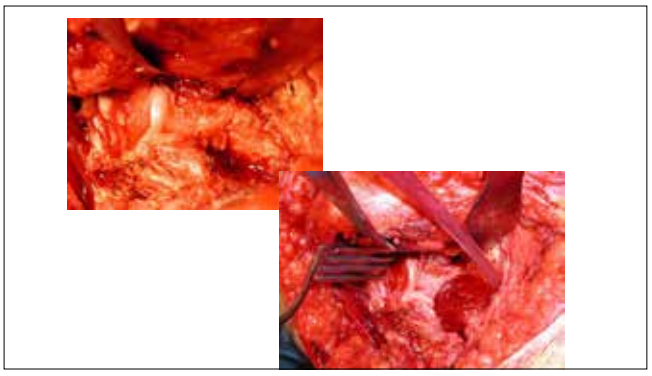


Fig. 38

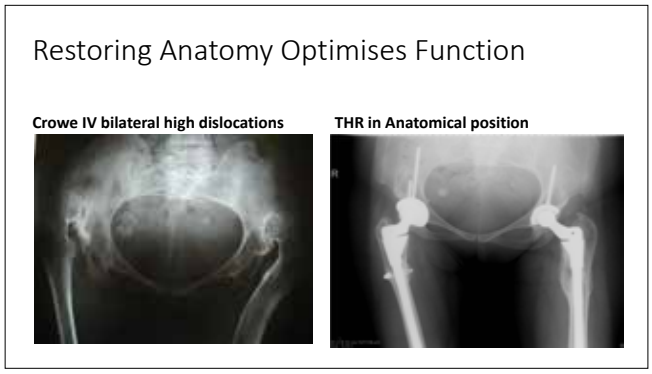


Fig. 39

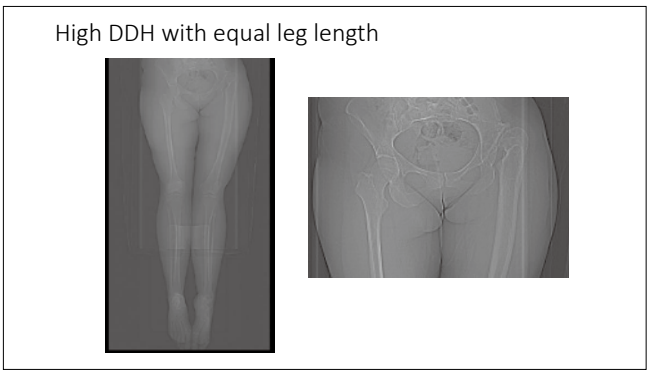


Fig. 40

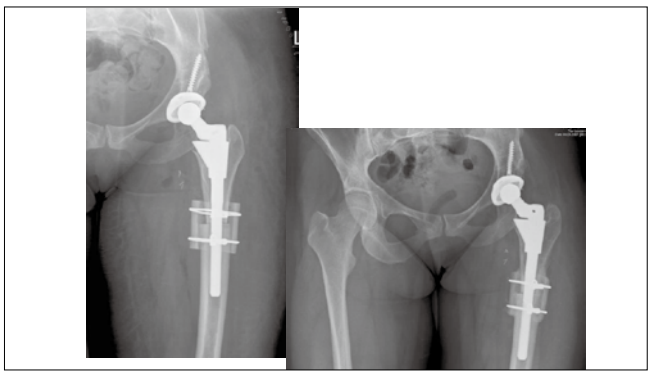


Fig. 41

it. It's not particularly painful, despite the hip looking like that.

So, I can't perform a hip replacement because it's infected. I would be wrong to do so anyway. (Fig. 46)

This is how she walks. It's not an elegant walk, but it's functional and with a cane, she can walk normally in full employment. (Fig. 47)

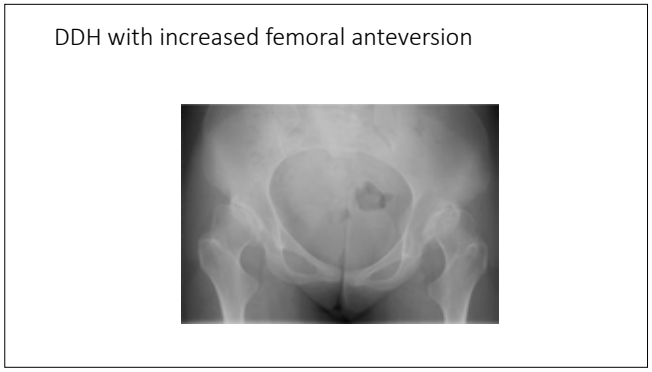


Fig. 42



Fig. 43

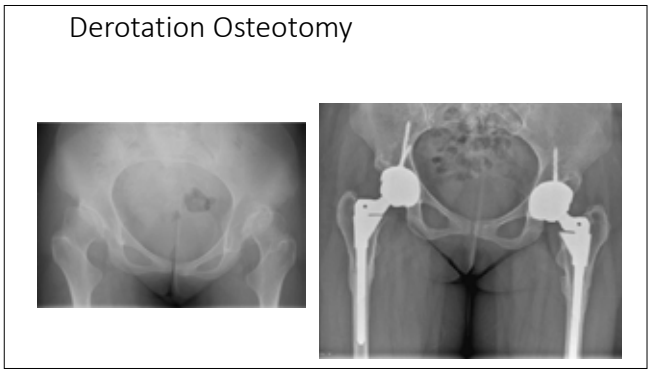


Fig. 44

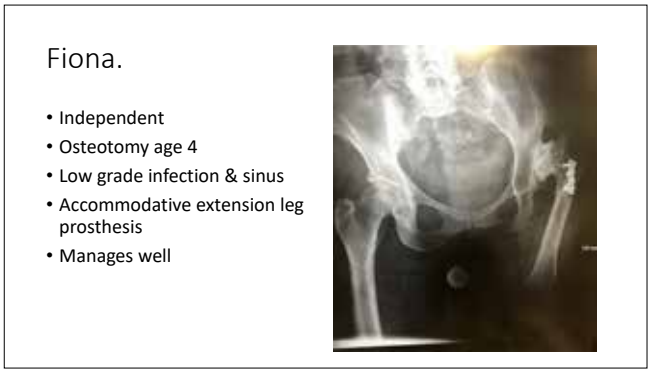


Fig. 45

This is a lady that you've seen before. This shows bilateral high dislocation, with poorly formed hips. But they seem to be working. This is her website. It's called "Flid-Fit", and this is what she puts on the website. She's amazing. This lady is small. She's 1.42 m tall, and she's lost 26 kg over time with exercise. She has a lifestyle website where she gives advice on diet and exercise. (Fig. 48, 49)



Fig. 46

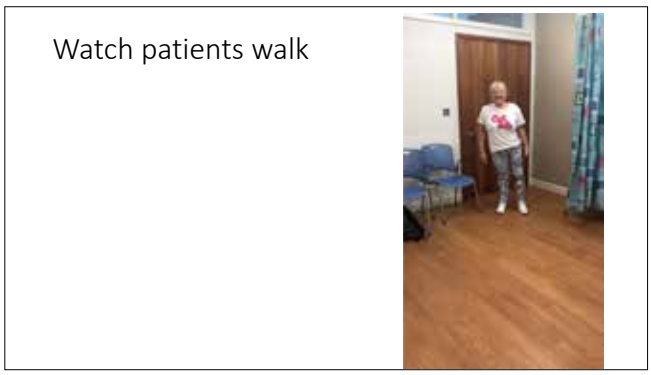


Fig. 47



Fig. 48



Fig. 49

These are those hips on an antigravity treadmill. We can't, we would never treat an X-ray. I think that's the most important thing we learned with these conditions in thalidomiders: you treat the patient. I am not going to make her much better than that, but I can make her a lot worse than that if I do a hip replacement, things don't go perfectly, and she gets stiff. So we've got to watch what we're doing. (Fig. 50)

Assess all patients individually. We have to know what the patient's goals are. There's no point in going for what my goals are or what Dee thinks they ought to be; it's what the patient wants to achieve. As well as how good their pain control is and what they want to do. A lot of thalidomiders are flexible; they've had to stretch and get increased movement and range to maximize their potential. We need to know these things because flexibility can be good or can be bad in joint replacement. We don't want them to have a dislocation. (Fig. 51)

What do human joints do? Well, very few of us do this, perhaps we are better in line, but the abduction, adduction and the rotation we don't do. A lot of thalidomiders can do this, and have learned to do this because they use lower limb function to use what's normally done with the upper limbs. So again, using detailed examinations, we need to know what they've done. (Fig. 52)

This child, I'd love to, we need to reproduce this, making it relevant to thalidomiders; this is what they can do. Put your foot on the floor to tie a shoelace, 124 degrees is the flexion you need. If you sit and bring your foot up to your lap and cross your leg, you need less flexion, but more rotation. Picking up objects, squatting, various things, you need 122 degrees. These are things we're looking at. You don't need so much flexion on stairs, but you do need some. So we need to work out what the goal should be. I'd love to do this now for thalidomiders and their function and what they do. (Fig. 53)

So we can do things. These are femoral heads, 28 to 36 mm. (Fig. 54)

The bigger we make the femoral head diameter, the greater the functional range of movement can be, and that's important. It's not just that, it's also the orientation of the cup. You set it to the maximize useful range of movement for any particular patient.

With 36 mm cups, it's always said that they wear. But materials have improved, so modern bearing surfaces are

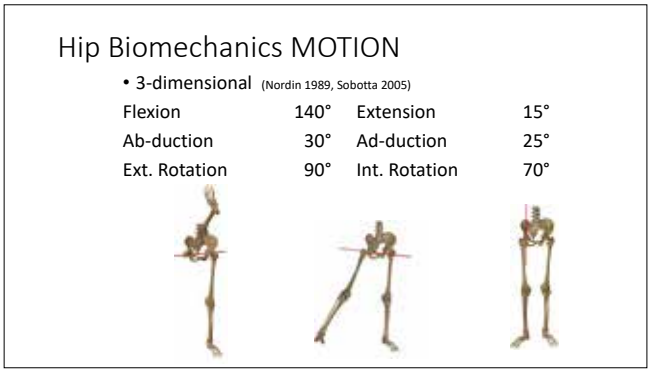


Fig. 52

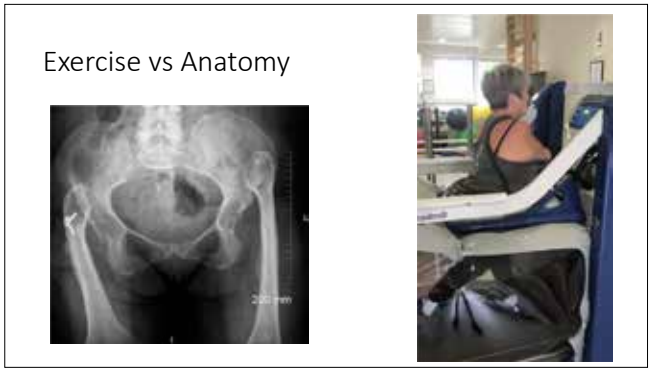


Fig. 50

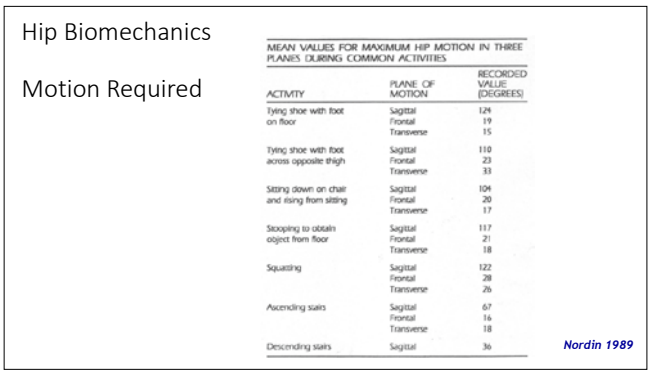


Fig. 53

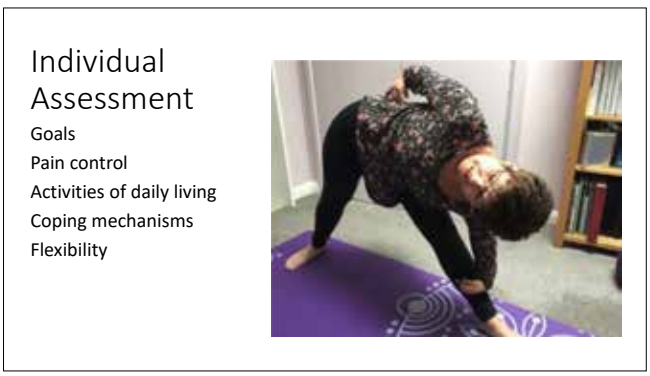


Fig. 51

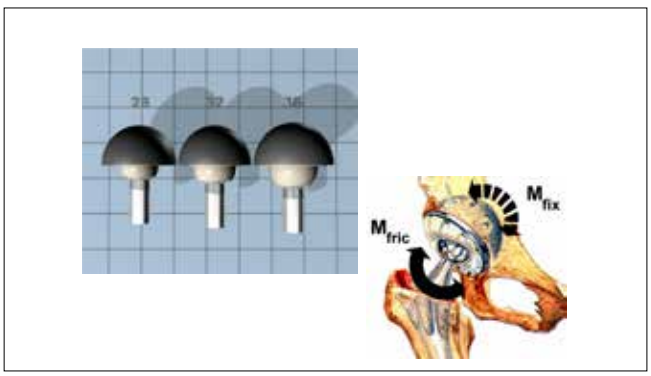


Fig. 54

wear-resistant. This is a tiny volume, you have ceramic on ceramic bearings. So implants have improved, and we just need to know what we are doing. (Fig. 55, 56)

So what are people doing? Working. Again, this lady works as a telephone volunteer with The Thalidomide Trust. (Fig. 57)

This guy is an actor and is amazing. He spent his first few years of employment as a rock drummer. He was a drummer in the opening ceremonies of the 2012 Olympics. He's an incredibly accomplished actor, and this is him playing Shakespeare's Richard III. (Fig. 58)

What else are people doing? Sue, this lady is a sports masseuse. Her arms aren't up to it, so she's learned to be incredibly skilled. She's in demand using her feet for massage, sports therapy, and relief. So people are doing amazing things. Everyone is different. (Fig. 59)

This is a patient with, from an orthopedic point of view, that's relatively straightforward. It is dysplastic. There are some considerations. We need to look at the femoral neck version. But this is end-stage arthritis in a dysplastic hip. (Fig. 60)

This is our assessment. This lady has short phocomelia with rudimentary fingers and no upper limb function. She has osteoarthritis from dysplasia, bilateral agenesis of upper limbs, and right-sided deafness due to TE.

So the first thing they say, it's anticipated that she is going to need 10 to 14 days. She's going to be in a hospital for a long time. They've noted that she's independent, has good trunk control, can go from sitting to standing comfortably, and can transfer. How does she shower? Well, she gets in the bath, where she has a stool, and she holds the shower head with her left foot. She independently toilets, despite having

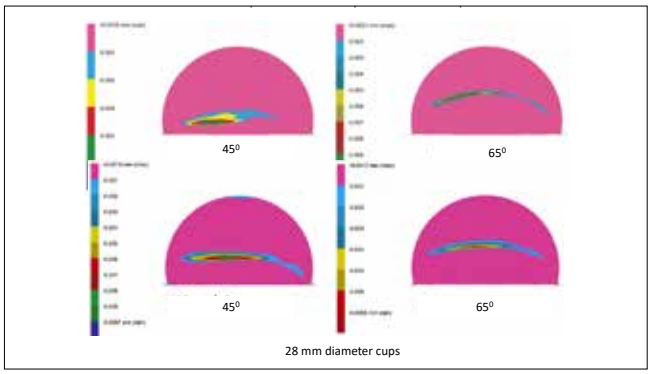


Fig. 55

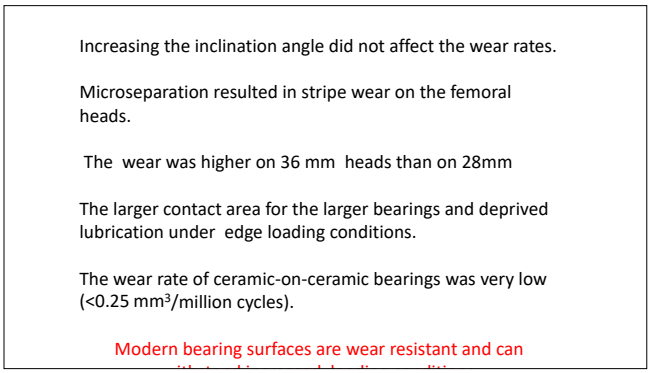


Fig. 56

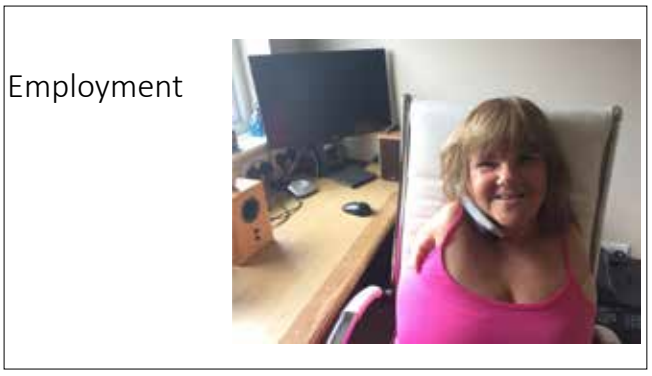


Fig. 57



Fig. 58

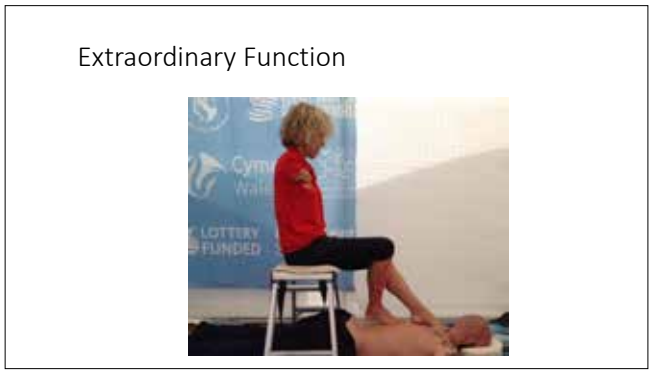


Fig. 59

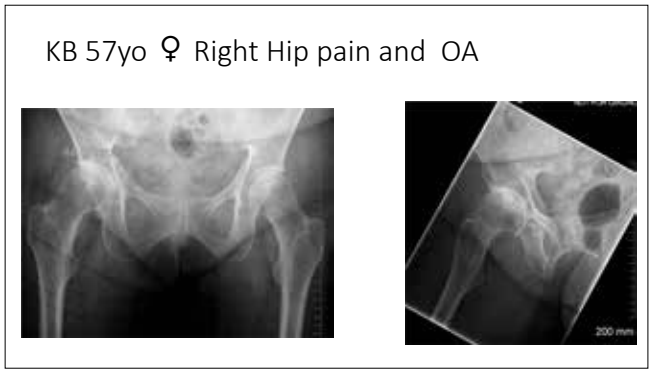


Fig. 60

no upper limbs.

For meal preparation, she still does some cooking tasks, and she can chop food with her feet while sitting on the worktop. My therapist said this may not be a good idea in the early stages after hip replacement surgery. (Fig. 61)

So, we need detailed plans what's going to happen and what could happen before surgery. What we've done, we've planned the position. If you make the cup slightly more vertical, you get more flexion, and if you antevert it slightly more, you can affect the range and position. She's got very good function and is still independent. (Fig. 62)

This is a different case. This is a quite significant problem on the right. Everyone thinks with hip replacements in thalidomiders, that this is where we are going to be doing joint replacements. I don't think I can do much for that, but this side, which has DDH (developmental dysplasia of the hip), there is a very poorly formed hip that has become painful. He's walked poorly all his life. He's got an extension prosthesis that he uses, but he's independent. He's had his L5-S1 segment fused, and this was painful. (Fig. 63)

So what we did again, we did a hip replacement slightly higher. I haven't brought it all the way down because I needed the bone to fix and to get onto here. You can see spinal fusion, good position, and good function. This was difficult early on. This was not a "fire and forget" operation. We had to bring him in for inpatient rehabilitation to optimize and maximize his function and to get his abductors working, because they never really worked in this sort of position. We have to do that. Sometimes with these patients, you have to plan and expect to do that to optimize function. (Fig. 64)

Another lady without upper limbs and really quite severe arthritis had come a long, long way before we did that. And again, because it's slightly tentative fixation, adding multiple screws, we've got to get primary stability for this


Royal National Orthopaedic Hospital NHS

THERAPY PRE-ASSESSMENT REPORT

Transfers:

Bed:

Chair:

Toilet:

Bath:

Management of ADLs:

Self-Care:

Toileting:

Meal Preparation:

Fig. 61



Fig. 62

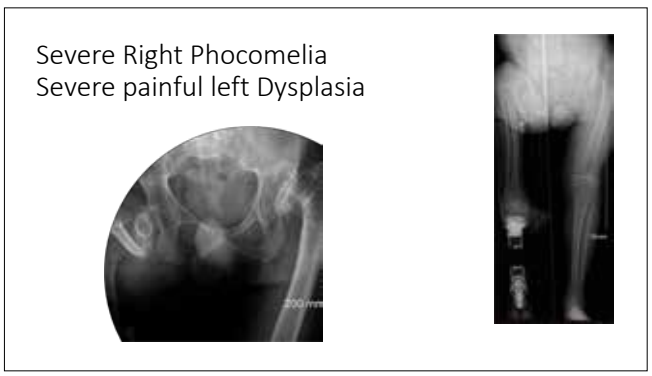


Fig. 63



Fig. 64



Fig. 65

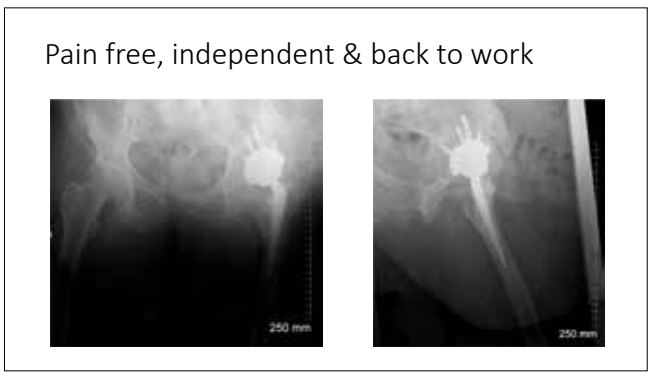


Fig. 66

implant. It's a small stem, but it has good function, and she was back to work 6 weeks after hip replacement surgery. (Fig. 65, 66)

What can go wrong? Joint replacements can be painful. This is a variation of a SPECT-CT image with some pain. That's probably loosening of the socket. We need to avoid that. (Fig. 67)

Dislocation is a disaster if it happens. We've got to make sure it doesn't happen. We haven't seen that in the ones we've done, thankfully. This is not a thalidomide patient, but just an example of dislocation. It can happen to anyone. The incidence is somewhere between 1% and 5%. (Fig. 68)

Again, regarding the increased femoral head size, we are making bigger heads to maximize the range and minimize this. (Fig. 69)

We're also using new technology and patient-specific instruments whereby we can use custom-made guides to show us where to make the femoral cut and how to position the acetabulum in the right place. (Fig. 70)

We can make 3-D models, 3-D printed models of the hip itself to check the anatomy and rehearse the operation. (Fig. 71)

We do CTs, we get cross-sectional images of the hip joint, and we can plan it. The important thing is segmentation with CT. This is the engineering part and the computer graphics part. You need to be able to separate the femur, the ball from the socket, and to plan it, to plan where you are going to put the femur. (Fig. 72, 73)

And so, again, this is the anteversion view. The top end of the femur transposed on the bottom. This is the epicondylar axis of the knee. The femoral head is usually 10 to 15 degrees anteverted from that axis. We can plan where we are going to make the neck cut and where we want to put the femoral component so we restore the center of rotation. (Fig. 74)

We get guides that fit. They match the surface and hold



Fig. 67



Fig. 68

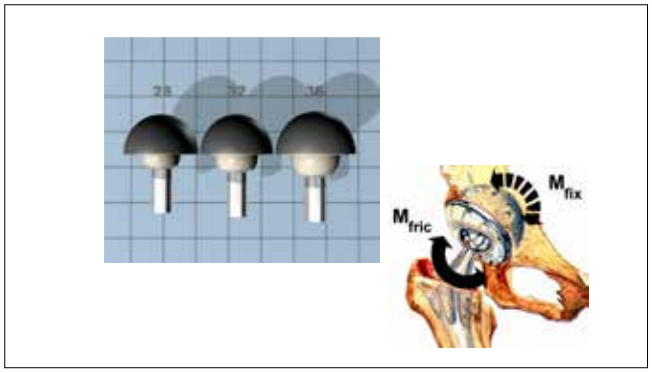


Fig. 69

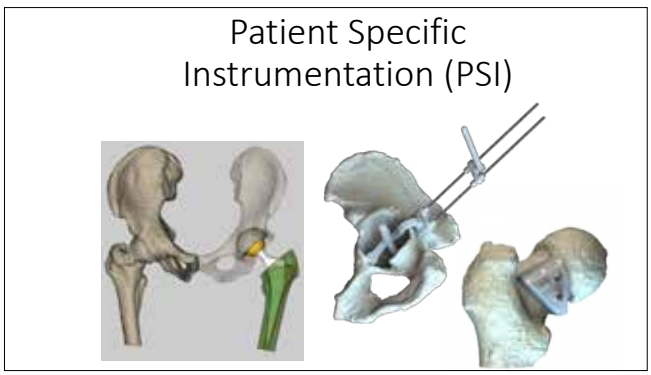


Fig. 70

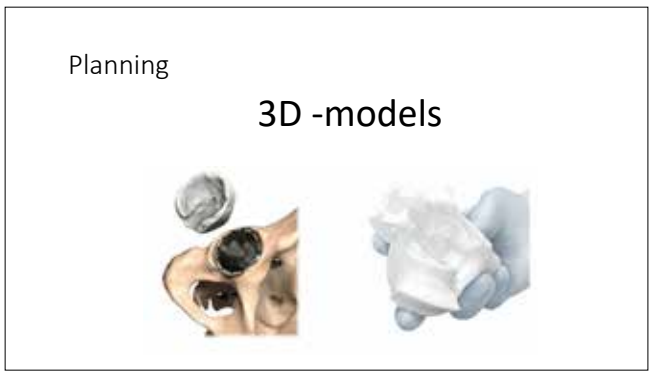


Fig. 71

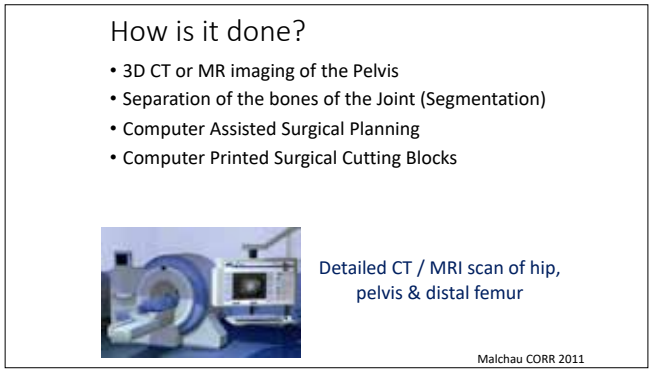


Fig. 72

them with screws, and then make the femoral cut for you and tell you exactly where you're going to be. (Fig. 75)

The ones in the socket are slightly more difficult to use, but by using this guide to put these pins in, we can put something over there that has exactly the right angle that we need to mimic putting the acetabular component in. (Fig. 76, 77)

This is something interesting we're working on with EOS scans that has real applications for planning surgery in thalidomide patients. This is a sitting and standing low-dose CT scan showing what happens to the angle of the hip going from sitting to standing. What we are planning is a series of thalidomide patients without upper limbs to see what position they put their legs in when they are brushing their hair or teeth with their feet, because that's a useful function to them. If we can work out the optimal position in which to place these components, then that's got to be a good thing to do using real-life information to plan function in the future. (Fig. 78, 79)

This again, is a thalidomide patient. This lady has no functional arms, phocomelia, with digits only, and really quite severe dysplasia and arthritis. She's independent, she drives herself, lives alone, and functions amazingly well, so she's got a lot to lose. But her pain is becoming unbearable. (Fig. 80)

We planned her anatomy, which is a problem. If you look at where the anteversion is, it's 66 degrees anteverted. Now that's incredible, it should be much lower than that. We've got to plan that out of the operation somehow, and where we are going to put the components. We planned 40 degrees of inclination and 20 degrees of anteversion. (Fig. 81)

Using technology mobilized at 2 days postoperatively,

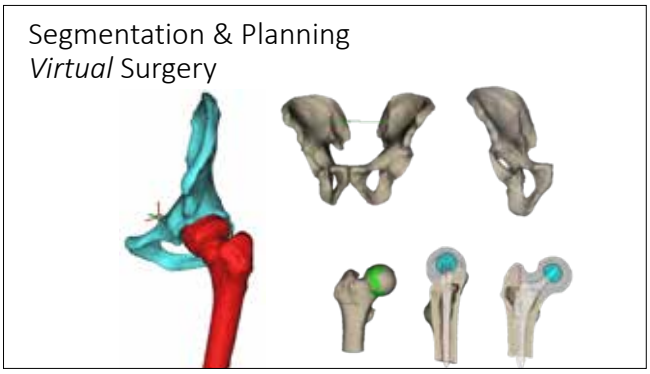


Fig. 73

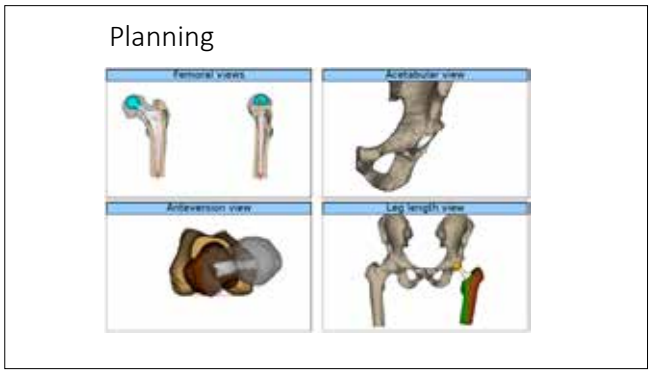


Fig. 74

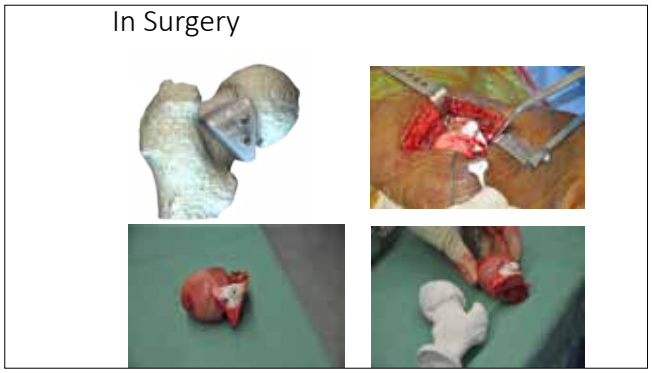


Fig. 75

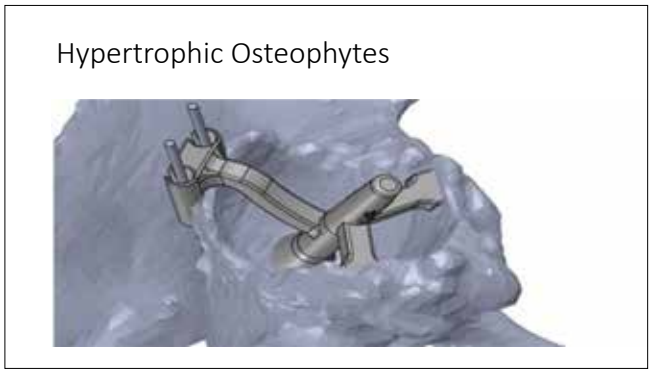


Fig. 76

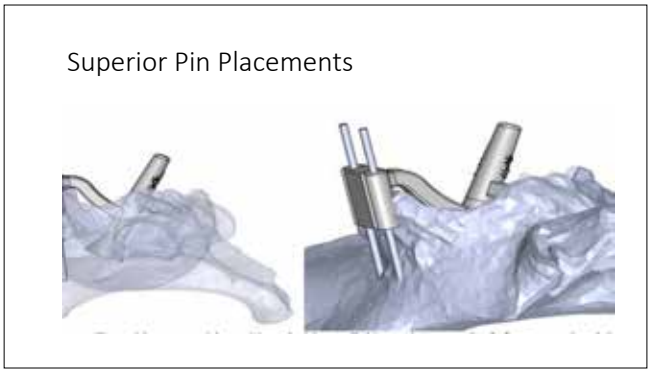


Fig. 77



Fig. 78

we got her walking pretty quickly. She was back driving her adapted car at 6 weeks. So if we get it right, patients get it right. I don't know if I mentioned it, but the last lady, for whom we predicted a 14-day stay, went home on the third day. So once it's right, the patients will go home. We'll plan the other side of this to get equal leg length. (Fig. 82)

Regarding results, dysplasia has been harder, but we've seen good 10-year survival for dysplastic hips. High hips have had problems in the past with fixation and what people were trying to do. We are looking at this. We haven't had any problems, but we're following our patients and we hope it's going to be much better than this. But yes, for difficult anatomy and difficult surgery, probably not everyone should be doing these operations. (Fig. 83)

So, for hip replacements in dysplasia and thalidomide patients, you really got to do careful preoperative planning. These are small components. You've got to make sure that you've got them, and if necessary, have them custom-made. That can be done, and they can be 3-D printed. (Fig. 84)

The stems are small, and the canals are narrow; it's a reduction of the whole limb. And you've got to watch nerve tension. Sciatic nerve palsy is very disabling and painful,



Fig. 82

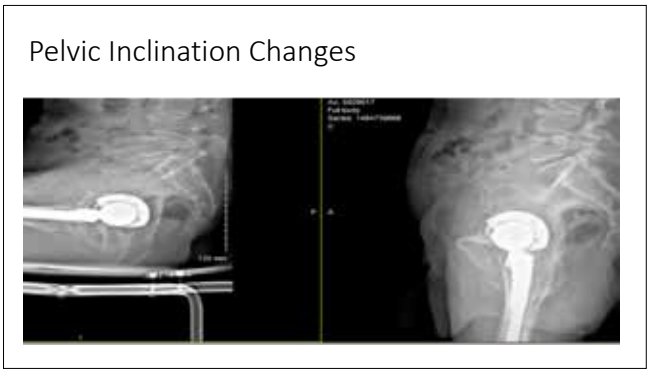


Fig. 79

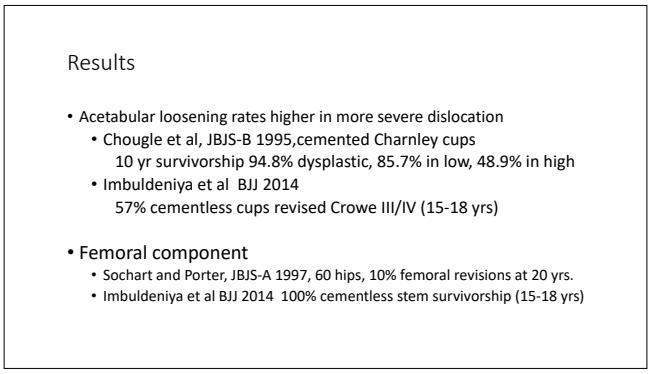


Fig. 83

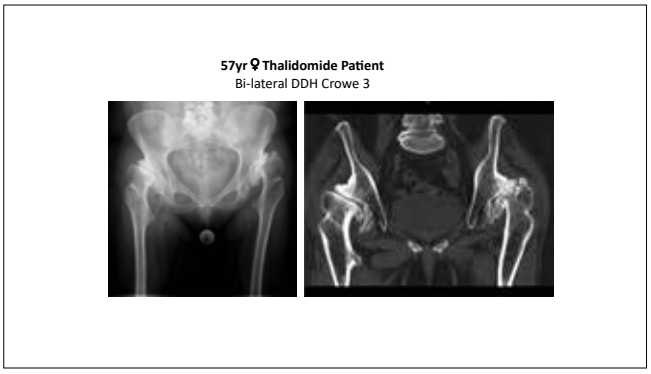


Fig. 80

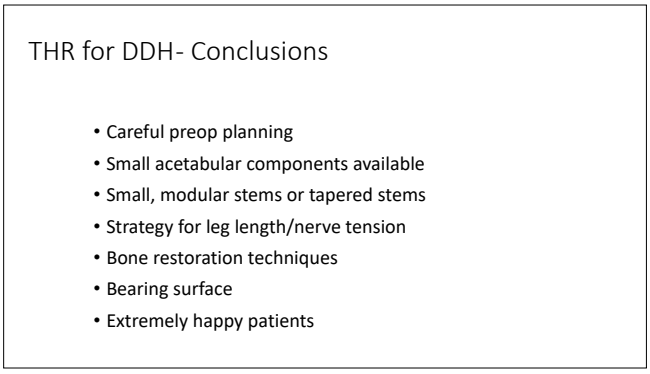


Fig. 84

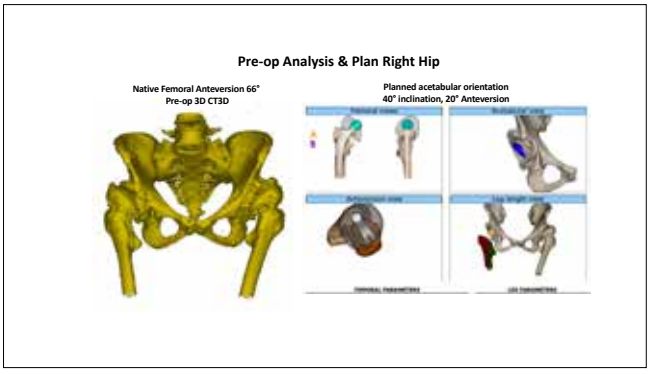


Fig. 81

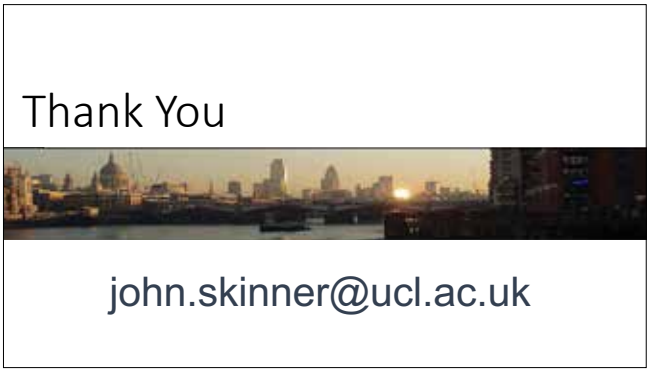


Fig. 85

and patients want equal leg length. We need to restore bone when necessary. We need to have bearings that are reliable and workable and will last hopefully the life of the patient, but certainly the life of the implant. And we know that if we get it right, these are some of the most satisfied patients. Thank you for your attention. (Fig. 85)

Q&A

Dee Morrison: Thank you, Professor Skinner. I can see why the staff think you are the best now. Any questions?

Yasuo Yamauchi: Thank you very much. Very interesting. I think I am the oldest one here in this room. I am 87 and I had a chance to visit Sir John Charnley in England. I was quite impressed by all he was doing there. First, the surgery itself, Charnley's method. Second is the operating room he was in, what we call greenhouse.

So considering that, my questions are: 1) In England, are you still using Charnley's original method, or is it sort of an old story? 2) Is his greenhouse system still popular in England? 3) Is Charnley's approach cutting the greater trochanter still valid? 4) One of the X-rays showed what my friend Tom Aitken in Grand Rapids called PFFD (proximal femoral focal deficiency). Is there any good measure to treat patients with proximal femoral focal deficiency? Thank you very much.

John Skinner: Thank you. I mean, of course, you're right. Charnley was the father of all this work and the pioneer. And he did an amazing job. Not only did he work out the materials, he found that poly(methyl methacrylate) was a way of fixing implants to the skeleton. But when he started, the infection rate was over 10%. That was a disaster, and infected joint replacement is still a disaster.

And yeah, I mean our operation theaters, we are neurotic about it, and yes, we do use, what we use is laminar flow, or ultra-clean theaters, and we have, there's a very clear system where the patient will be, where the instruments will be, and you have everything within the, it's based on the greenhouse effect. We don't actually erect a greenhouse in the theater anymore, but we do have Perspex dividers at the ceiling level that come down, so that shows where the laminar flow area is.

So you are absolutely right. All patients get prophylactic antibiotics in advance. All patients are swabbed in advanced for MRSA and Staphylococcus. Those that are positive are treated prior to surgery, and we are very meticulous about scrubbing. If the trainees don't scrub for the right amount of time, they are sent back to do it again. The next question was, I am trying to remember, what was your next question?

Yasuo Yamauch: The approach.

John Skinner: The approach. The Charnley approach with trochanteric osteotomy, I don't use, and I think people have stopped now because, I mean, it's the best approach to get you down the middle of the femoral canal. The problem was that I could not guarantee 100% of the time not to get a nonunion. We think it is very serious to have a 10% trochanteric nonunion rate, and I think that that's too much of a risk to take. So I use a posterior approach, which just divides the shorter external rotators and the capsule, leaves the gluteal medius and minimus on, and goes underneath to get into the hip. That works incredibly well. It's an extensile approach. In large patients, you can make a big incision to improve the access. So I take your point, but I don't use it. I don't think many people do now. There's a few Charnley devotees that do, but not many.

And then...

Yasuo Yamauchi: My next question was on PFFD.

John Skinner: PFFD? PFFD is a difficult condition to treat that, I work with colleagues who use techniques such as the Ilizarov technique and lengthening techniques to improve them, and they work with them; it depends on the type. But yes, sometimes you can lengthen and straighten bones using the tailor spatial frame, so you can grow them not just longer, but also straightened. If you've got a deficiency in soft bone, sometimes a bone graft, it's difficult work. Occasionally, if they've got significant improvement and restored anatomy, then I will do a joint replacement a long time down the line, but I couldn't do joint replacement in the one that I showed you, and you picked up on that.

Yasuo Yamauchi: Well, what I learned from Tom Aitken was that the enemy of PFFD is simply obesity.

John Skinner: Yeah. You are right, and this guy was mobile on that leg. He had a prosthesis and worked with it, and just got on with things, absolutely. Good point.

Yasuo Yamauchi: Thank you very much.

Dee Morrison: Any more questions?

Shadi-Afarin Ghassem: Thank you very much. Very, very interesting. Being an orthopedist, I always enjoy these kinds of lectures, really. But I noticed that you've never used any cement in any of these patients; however, they might be much younger. But having antibiotics in the cement, and you don't use it, can you just explain it a little bit more?

John Skinner: Sure. I do use cement. I tend in some cases, in some difficult anatomies with very wide femoral canals, I will use cement. The reason that I tend not to is because, in the ones where you are doing derotation or bone shortening, what you need, or what I think you need, is to be able to get rotational control proximally and distally. With the S-ROM prosthesis, the one you saw in quite a few of those, the metaphyseal sleeve gives very good rotational control of the top, and then the bottom has got flute, it's got cutting flutes on the surface. So if you jam it into the distal part, the cutting flutes will give rotational control distally. That's why my preference is actually not to use cement in younger patients. We give a high dose of intravenous antibiotics. We give teicoplanin and gentamicin prior to surgery. I don't think you need it just to deliver local antibiotics. But it's a good point.

And different people would approach these in different ways. There are people who would cement some of these shortening components, but I worry about getting cement in between the bone surfaces when I want them to heal.

Fumihiko Hinoshita: Okay, next please feel at ease after this series of very difficult, technically difficult questions. I am an internal physician. When I listened to your lecture at the beginning, at first, I thought this total hip replacement would be very difficult for orthopedic surgeons to do for thalidomiders because thalidomiders would have different anatomical problems from ordinary people. But the more and more I heard your stories and explanations, the more fully I could understand that you are very good at operating on the hip joint.

But I am afraid those highly technical operations will be done by younger orthopedic surgeons who are not so experienced. Can they do that difficult operation, total hip replacement, in thalidomiders? That is my question.

John Skinner: It's a very good question. In the UK, in surgery in general, we talk about indicative numbers. We think the occasional surgeon is almost certainly a pest. If you're not doing an operation regularly, are you doing it as well as you could, and are you doing it as well as someone who is doing it? Of course, that's an incredibly complicated question because some people, there's a different range of natural inherent abilities, and some people will be okay. But you're absolutely right. This is a complex surgery. Dysplasia surgery is complex, and the needs of thalidomiders are more complex. I mean, we shouldn't shy away from difficult problems. That's why we go to work, to solve difficult problems, but it behooves all of us to train the next generation. I don't think I would like to be the first, second, or third time someone has a go at one of these difficult hips. It's about training, it's about supervision, it's about working in teams, and it's an issue, particularly something as rare as thalidomiders.

Fumihiko Hinoshita: So you need great training experience to operate on thalidomiders for hip joint replacements, right?

John Skinner: I think you do. I mean, I think it's...

Fumihiko Hinoshita: Without any daily training, namely regular operations for hip joint surgery, it's impossible for them to operate on thalidomiders, right?

John Skinner: It's not impossible, but it's difficult. And you see that we had a very detailed pre-assessment, and we have that for all the patients because they are all different. And it's not just one surgeon, it's also the rehab team. It's also a good anesthetist. I mean, some anesthetists get terrified if you are not going to give them any arms to measure blood pressure. So it's, again, it's working the team, it's building experience. I think in the UK, we have a national joint registry, which does plot something called outlier surgeons. If your revisions are higher than average, you get told about it, and the chief executive at your hospital gets told about it. So, most surgeons are sensible. I would hope that most surgeons wouldn't take on an occasional case like this, and they do tend to refer them to specialist centers, which I think is how it should be, because specialist centers are not necessarily better, but they get very good at dealing with complex problems, because that's what they do.

I think that's the mindset we need in probably all aspects of healthcare, not just orthopedists, but also surgical specialties particularly.

Fumihiko Hinoshita: One more question, so can you accept Japanese thalidomiders who have an indication for hip replacement surgery with difficulty?

John Skinner: There will be some exceptionally good Japanese orthopedic surgeons. I am very happy to collaborate with them.

Fumihiko Hinoshita: Thank you very much.

John Skinner: Thank you.

Elizabeth Newbronner: It's more of an observation, really, Professor Skinner, than a question. But what struck me was the sort of meticulous way that you both plan the operation and the postoperative care. And sort of talking to thalidomide survivors, it strikes me that the lessons, there could

be broader lessons learned from that for more routine procedures. I think it would be great if there was some way to capture some of that and use that as advice for other doctors undertaking obviously much less complex procedures. But it's just an observation.

John Skinner: It's a good one. I think Klaus mentioned as well that thalidomide patients are at an age where they've had one doctor all their lives, and then the doctor retires, and there's no one there. And then there are other people who will say to them, I don't know anything about thalidomide. Why would you want to go to a doctor who is going to tell you that? I mean, we can find idiots anywhere. What we need when we go for healthcare problems is someone who is going to look into the problem and solve it. If that means referring to someone else, then that's what needs to happen. But it makes me cross when doctors say, I don't know anything about what you've got. Why would you stay?

Dee Morrison: Should I make this the last question?

Shadi-Afarin Ghassem: Yeah. Well, since we were talking about iliac malformations, now I wonder if you do any investigations before you have a TE-affected patient, if you look at the blood vessels before you do the surgery? I also wonder if you could think of doing bilateral surgery at the same time. Because actually, recent studies have shown that in the normal population, you can actually have bilateral surgery of the hips, and they are much, much better; they improve much, much earlier, much quicker, and leave the hospital. Those are my last two questions combined into one.

John Skinner: All of our thalidomiders have CT scans, that's cross-sectional imaging, where you can see the blood vessels, so we'll look for them. If there is anything abnormal or concerning, then we'll go on to do either a CT angiogram or visualize the vessels more often.
The second, what was the second question?

Shadi-Afarin Ghassem: If you do the procedure bilaterally?

John Skinner: Yeah, I tend not to do it bilaterally, I mean, I do some things, and certainly we've learned with patients with rheumatoid arthritis that it's better to do both ankles together, replace both knees together. Hips, you can take a view. When I've done total hip replacements, so hip replacements are quite a big insult to the patient. We don't lose much blood anymore because we give tranexamic acid, and we are meticulous about stopping bleeding, but these operations are big, and they are tiring. I think I am probably not at my best to do another complex operation just after I've done one.
So, we have done them at short intervals. We've done them in, if the patient is in good condition, done them a week later. But that gives the patient the option to say, actually, I need to go home and recover, and then they go home for 6 to 8 weeks, and then come back for the second side. Sometimes, you don't have to do the other one. I mean, the lady I showed with an awful bilateral disease, once you have one replaced, that becomes your good leg, so you offload the other one and this buys time, so that's something we see. Whereas, if it looks like it's a crisis, we must rush in and do everything today. Often, you buy time just by doing one.

Dee Morrison: Thank you, Professor Skinner.

John Skinner: Thank you very much.

Thalidomide in Brazil: Recent Experience

Lavínia Schuler-Faccini

Federal University of Rio Grande do Sul Genetics Department, Porto Alegre, Brazil

Fumihiko Hinoshita (Moderator)

Okay. Let's now proceed with the symposium, beginning with a special lecture by Professor Schuler-Faccini. She graduated from the School of Medicine at the Federal University of Rio Grande do Sul. She obtained her PhD in Genetics at the Federal University of Rio Grande do Sul. She subsequently held several postdoctoral positions and is now a professor at the Federal University of Rio Grande do Sul.

As you may know, she has carried out much research on thalidomide embryopathy (TE) in Brazil and has much experience in this area. Today, she will present a special lecture, entitled "Thalidomide in Brazil: Recent Experience." Professor Schuler-Faccini, please.

First of all, thank you very much Dr. Hinoshita, for inviting me here and to everybody, for this wonderful conference thus far. So, let's now move to a completely different reality. The title of this slide is "Gravidez Segura" in Portuguese, which means "safe pregnancy". We have a nationwide Teratogen Information Service in the Medical Genetics Service at the Clinical Hospital of Porto Alegre (Hospital de Clinicas de Porto Alegre), a public and free-of-charge hospital. We chose the term "safe pregnancy" in an effort to reach patients and the wider population who might not understand the meaning of the word "teratogen" we focus on the safe side, so safe pregnancy.

This service is now 27 years old and is directed at both the general population and doctors. It is open to anyone who wants any information about environmental exposures, drugs in pregnancy, infections, or other concerns. This is the reason for my becoming involved in the thalidomide problem in Brazil. (Fig. 1)

This slide shows what we expect to be Brazil. This is Rio de Janeiro, this is the Christ (statue). Here is Brazil. We are below the equator line in the Southern Hemisphere. We also have a completely different reality. (Fig. 2)

This slide shows where I live, in Porto Alegre, in South Brazil. It shows the Clinical Hospital and the Medical Genetics Service, where we work. Looking at these pictures, Brazil appears very nice and it is but one of our biggest problems is the inequality. (Fig. 3)

This slide shows that we do have good hospitals, but we also have a huge underserved population. So here you see my city, our group is working there. This is the city where I live and work. (Fig. 4)

This slide shows some important data for Brazil. We now have a population of 190 million people, and 3 million births per year. Therefore, to offer proper healthcare to all the popu-



Fig. 1



Fig. 2

lation, in a middle-income country, is very difficult. It is also difficult to have/provide good health information about the number of congenital anomalies and/or genetic diseases. In recent decades, our infant mortality has decreased mainly due to the decrease in infections and diarrhea. Therefore, congenital anomalies are progressively becoming an important cause of infant mortality. Our government is now trying to address the problem of congenital disabilities. Even so, we still face the problems of underdeveloped countries. (Fig. 5)

In this slide, we have the classic photographs of Thalidomide Syndrome that you used to see. I have included them here, to introduce the history of thalidomide in Brazil. (Fig. 6)

The first cases of malformations associated with the use of thalidomide in Brazil were reported in 1960. The official number of people born with thalidomide syndrome in Brazil prior to 1965 is about 300 cases but this is considered an underestimation. It probably reached 1000, according to the Patients Association of Brazil. This is partly because some cases were difficult to prove due to the high prevalence of self-medication. Thalidomide was an over-the-counter medication, worldwide, including in Brazil. By the time affected persons applied for compensation or to have their rights recognized, much time had elapsed between drug ingestion and diagnosis. Hence, in many instances, proof of thalidomide harm was difficult to prove and it was difficult to acknowledge individuals affected by thalidomide. (Fig. 7)

This slide is in Portuguese. I don't want you to read all this, but I have included it as it if from a newspaper. It states: "3,008,965 bottles of thalidomide drugs were apprehended in 1962, when the thalidomide was withdrawn from the market." Even so, as we heard yesterday, it was not in effect countrywide. We do know that many pharmacies still dispensed thalidomide after 1962. (Fig. 8)

Apparently, by 1965, there was not a significant amount of thalidomide available on the Brazilian market. However, as Dr. Emma Baple showed yesterday, Brazil, still today, is competing with India as the leading country in the number of leprosy cases. India probably has more absolute cases because of their huge population, but the prevalence in Brazil might be even higher than in India. (Fig. 9)



Fig. 3



Fig. 5



Fig. 4

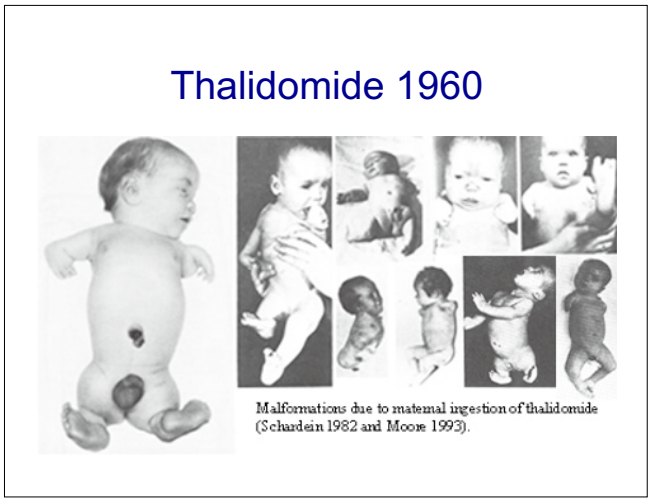


Fig. 6

In this slide, we show the number of new cases of leprosy in Brazil: almost 35,000 new cases each year. The country-wide distribution is unequal there are higher numbers in the North compared to in the South. This North–South difference reflects also the economic distribution. North is poorer and South is richer. So, we have geographic inequality related to economic inequality, and also lack of proper access to health services. In northern Brazil there is the Amazon jungle, where you have to take a boat to travel, sometimes for 2 or 3 days, to reach isolated communities. Access to modern communication systems like the Internet is also difficult. (Fig. 10)

As was previously shown "erythema nodosum leprosum" (ENL) is a common complication in leprosy. It is a very painful skin reaction, and people affected by ENL endure great suffering. It is interesting, because, in 1965, in Israel, Dr. Sheskin treated six cases of ENL with thalidomide. According to his report, he used this treatment because of the sedative effect of the thalidomide. To his surprise, he found that not only did the patients sleep well and have less anxiety, but their ENL regressed. Hereafter, thalidomide returned not as an anxiety drug or antiemetic, but as an immunomodulatory drug. ENL is a reaction that is more common in cases of lepromatous leprosy, which means a leprosy that is not treated from the beginning (it has a longer evolution). In Brazil, almost 50% of patients with leprosy have ENL due to late diagnosis. This late diagnosis if often related to prejudice against leprosy. We know that leprosy is treatable and that it is not very contagious, you do not get it from only shaking hands, for example. However, in the community, this is not known, and if someone is diagnosed with leprosy, probably he is going to lose his job and be excluded from society. Consequently, many people hide the symptoms and only seek care later. (Fig. 11)

In this slide, we show our paper published in 1996, in the journal Teratology. ECLAMC is the Latin American Collaborative Study of Congenital Malformations that registers congenital anomalies in the majority of South American countries. ECLAMC was established in 1967. Between 1969 and 1995 it registered 34 cases of thalidomide embryopathy (TE); 33 of the cases were born in Brazil all were related to the use

Thalidomide in Brazil

- The first cases of malformations associated with the use of thalidomide-based drugs in Brazil were reported in 1960;
- The official number in Brazil until 1965 is about 300 cases;
- Some cases were difficult to prove due to the high incidence of self-medication and the time elapsed from drugingestion until diagnosis

Fig. 7

Thalidomide 1960 - Brazil


Diário Oficial

ESTADO DE SÃO PAULO — (ESTADOS UNIDOS DO BR.

Sòmente na Capital

APREENDIDOS 38.964 VIDROS DE DROGAS À BASE DE THALIDOMIDA

Inutilizados, também, mais de um milhão e meio de comprimidos — Constituída um Serviço Especial de Emergência

Fig. 8

Leprosy – worldwide distribution



Fig. 9

Leprosy – Brazil

35,000 new cases each year

Inequal distribution over the country

North: 8/10,000

South: < 1/10,000

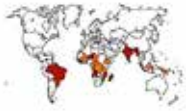


Fig. 10

of thalidomide in leprosy. At that time, thalidomide was not available in the pharmacies, but it was easily obtained by people affected by leprosy through government programs.

I had one case, and this case shocked me, still to this day. It occurred in the late 1980s, in 1987 or 1988. I was beginning my career as a medical geneticist. I had this patient with limb reduction defects. However, the patient had a brother who was affected. Therefore, to my mind, as a medical geneticist, it would be an autosomal recessive disorder. This was before we had many genetic tests available. But it caught my attention that it was not the mother that brought the child in, it was always an aunt. I then asked the aunt why the mother could not come to the clinic. They were from inland Rio Grande do Sul (my home state). She replied that the mother was ill. I proceeded to ask, "Which illness?", to which she responded "She has leprosy". At that moment, and it still shocks me, I realized that I was facing a thalidomide case. Furthermore, there was a brother that was affected. When I collected their history, I noted that the health professional that was taking care of this family had told the mother "You cannot use this medication when you are pregnant. When you discover that you are pregnant, you should stop the medication." Therefore, the woman didn't relate the problem in the baby to thalidomide, because she followed strictly what her health professional has told her. (We know that the teratogenic window for thalidomide is in the very beginning of the pregnancy when most women do not even realize they are pregnant.) (Fig. 12)

In the 1990s, many changes were made to the regulations in Brazil. Presently we have thalidomide approved officially for leprosy, lupus, multiple myeloma, AIDS, and some individual indications that doctors can apply and they have the license to prescribe. (Fig. 13)

Here is how the thalidomide is dispensed in Brazil. It is not commercialized and it cannot be bought. It is distributed only through health programs by the Ministry of Health. Herein lies the problem the problem and the solution. Because it is widely available and inexpensive, and because many patients with leprosy live far away and in places difficult to access, they may get one box containing 30 pills, or the amount required for one month of use. That means they may have 30, sometimes 60, pills at home. Thalidomide is produced only by one laboratory, under governmental supervision, and given to patients only by doctors, by the Brazilian Health Service, free of charge. Patients have to sign for informed consent, but we know that often the patient doesn't understand exactly what is written. People with low education are sometimes even unable to read. So, it depends very much on how the information is given by the health professionals. Women of reproductive age should not be prescribed, unless in special circumstances.

But again, here is a problem. Leprosy runs in families, not because it is a genetic disorder, but families do have susceptibilities. In the communities and families, generally,

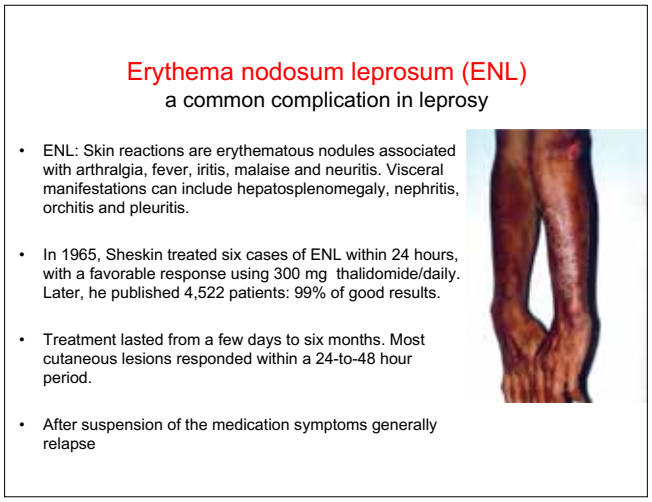


Fig. 11

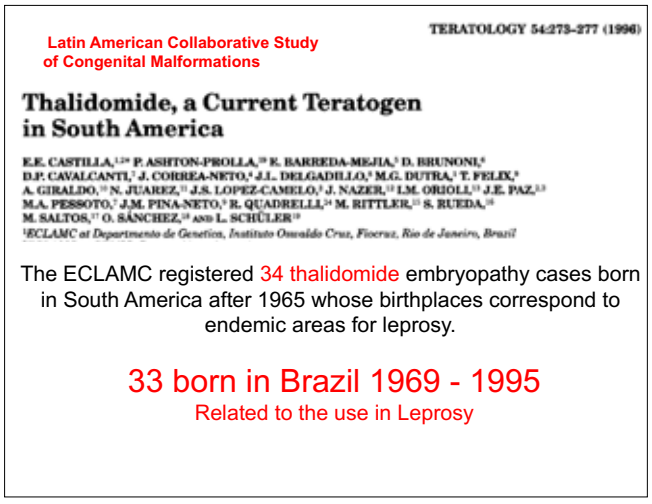


Fig. 12

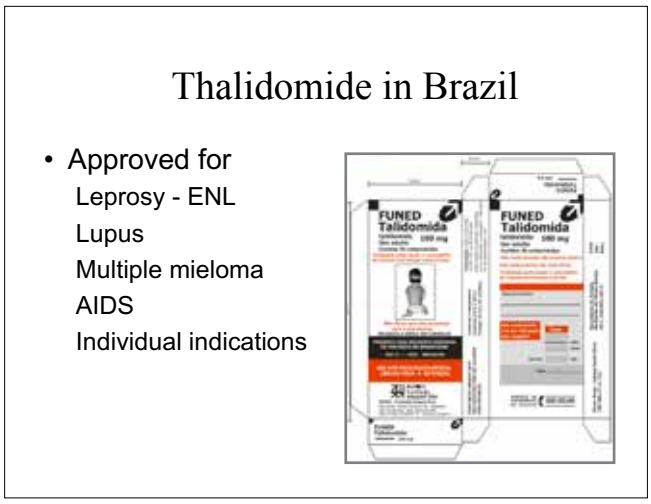


Fig. 13

more than one is affected. Women know that thalidomide is wonderful and, if they have pain, they may try many times to get the medication.

As I am going to show you later, this is like giving guns to children. It is not exactly the same, but you know that the risk is there. It is almost impossible to imagine that, during the use of thalidomide or misuse of thalidomide, we are not going to have inadvertent pregnancies in women that have a low level of education. Women with a prescription for thalidomide should use two contraceptives: one hormonal and the other by barrier. But look at that, in Brazil, 3 million to 4 million tablets of thalidomide are dispensed every year.

Once, an effort was made to disallow women of reproductive age to use thalidomide. However, the association of patients with leprosy complained that it was unfair for the women to suffer more consequences than men. Therefore, the Patients Association campaigned for the right of the women to have the same access to thalidomide as men. As a consequence, the regulation now doesn't exclude women of reproductive age from using thalidomide. (Fig. 14)

This slide shows our paper published in 2007. It shows that there are still babies being born with TE in the twenty-first century. (Fig. 15)

Here we show the distribution of the new cases of TE in Brazil after 2000. Imagine that in the twenty-first century everybody knows that thalidomide is a teratogen and yet we have new cases in Brazil. (Fig. 16)

This case, shown yesterday by Dr. Emma Baple, was born in 2005 in the north of Brazil. Initially, I thought it was impossible that there were still thalidomide babies being born at that time. But when the first pictures were seen, I realized that I was wrong, and that there was a strong possibility of this being a child with TE. I travelled there and we confirmed that it was indeed the case. (Fig. 17)

In this case, the mother was not affected by leprosy, but her husband was. They were very poor and illiterate, and the mother denied using thalidomide during pregnancy. So, I rephrased the question, because many women do not know that they are pregnant before they get tested. Often, when a woman recognizes her pregnancy, she is already

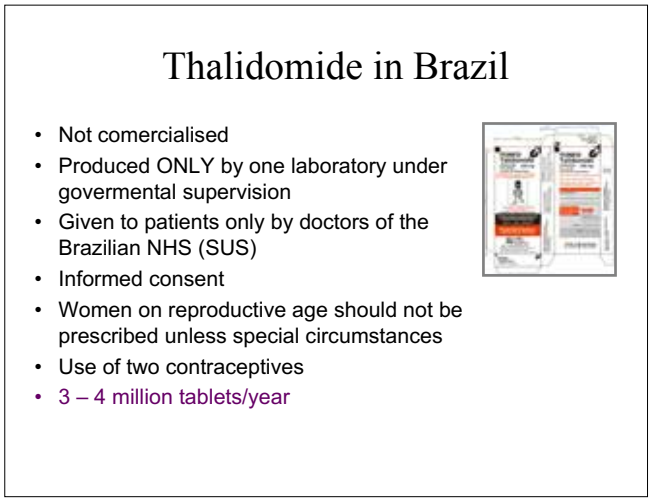


Fig. 14



Fig. 15



RECENT CASES (AFTER 2000)

Fig. 16



Fig. 17

several weeks pregnant. So, I asked her in a very polite and sensitive way (to not let her feel accused): "By any chance, have you taken this pill just before you got pregnant?" She said: "Yes. I was sick, and we have this medication at home. It was in the cupboard, beside the sugar." She took the pills and she felt better. In her mind, she was not yet pregnant. She only recognized her pregnancy when she was already 2 months pregnant.

One important thing in Brazil is that we also sometimes have cases prenatally diagnosed. However, in Brazil, pregnancy interruption (abortion) is not only medically unacceptable, it is a crime. So, anyone who performs an abortion might go to jail, both the doctor and the woman. Regrettably, it is very, very complicated. (Fig. 18)

The second case emerged in 2006. (Fig. 19)

One year later I saw this patient with upper limb defects and also cardiopathy. She died at 6 months of age. Amazingly, she was not initially diagnosed as having TE. (Fig. 20)

She was reported when she presented for the first vaccination shot (which is mandatory in Brazil). The healthcare worker didn't know where to apply the vaccine she had no upper limbs. The Ministry of Health was approached and asked how to perform a vaccination in a patient who doesn't have limbs, arms. Considering the region, where leprosy is highly prevalent, the suspicion of TE was raised and later confirmed. The mother had used thalidomide for leprosy because the doctor told her that she could not get pregnant while using thalidomide. Her conclusion was that thalidomide had contraceptive properties, which we know is completely untrue. Besides that, her husband didn't know that she had a past history of leprosy, and she didn't want to disclose it to him. So, the baby was born and died, secondary to a severe heart problem. (Fig. 21)

The third and the fourth cases were a twin pair in Porto Alegre, my home town, where we don't have leprosy. However, the grandmother of this baby was affected by multiple myeloma. (Fig. 22)

The mother of the baby was a pregnant teenage woman. She took thalidomide from her mother, thinking that thalidomide had abortive properties, because on the label it stated

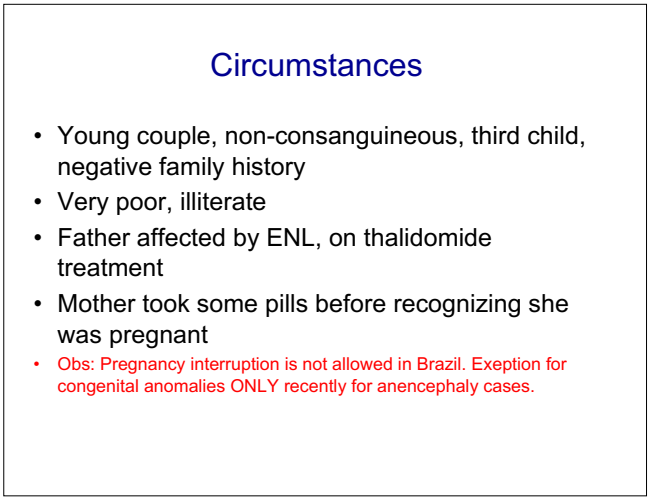


Fig. 18



Fig. 19



Fig. 20

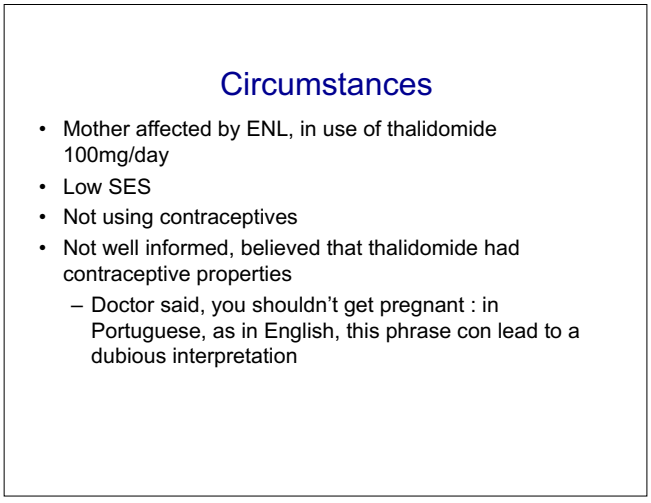


Fig. 21

the following: "Many times it causes the loss of the pregnancy." One of the twin births was a stillbirth, with the absence of thumbs, and kidney agenesis and pulmonary hyperplasia. (Fig. 23)

At this point, we started a project that focused on a follow-up of these cases and we also tried to find out if there were other cases. (Fig. 24)

Once again, we found more cases in Northeast Brazil from mothers with leprosy. (Fig. 25, 26)

In this slide, we show this small town called Cajari, where this affected girl was born. (Fig. 27, 28)

Here is the same patient showing the eye anomalies.

Here is another case, never yet reported. The child was 9 years old at the time, from a family where almost all relatives had leprosy, in the vicinity of Cajari. (Fig. 29)

In this slide, the year was 2017, and I was called to see a patient born in 2012. So, she was 5 years old at that time. Again, the socioeconomic status was very low. And look, it's interesting to find the acromion is a very prominent characteristic of TE as Dr. Emma told yesterday. She also had anal atresia. She was uncared for. The history is very sad. Prior to my visit she had obtained compensation but received inadequate care. All the money went to the parents her father took the money and bought a big car. Furthermore, even worse than that, her father used her as advertisement. He would say: "Look, I have this deformed…"apologies for the word, but"…deformed child, we are poor, we need support from the community" and placed it on social networks. It was through the social networks that we noticed this patient. She had hearing and eye problems, and was not being properly cared for.

In conclusion, we are trying to now establish some basic defects to follow and for mandatory reporting in Brazil so that these cases can be established soonest. (Fig. 30)

Here we present our decision tree, very similar to what Dr. Emma Baple presented yesterday, to define a phenotype for surveillance. (Fig. 31, 32)

We have also published a booklet, in Portuguese, available in both printed form or through a website, which is freely available to all doctors and health professionals. It



Fig. 22

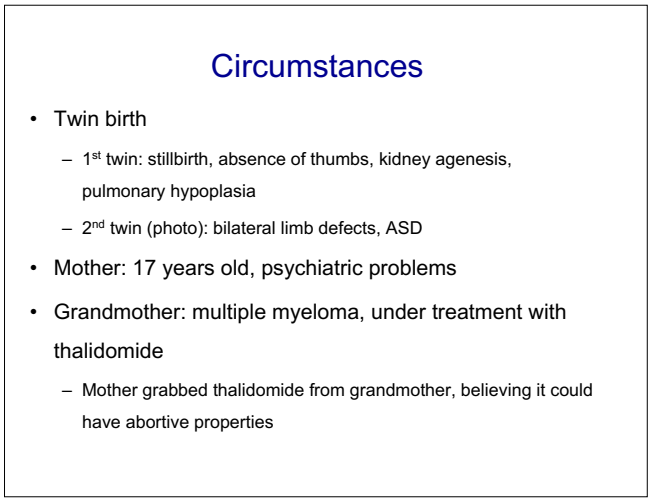
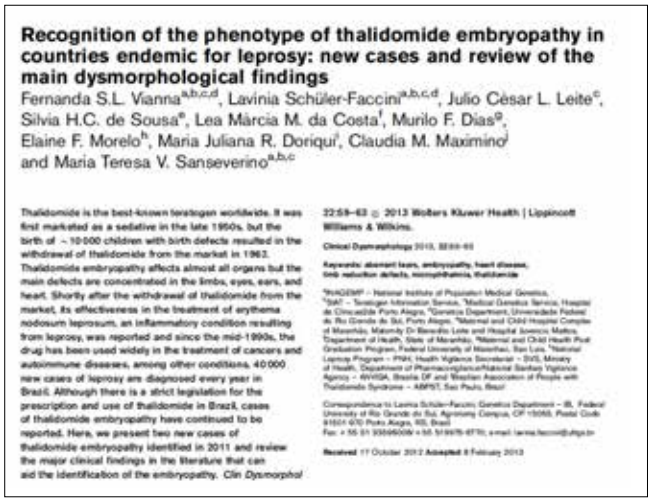


Fig. 23


Recognition of the phenotype of thalidomide embryopathy in countries endemic for leprosy: new cases and review of the main dysmorphological findings

Fernanda S.L. Vianna[a,b,c,d], Lavinia Schüler-Faccini[a,b,c,d], Julio César L. Leite[c], Silvia H.C. de Sousa[e], Lea Márcia M. da Costa[f], Murilo F. Dias[g], Elaine F. Morelo[h], Maria Juliana R. Doriqui[i], Claudia M. Maximino[j] and Maria Teresa V. Sanseverino[a,b,c]

Thalidomide is the best-known teratogen worldwide. It was first marketed as a sedative in the late 1950s, but the birth of ~10 000 children with birth defects resulted in the withdrawal of thalidomide from the market in 1962. Thalidomide embryopathy affects almost all organs but the main defects are concentrated in the limbs, eyes, ears, and heart. Shortly after the withdrawal of thalidomide from the market, its effectiveness in the treatment of erythema nodosum leprosum, an inflammatory condition resulting from leprosy, was reported and since the mid-1990s, the drug has been used widely in the treatment of cancers and autoimmune diseases, among other conditions. 40 000 new cases of leprosy are diagnosed every year in Brazil. Although there is a strict legislation for the prescription and use of thalidomide in Brazil, cases of thalidomide embryopathy have continued to be reported. Here, we present two new cases of thalidomide embryopathy identified in 2011 and review the major clinical findings in the literature that can aid the identification of the embryopathy. *Clin Dysmorphol*

22:59–62 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Clinical Dysmorphology 2013, 22:59–62

Keywords: abnormal toes, embryopathy, heart disease, limb reduction defects, microphthalmia, thalidomide

[a]HUGENP – National Institute of Population Medical Genetics, [b]INAGEMP – National Institute of Population Medical Genetics, [c]GAT – Teratogen Information Service, [d]Medical Genetics Service, Hospital de Clínicas de Porto Alegre, [e]Genetics Department, Universidade Federal do Rio Grande do Sul, Porto Alegre, [f]Maternal and Child Hospital Complex of Maranhão, Maternity Dr Benedito Leite and Hospital Juvencio Mattos, Department of Health, State of Maranhão, [g]Maternal and Child Health Post Graduation Program, Federal University of Maranhao, São Luis, [h]National Leprosy Program – PNH, Health Vigilance Secretariat – SVS, Ministry of Health, Department of Pharmacovigilance/National Sanitary Vigilance Agency – ANVISA, Brasília DF and [i]Brazilian Association of People with Thalidomide Syndrome – ABMST, São Paulo, Brazil

Correspondence to Lavinia Schüler-Faccini, Genetics Department – IB, Federal University of Rio Grande do Sul, Agronomy Campus, CP 15053, Postal Code 91501-970, Porto Alegre, RS, Brazil
Fax: + 55 51 33086009; e-mail: lavinia.faccini@ufrgs.br

Received 17 October 2012 Accepted 8 February 2013

Fig. 24

Fig. 25

explains how to use thalidomide and all its consequences, with the aim of providing health professionals with more information about the risks of thalidomide use. (Fig. 33)

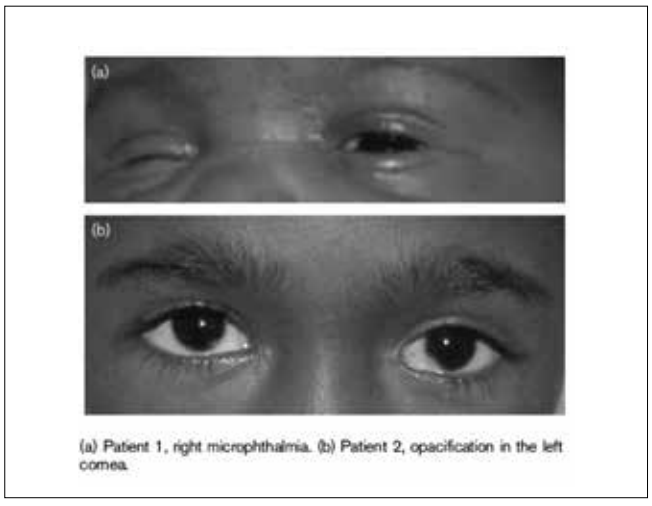
Here we show other work, similar to what is being presented here. In this paper, published by Salzano (my thesis director), 93 Brazilian teenagers with TE were evaluated during the 1980s, when they began to pursue compensation. (Fig. 34)

From 2010, we tried to recontact those who lived in our state for a follow-up. (Fig. 35)

This is the Kowalski paper published in 2015. Here, we took a picture of some of them. When we explained what the project was about, i.e., a follow-up of their health conditions, some didn't want to participate in the project. They even didn't like being recognized as a "thalidomider" they hate this word. That means that someone is defined by her medical condition and not being Paula, June, or someone who, amongst other things, has thalidomide syndrome. Here we see other project participants: Teresa, Fernanda, and this is Thayne Kowalski (all women).



Fig. 26



(a) Patient 1, right microphthalmia. (b) Patient 2, opacification in the left cornea.

Fig. 27

As we can see from the table, we registered the following as being frequent problems: deafness, hearing problems, and dental loss. We were unable to obtain good blood pressure measurements, but some cases had medical records of cardiovascular problems. This was compared with the general population; however, our sample was only 23 individuals. But just imagine, 30 years later, to get 23 individuals again

The patient's mother had leprosy in the past and was treated with antibiotic therapies (rifampicin, dapsone, and clofazimine) over a 1-year period. Eventually, she developed ENL, for which she received thalidomide 100 mg/day, and was advised to follow a contraception program because of the risk of teratogenesis. As she did not use contraceptives, further thalidomide treatment was denied. However, she took some leftover pills before realizing that she was pregnant. The exact dose and period of use of thalidomide during pregnancy was not recalled.

Fig. 28



Fig. 29

During the interview, the patient's mother reported that she had had leprosy in 1995 and described the symptoms of ENL. She was treated for 5 years in different clinics until she became pregnant with Case 2. She could not recall the exact dose or period of use of thalidomide during pregnancy. Many members of her family were also affected by leprosy and reported having ENL. They live in an isolated area under very poor conditions (Fig. 3).

Fig. 30

a high proportion. We also observed a higher frequency of psychological or mood disorders, mostly stress or depression. We can guess that there is some bias since they are voluntarily participating individuals, so we might imagine that people who had endured more suffering would be more willing to participate. But the opposite could also be true. If you are too depressed, you might even think the following: "Okay, why do I have to answer all these questions for this doctor?" We therefore think that the bias of voluntarily participating is not quite relevant. And, as I have heard from you earlier, mood disorder is expected. Nonetheless, it is important that we register this disorder, and register that it is above what we see in our population.

Currently, we are trying to expand the study because the subjects are now approaching their 60s. We would like to have a group (all together), not only from our state but from other parts of Brazil, and to empower them a little bit more. I think that one of the most interesting things for me, to be here/to take home, is the sense that these women can be empowered and take care of themselves. Many of them believe that because they have a congenital anomaly there is no future for them. They feel as if they are not part of this civilization, they have felt worthless and excluded from the very beginning. Furthermore, as they do receive a compensation, they might think that they are not entitled to complain. (Fig. 36)

Finally, the conclusions. Even with stricter surveillance and regulations, indications, from case history, are that Bra-



Fig. 31

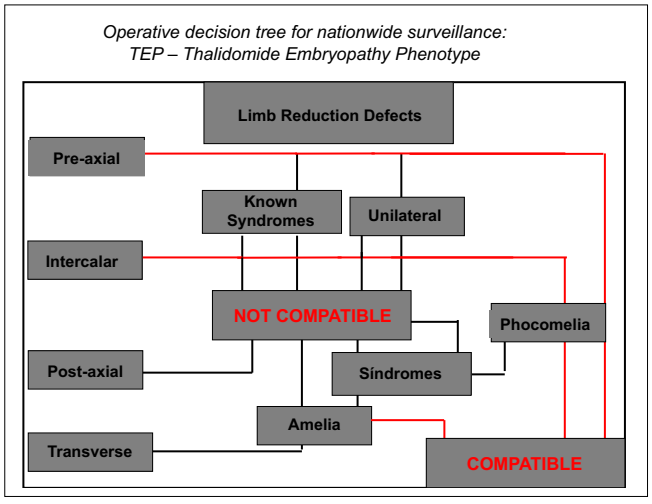


Fig. 32

Booklets produced by the Brazilian Ministry of Health to educate health professionals

92 pages

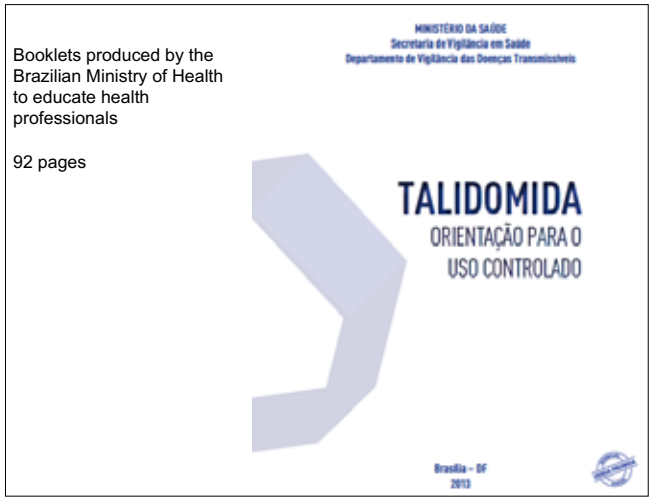


Fig. 33

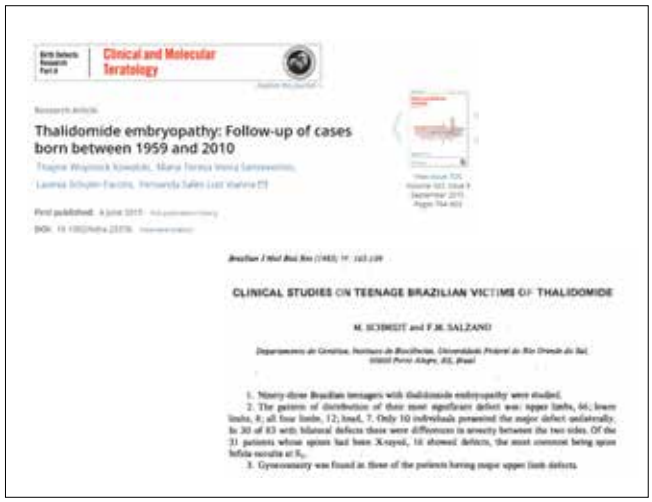


Fig. 34



Fig. 35

zil is reticent to introduce any thalidomide analogue. Lenalidomide and pomalidomide are only available through importation and are much more expensive than thalidomide. However, the inequality remains: richer people can afford to use pomalidomide and lenalidomide, which, although teratogenic, have fewer side effects. (Fig. 37)

So, thank you very much. This is our group, with all four "scientific generations" working with TE: Salzano, myself, Fernanda Vianna, and Thayne Kowalski. I wish to thank them for this collaborative work. (Fig. 38)

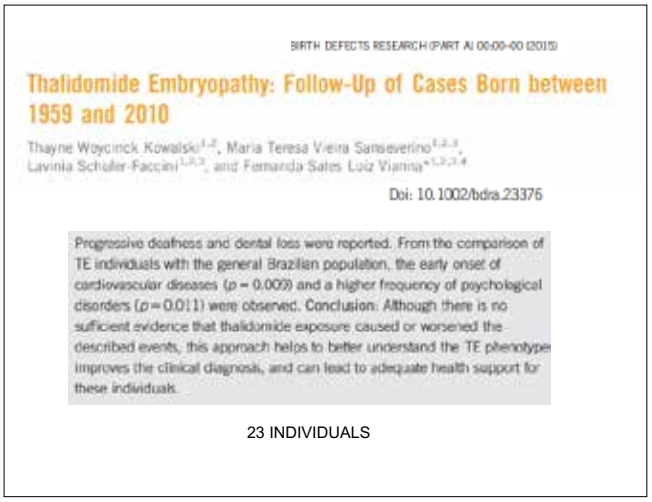


Fig. 36

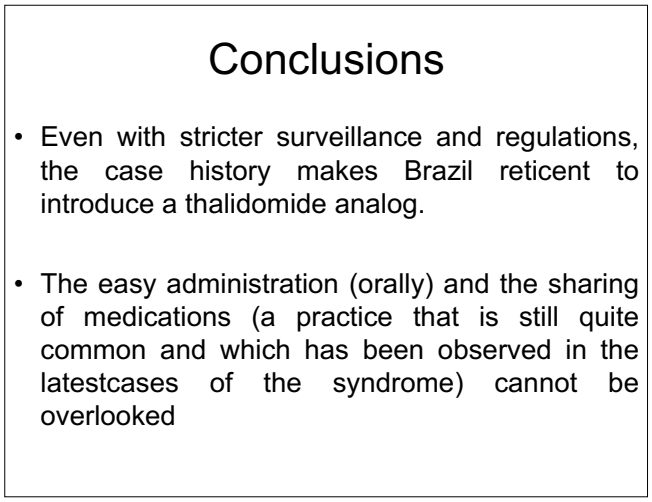


Fig. 37

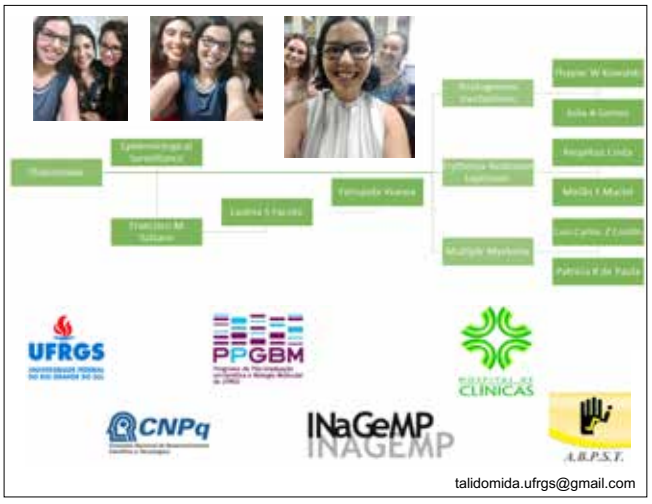


Fig. 38

Q&A

Fumihiko Hinoshita: Thank you very much, Professor Schuler-Faccini. We are now open to questions and discussion.

Tsugumichi Sato: I am Sato from the Ishizue Foundation. Congratulations and thank you very much for your impressive presentation. Yes, we Japanese thalidomiders feel very sorry about the story in Brazil. And my question is I actually have two questions. First, regarding the number of new victims after 1965 I've heard from Cláudia that there are 120 new victims in Brazil.

Lavinia Schuler-Faccini: Yes, Cláudia. Yes.

Tsugumichi Sato: Is it right or wrong?

Lavinia Schuler-Faccini: Yes, it is. However, I put this number of 34 in our paper because those 34 were the patients that we have seen. Regarding the 120, I am not sure that all of them have TE. Limb defects are quite common. But the problem is, it's quite ethic. They are receiving the compensation. They have limb defects. So, it would be harmful if we now go to them and say, "Okay, you have a genetic condition."

So what we did is, in some cases, some particular cases we have some cases of ectrodactyly that we know that are not due to thalidomide. So, we call them for a private consultation, and say "Okay". But we are mindful that some cases can be confounded with thalidomide. We try not to, you know, not make them spiteful but try to conceive that they have a risk for future generation or something. But Cláudia is mostly right. Cláudia is very, very strict in diagnosis. She is very good in diagnosis right now. She says "You are not" or "Yes, you are". Now you can call Lavinia, because she is going to tell that you are not an individual with TE or you can rightfully ask compensation for the newer cases."

But it is around 100, I guess. And even so sorry to say something more regarding these cases, I strongly believe that these cases I am showing you is what we saw just by chance. There are probably more that are not registered or reported. The regulation now in Brazil is so strict on thalidomide use that even the parents can be prosecuted or be considered accountable for their children being born with an anomaly that could be preventable. This is very, very bad, you know.

I am pretty sure that we have many more cases being born in Brazil, but we are not being informed.

Tsugumichi Sato: Thank you. And the second question is about recent cases. I have a photo yeah, this one. So, do you know the case, born in 2006?

Lavinia Schuler-Faccini: Okay. It is not ours.

Tsugumichi Sato: And this?

Lavinia Schuler-Faccini: This, was born in 2006?

Tsugumichi Sato: Swedish thalidomider gave me the photo.

Lavinia Schuler-Faccini: Okay. Yeah. It's so similar to the patient we saw in 2005. I don't know…

Tsugumichi Sato: 2005.

Lavinia Schuler-Faccini: Yeah. But I am not sure it's the same case, because there is the…
Do you know in which state or city was the case born? No? Because it's quite similar to, I looked at…
Yes. Yeah, it's my patient. Yeah. I am sorry it's my patient. It's the same one that I showed. Yeah. Yeah, I know him very well. Yeah. Yes. Exactly, yeah. I even know his name. Sorry. It's the same baby that Emma presented yesterday and I showed today; I followed him.

Fumihiko Hinoshita: Okay. Now, it's okay to confirm the case, you know…

Lavinia Schuler-Faccini: Yeah, it's a confirmed case. Yeah.

Fumihiko Hinoshita: Okay. Is there any other question or comment?

Christina Ding-Greiner: In Germany, in the scientific service from the Bundestag, I found a paper dating from 2008. There I found details about thalidomiders in Germany. They mention Brazil, and they say that there were 480 acknowledged thalidomiders in Brazil. What do you think of it?

Lavinia Schuler-Faccini: Yeah, it might be possible. Considering those born in the 1960s, before 1965 and later, I think it's accurate.

Christina Ding-Greiner: It's correct?

Lavinia Schuler-Faccini: Yeah.

Christina Ding-Greiner: Thank you.

Fumihiko Hinoshita: Okay. Do you have any other questions? You have nothing? Okay, please.

Junko Fujitani: Do new thalidomiders have some pension or compensation?

Lavinia Schuler-Faccini: Yes, they have. They have compensation because of thalidomide, because as the government gives the medication, the government is responsible. So they have a compensation, they have a moral compensation. It's a huge amount of money. The problem is like this it's like the car (the story I described earlier). The father bought a huge car let me see, in US dollars, imagine something that is around $30,000. Then, even worse than that, after buying the car he left the family. So, when I was there, they called us, because they (the family) were in misery again. So, they didn't have this huge moral compensation. The thalidomider still has a monthly, how can I say, payment. But, besides the monthly payments, any patient with thalidomide syndrome receives this, like, compensation, big compensation, and they spend it all. Yeah.

Junko Fujitani: Then, diagnosis: who diagnoses whether the baby is a thalidomider?

Lavinia Schuler-Faccini: Yes. Why this baby? Why was she diagnosed? Because she was on Facebook. As that region has a high prevalence of leprosy, we communicated with the Ministry of Health and we went there to examine the baby. Of course, there was proven exposure of the mother. She used. She was still using. We also did some medical tests, genetic tests that drill other common conditions' phenocopies.

Junko Fujitani: Thank you very much.

Fumihiko Hinoshita: Okay. Nothing else? So, thank you very much, Professor Schuler-Faccini. Thank you.

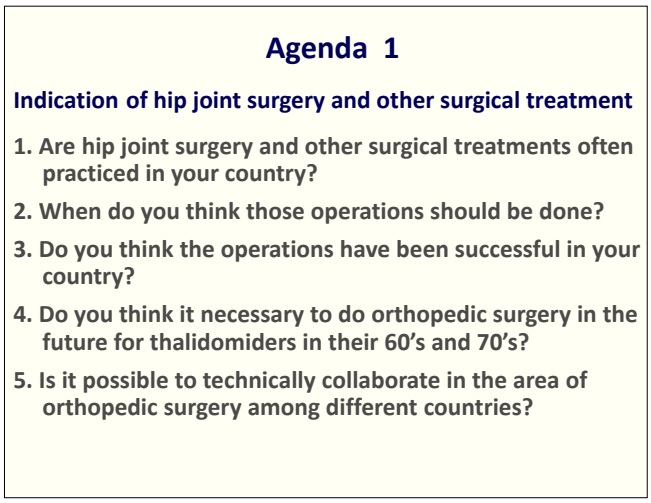
Staff: Thank you very much, Drs. Hinoshita and Schuler-Faccini. And now, let us move on to the panel discussion. Please first allow us a few moments to rearrange the tables.

Panel Discussion

Chairperson: Dr. Fumihiko Hinoshita (National Center for Global Health and Medicine, Tokyo)

Discussants: Dr. Ryoji Kayamori (Teikyo Heisei University, Tokyo)
Dr. Junko Fujitani (National Center for Global Health and Medicine, Tokyo)
Dr. Dee Morrison (The Thalidomide Trust, St Neots, UK)
Dr. Christina Ding-Greiner (Institute of Gerontology, University of Heidelberg, Germany)
Prof. Dr. Klaus M. Peters (Dr. Becker Rhein-Sieg-Klinik, Nümbrecht,Germany)
Dr. Shadi-Afarin Ghassemi (Unversity of Gothenburg, Gothenburg, Sweden)
Dr. Jan Schulte-Hillen (Notfallzentrun Klinik St. Anna, Luzern, Switzerland)
Prof. John Skinner (Royal National Orthopaedic Hospital, Stanmore, UK)
Prof. Lavínia Schuler-Faccini (Federal University of Rio Grande do Sul Genetics Department, Brazil)
Dr. Emma Baple (Royal Devon & Exeter NHS Foundation Trust, Exeter, UK)
Ms. Elizabeth Newbronner (The University of York, York, UK)





Fumihiko Hinoshita (Moderator): Okay, are all of you ready? I have an agenda for the panel discussion. There are three main points.

The first one is indications of hip joint surgery or hip replacement therapy, and other surgical treatment for thalidomiders. The second one is new claimers and new cases with TE. The third one is how to diagnose TE.

Let's start with point number one: indications of hip joint surgery and other surgical treatment for thalidomiders.

Professor Skinner gave a special lecture on total hip replacement surgery. So, hip joint surgery and other surgical procedures are often practiced in your country, the UK. First, I should ask the English panelists about it : how about in your country, Professor Skinner or Dee Morrison.

John Skinner: It's not commonly performed, but then it's likely to be indicated more frequently in the future as patients get older. The question earlier about 1% of patients with thalidomide having joint replacement in the UK the national averages are as follows: 0.8% hip replacements and 1.5% knee replacements. But it is age related. So, by the time you get to 80, 5% of the population has had a hip replacement and 10% has had a knee replacement. So, there is a diagnosis issue and there is also a time issue.

The commonest indication that we've seen has been dysplasia, which is probably a pre-arthritic condition. So, these patients with dysplasia do have a risk for generating osteoarthritis. The indication is always pain there has to be pain. I don't think you would perform hip replacement in the absence of pain. It is a very effective form of pain relief and it should be considered. It does often improve function, stamina, walking, and quality of life. So, it needs to be considered in those contexts really.

Fumihiko Hinoshita: Thank you. How about in Sweden, Dr. Ghassemi?

Shadi-Afarin Ghassemi: As far as I know, we have one

patient who has received a total hip replacement. He was actually displaced from the beginning. In the five PFFD individuals in our group, none of them have even asked for it. Some of them are using wheelchairs, they are not using crutches for walking. Those who have a prostheses, they haven't been, they haven't loaded that much probably. So, they haven't actually asked for it.

I mean, when we did our first study and found that they have a lot of … that they have a much higher risk of osteoarthritis in both hips and knees, that level of osteoarthritis was discovered by computer tomography. So, it was not related to how much actual pain they had. So, they haven't got these symptoms yet.

So, we are prepared. If they come, then we know that it might be because of osteoarthritis. But no, we haven't got more.

Fumihiko Hinoshita: So, do you think you will have an increasing number of chances to carry out hip joint surgery in Sweden in the future?

Shadi-Afarin Ghassemi: Yes, I definitely believe so. However, it doesn't mean that it should be for those with PFFD. It could actually be also for others.

Fumihiko Hinoshita: How about in Germany?

Klaus M. Peters: I think we have the highest number of thalidomiders in Germany. There is an increasing number of patients with coxarthrosis due to hip dysplasia and we have already done several hip replacements. I think it started in the last 10 years.

Fumihiko Hinoshita: Okay. Before the next question, how about it in Japan, Dr. Kayamori?

Ryoji Kayamori: I don't have any knowledge about that. Thank you. Dr. Skinner, in front of you are some Japanese thalidomiders waiting for your advice. They are suffering from hip pain with dysplasia. So, they want to know your advice on surgery. They want pain relief, but they don't know what to do. So, they are asking whether they would be better off going to you in the UK or remaining in Japan and waiting for a couple of years. So, could you give us, or give them, some advice for a Japanese thalidomider with a painful hip? Thank you.

John Skinner: It's a good question. For non-orthopedic surgeons, the best way to screen the hips clinically is, if the patient is supine, lying flat on a couch, if you just ask them to do a straight leg raise; that's a good screening test, because of the length of the lever arm, it puts approximately two times bodyweight force directly through the hip joint. And if that's painful, then the other test is to flex the hip up passively and internally rotate a flexed hip. If that generates pain, then, together, these are two very simple and quick screening tests for hip pathology, and almost certainly degenerative change, irrespective of whether or not there is dysplasia. And I think if we look for patients I think, if patients have got hip pain or leg pain, as they are aging, we ought to be screening them more, because we genuinely have a good treatment for those patients in pain. So, that would be my advice, to look for it. If either of those tests generate pain, or mechanical pain, that's pain on weight-bearing and with-activity, often with night pain, then those are the signs of arthritis. It would certainly be worth getting an X-ray and then evaluating from there.

Fumihiko Hinoshita: So, it's very important for us to do the appropriate evaluation before thinking of the operation. If we found some Japanese thalidomiders who were suffering from pain, and then got the results for the operational indications, we would ask you. Anyway, are there any other comments on this question?

Christina Ding-Greiner: I have a question. How many people with TE in Japan have actually affected lower limbs?

Fumihiko Hinoshita: Lower limbs?

Christina Ding-Greiner: Yeah.

Ryoji Kayamori: We have a lot of thalidomiders who are suffering from hip dysplasia, even though there are only two victims with lower limb defects. Ms. Honma, a thalidomider, is she suffering from one side or both sides?

Otomi Honma: It's bilateral.

Fumihiko Hinoshita: Bilateral, and already undergone surgery?

Otomi Honma: Right. A pelvis rotational osteotomy was conducted.

Ryoji Kayamori: How many people are there who are suffering, do you know that?

Otomi Honma: In Osaka, in Tokyo, and here, five altogether. Five patients have this dysplastic hip among Japanese thalidomiders.

Ryoji Kayamori: There are more thalidomiders who are suffering from hip problems, but they are thinking of having surgery. However, we don't have much knowledge about who is indicated. Any comments, Dr. Yamauchi? (He is the

former president of the Japanese Orthopedic Association.)

Yasuo Yamauchi: My experience is very limited. I have no definite answer. But as far as I am concerned, there is no specific type of surgery applied to thalidomiders. I think, if the patient has pain, I think we may consider surgery, as for other patients. But there is no special technique for the thalidomiders.

Shadi-Afarin Ghassemi: Can I just comment on that because, I mean, having hip displacement, it doesn't need to be related just to the thalidomide itself, and especially in women, I mean it's more common. So, it probably should be more than 10 patients in Japan with hip displacement that are not recognized at the birth.

Yasuo Yamauchi: Well, this hip dysplasia, or dysplastic hip, is very common among Japanese. But, I don't see anything specific related to thalidomide.

John Skinner: I think that's a good point. And the lady talked about the periacetabular osteotomy. There are plenty of surgeons skilled in Japan at treating dysplasia and reorienting the pelvis for dysplasia, whatever the cause. The only problem may be with thalidomide patients with short phocomelia and non-functional upper limbs, whether they can manage protected weight bearing for the longer length of time than an osteotomy may require. But that's the only difference. I agree.

Yasuo Yamauchi: Again, we had what we do for just regular hip dysplasia, the high osteotomy or rotational osteotomy. Again, I don't see anything special for thalidomiders.

John Skinner: I mean, I do agree with that. I think that the ones that I operate on-it's usually the surgery of the dysplastic hip of any etiology. I think there is no particular anatomical variance but it's the rehabilitation, the planning and what's expected, and what needs to be achieved afterwards…

Yasuo Yamauchi: Well, I think the way of rehabilitation is different. As I said about PFFD, rehabilitation is very difficult if the patient has obesity.

John Skinner: And if there are two hips that are differently affected, it's the one that's closest to normal anatomy that's hugely relied upon as the weight-bearing joint that we tend to be replacing. In my experience, the ones with PFFD, the severe malformations of the lower limb, tend not to get joint replacements.

Yasuo Yamauchi: You are asking me? I have no answer.

Fumihiko Hinoshita: Thank you very much, both of you. Then, in Japan, we are generally likely to wait for hip joint surgery or hip joint replacement, especially among thalidomiders. You know, Professor Kayamori talked about it previously. But when is the appropriate timing to do the hip joint surgery? In the 60s or 70s, it that okay? Thalidomiders in their 60s or 70s?

Klaus M. Peters: I think it depends on the pain. As Dr. Skinner already said, if you have pain even during the night, that's the last sign, and then you should do it. And if the patient wants it to be done.

John Skinner: I'd agree with that. I don't think this is age-based at all. It's symptom-based. If the pain is bad enough, you are old enough. And it's very simple, the patients can share in decision making. And the question I always ask is "Is your pain bad enough to consider an operation?" Patients will have a view on that. It's our duty to inform them what the options are, but that's a basic step towards surgery.

Fumihiko Hinoshita: In the case of an Ishizue Foundation member, the woman was in too much pain to sleep well. Under those circumstances, the surgery might be indicated. Any comments or feedback, particularly from the President of the Ishizue Foundation?

Otomi Honma: So, in my case, maybe someday artificial joints have to be implemented, otherwise my daily life will be miserable. I understand it. I recognize it that way. However, I have already undergone the arthroplasty, which means that I am not sure whether the artificial joints fit me well or not. That is the biggest concern. So, if the surgeon can explain my concern well, if I have an opportunity to meet a good surgeon who provides me with a good explanation to overcome my concern, that might be a different story. But I understand that I am indicated for the surgery, but I have not yet been convinced. I have never yet met a surgeon that has convinced me.

This is one of the issues that I am facing right now. There is also a muscle-related issue, which is a headache for me. I am not medical expert. I am a patient with TE and my muscle power is really weak. I am deficient in terms of muscle strength, I feel I am weak. So, that is why the insertion of an artificial joint will make me walk properly, without crutches or canes. That is another concern I have right now. So having an artificial joint means having an osteotomy to remove my own bone, to make space for artificial bones. So, after an artificial joint is implanted, I realize that my native bone is better. I do not want to have that kind of regret. So before

undergoing surgery, I would like to be convinced. So, I am looking for a surgeon who will convince me.

Fumihiko Hinoshita: Well, you mean "I don't know whether I explained it well or not."
As for total hip joint surgery, without enough explanation and of course without any sophisticated technique or support, operational support, you cannot reach the conclusion "I myself should receive that operation." Is that what you wish to say?

Jan Schulte-Hillen: I would like to answer to you. Maybe, if you don't find a doctor who convinces you, I would like to show you my total hip replacement which I had 2 years ago. Prior to the op, I was walking almost like you. I think it (the op) was the best, my best decision within the last 5 years.

Fumihiko Hinoshita: Yeah, you walk smoothly. Exactly.

Ryoji Kayamori: Jan, you didn't tell me.

Jan Schulte-Hillen: I am telling you now.

Fumihiko Hinoshita: I listened to Professor Skinner's presentation. He showed us a very sophisticated example of an operation. Then we are afraid we can find such excellent orthopedic surgeons in Japan or possibly in other countries. We are also worrying about it anyway. Dr. Fujitani?

Junko Fujitani: Allow me to speak in Japanese. I have experience in perioperative rehabilitation of a patient with polio sequelae. We made plans for the surgery much earlier than in normal cases. Before the surgery, I carried out long periods of rehabilitation to build muscle strength. This is because patients with low muscle strength have low walking ability after surgery. The skills of the orthopedic surgeon performing the surgery are also important, but proper training of muscle strength in advance will increase the effectiveness of the surgery. So, I am willing to refer you to many surgeons until you yourself are convinced.

John Skinner: Your concerns are very natural and very understandable. The condition of arthritis causes pain, and the body is very good at doing anything it can at a subconscious level to minimize your pain. So quite often something happens, it is called pain inhibition, whereby if you are about to put weight on that, it's going to hurt. The body switches the muscles off and it makes it feel like you're going to give way. And the reason why people limp is because it's the body's way of minimizing the pain, subconsciously.
Furthermore, the muscles do weaken because you are not using them. You start to use different muscles; you start to use the iliotibial band down the outside. You may get knee pains or you may get outer leg pains because the body is compensating. So, a good orthopedic surgeon will have a look at you and assess what's going on. Maybe a good physiotherapist would be very helpful in looking at the muscle patterning and optimizing your function at this level. But generally, as Jan said, if you get rid of the pain, it's much easier to rehabilitate.

Fumihiko Hinoshita: Okay. Then, we move to the final question of the first agenda. Is it possible to technically collaborate in the area of orthopedic surgery among different countries? You know, in the UK, you have been using 3D copy techniques before practicing the operation of hip joint surgery. In Germany, you have maybe advanced in some respects of the operation. So, I think, and I believe, we should collaborate with the other specialists in other countries. So, let's communicate more with the specialist or surgeons in other countries. What do you say to this?

John Skinner: I think it's not only possible, I think it's essential that we collaborate and talk to each other. The world is a very small place and if we are all facing the same problems it's important that we learn from each other and so we don't keep making the same mistakes. And I think there is a lot to learn. It's small groups of patients, as we've heard; it can be broken down into small parts which are treatable. It's the rehabilitation and the expectations that may be different and we do need to fully understand them all. So, I think we can and should collaborate, and I don't see any reason why we shouldn't or why it's not possible.

Fumihiko Hinoshita: What do you think of that, Dr. Peters?

Klaus M. Peters: I totally agree with Dr. Skinner. Collaboration is a good thing, and we can learn from each other.

Fumihiko Hinoshita: Yeah. So, Dr. Kayamori, let's promote the international collaboration in respect of surgery.

Ryoji Kayamori: I am now too old. I was once retired. Rather than approach me, you should approach Dr. Nobuhiko Haga who is an orthopedic surgeon as well as physiatrist. I hope he could organize to perform orthopedic surgery for hip pain, internationally. Unfortunately, he is not present now (he has some other urgent business).

Fumihiko Hinoshita: Then, you have changed your opinion now, compared with that of several years ago. You previously said we should wait for the operation for as long as possible.

Ryoji Kayamori: Yeah. So maybe the Ishizue Foundation can take central position in organizing, internationally, discussion and cooperation for surgical treatment for thalidomiders with painful joints under the Chief Director of the Ishizue Foundation, Dr. Sato.

Fumihiko Hinoshita: And of course, the specialists in Germany and the specialist in the UK, including Dr. Morrison, please give us some information about surgeries in the future, too. Are there any further comments or opinions on this first question: indications of total hip replacement?

Yasuo Yamauchi: As far as collaboration goes, it depends on whether you are going to operate by yourself. Medical license is required in the particular country. I mean, only academic collaboration can be realized by the way of the Internet, and all kinds of things.

Fumihiko Hinoshita: Thank you. Then, let's go ahead to the next agenda. You know, we have now many new claimers for TE in developed countries, and we also still find new cases with TE, for example, in Brazil. We would now like to talk about the new claimers and the new cases with TE. So, how many people have been diagnosed with TE in Brazil, in reality?

Agenda 2

New claimers and new cases with TE

1. **How many people have been diagnosed with TE in Brazil?**
2. **Why are thalidomiders still born in Brazil? Is there good method to prevent it?**
3. **Have you recently found new claimers for TE in your country? Germany, the UK, Sweden, Brazil and Japan.**
4. **How many people have been really diagnosed with TE in your country in recent years?**
5. **Why do new claimers claim to be true thalidomiders now? Do you have any opinion about the reason?**
6. **Do you have any newly recognized thalidomiders in your country? Do they get any pension and/or compensation as thalidomidrs who were diagnosed long ago?**

Lavinia Schuler-Faccini: I think I have already addressed some of them, but, after 2000, we have confirmed seven cases. These are the ones that I presented, and one was stillborn. Okay? So, six born alive, one stillborn, and one has died, confirmed. However, as thalidomide never disappeared from Brazil, there are many claims. Many claims are from people born during the 1970s and 1980s, they are only claiming now. So, it was mentioned that for what we call the second generation of thalidomide-affected people in Brazil, which means those born between 1965 and 2000, the figure is around 120. But at that time diagnosis was not clear. Not everyone had gone through proper genetic or dysmorphological evaluation. As Dr. Emma Baple mentioned yesterday, there were some diagnoses of phocomelia that were not really phocomelia, but it was accepted. These new claimers, they don't look exactly, they only went through a legal route to get the compensation. So, it's not like a medical patient interview that you can go through. Many times, when they feel that it's not thalidomide, they say "Okay, I don't want to go further, because if you tell me that I am not, I am going to be denied the compensation." So, what I can say is that, presently, there are many new claimers, but we didn't carry out any new diagnoses, besides these 120 and the seven more after 2000. Okay?

Fumihiko Hinoshita: Okay. So, you found the true thalidomiders to be about 120, plus seven new cases.

Lavinia Schuler-Faccini: Yes.

Fumihiko Hinoshita: But there are many subjects who claim to be real thalidomiders. In fact, they may have other/different diseases, you know.

Lavinia Schuler-Faccini: Yes. Because limb defects were one of the commonest birth defects. So, a claim is just claim. So, there are many unilateral amputation defects that we know are other conditions. Ectrodactyly, Poland anomaly, unilateral, many unilateral defects. But what I want to stress is that in all these confirmed cases we are sure of the exposure because we followed the mother, we followed the baby. No one had unilateral defects. So, I totally agree we are going to go through the diagnosis of TE on DATE and ValiDATE. I totally agree with Dr. Baple that bilaterally it can be asymmetric, because we are all asymmetric. But unilateral defects are not part of the thalidomide syndrome.

And what has happened, I think because even in the Brazilian paper published by my supervisor there were some unilateral defects. I think it's the same as occurred with these patients that had children affected. Thalidomide, prior to and during the 1960s, was used by many. So, of course, by chance, even someone taking thalidomide could have a child with a Down syndrome, for example. We know that Down syndrome has nothing to do with thalidomide use. So probably there are some coincidental cases, just by chance, because after that we never saw any persons with unilateral defects with confirmed maternal exposure.

Fumihiko Hinoshita: Okay. Then, did you find any new cases in the developed countries? I mean, for example, in Germany. Dr. Greiner, how about it?

Christina Ding-Greiner: I found some data from 2017, from the Foundation, in the yearly newsletters. You can read: "Since 2009, we have had 833 new claims." Later I found that in the last 5 years, from 2014 to 2018, there were 21 claims accepted and 211 new claims not acknowledged.

Fumihiko Hinoshita: And the officially recognized thalidomiders, 10 or so, in Germany, right?

Christina Ding-Greiner: Overall, 21 were accepted in the last 5 years and 211 were not acknowledged. So, you see the proportion.

Fumihiko Hinoshita: Okay.

Lavinia Schuler-Faccini: May I just ask a question? My question is very simple. Of these 21, were all born in Germany? Because I know of Brazilians that were already confirmed in Brazil and now they are claiming in Germany. So, I am just wondering if there is superposition of cases, that we are not counting twice. Just a question.

Christina Ding-Greiner: I can't tell you. I have not had the time to check. It was the day before I started travelling. But I can look, I can ask the Foundation.

Jan Schulte-Hillen: I can tell you: there were two from Brazil.

Lavinia Schuler-Faccini: Okay.

Fumihiko Hinoshita: Okay. Overlapped.

Lavinia Schuler-Faccini: So, a double count here, because those were already in Brazil.

Fumihiko Hinoshita: Okay. Is there any opinion about it? Dr. Peters?

Klaus M. Peters: Every year I see about 10 to 15 people enquiring about claiming, but most of them are not thalidomiders. I think one or two per year, they may be possible ones.

Fumihiko Hinoshita: How about it in the UK?

Dee Morrison: We have a small number of new claimants who we do accept into the Thalidomide Trust. As I say, it's a small proportion and I've forgotten the actual statistics. In 2016, I think, we accepted six claims from the lawyers. In 2017, we had two people who came into the Trust. And we have just sent two to St George's for them to have a look at. So, the numbers are small, but they are still coming through. Some of these cases are very difficult to decide. We look at the pattern of damage, as well any history of ingestion. And then, finally, we have a committee that looks at all the information together. So, we have lawyers on that committee, and medical experts, and it's a combined decision. Some of the cases are difficult, to try and get the consensus. I think we've had 30 submissions since 2017. So, out of 30, we have put two forward. So, the numbers that actually go to committee and then get accepted are very small.

Fumihiko Hinoshita: Okay. Even after the report by the group of Dr. Emma and Professor Mansour, you can still have difficulty in really diagnosing TE in the UK.

Dee Morrison: Yes, and we are quite favorable in our approach. If it's 51% more likely than not that a new claimant has a pattern of the damage consistent with that caused by thalidomide and if it is likely that the mother had access to thalidomide in the susceptible time period during pregnancy, we will accept the claimant into the Trust.

Fumihiko Hinoshita: How about it in Japan, Dr. Kayamori?

Ryoji Kayamori: Just yesterday, I presented my two cases. So far, we don't know that these cases are really thalidomide embryopathy (TE), or not. Judging from DATE, a diagnostic algorithm for TE, with an emphasis on the epidemiological point of view, the first case is more likely to be a thalidomider. However, the second case was born in 1971, nine years after recall of the drug, even though her malformations really fit TE, with agenesis of the right kidney.

Fumihiko Hinoshita: Okay. What is the reason, why would those people in Japan claim to be thalidomiders themselves? The reason, why? Could you comment on the reason? Why would they claim to be real thalidomiders? I mean new claimers.

Ryoji Kayamori: Yeah, new claimers. Dr. Sato, as Chief Director of the Ishizue Foundation, could you explain this to us? These two cases were referred from the Ishizue Foundation, were they were involved in TE?

Tsugumichi Sato: In the first case, the mother said to him that his disability is due to thalidomide, but his parents did not claim at the time of the resolution of the court in 1974. Furthermore, his mother had health problems. In his family, talk about a thalidomider is not allowed. So now he has decided, by himself, to claim; he has claimed whether he is a thalidomider.

Fumihiko Hinoshita: How about another one?

Tsugumichi Sato: Another one, the second case. I don't know much about the second case. Yeah, the second case is similar. In the second case her parents also did not claim,

they were worried about discrimination in the rural area in Japan.

Fumihiko Hinoshita: I see.

Tsugumichi Sato: In the third case, her or his mother could not write characters. She was unable to fill out the claim form.

Fumihiko Hinoshita: So, it appears that in Japan there are no new claimers who would like to get, or who would like to seek, some compensation or monetary gain. Is that right?

Tsugumichi Sato: Not yet.

Ryoji Kayamori: All the Japanese cases are too modest to ask their mothers or fathers whether they are suffering from TE or not; they are not moneywise. So, that is the one of the characteristics of the Japanese new claimers.

Fumihiko Hinoshita: But in Germany and Brazil there are so many new claimers. I am afraid that, among them, there are some cases with the deformities who would simply like to get some monetary assistance or compensation. How about it, Dr. Ding-Greiner?

Christina Ding-Greiner: I don't have any statistics, but as far as I have spoken to people, I found many people with hearing loss, with deafness, without orthopedic damage. They didn't know that they were thalidomiders, and they oriented themselves to associations of deaf people. And now they are growing older. They are more vulnerable, too. They are starting to have problems with arthrosis, with the spine, and with internal damaged organs. And they remember what was said in the family - maybe they could be thalidomiders.

The other group that I spoke to were people with a low extent of damage and disablement. In some families, it was taboo to speak about thalidomide and, if almost no bodily deformities were to be seen, children weren't told. Now these people are getting older, and they are suffering pain and becoming increasingly disabled. They are asking more questions in order to find out about thalidomide.

All others who were severely damaged, I suppose, were screened out as children. They were examined and officially acknowledged. The new claimers are mainly people who, at first glance, do not appear to be thalidomide-affected people. For the families, it is difficult to live with the idea of having a thalidomide-affected child, but for the mothers it is even worse: it is very difficult to say "I took thalidomide, and therefore I have such a child." Most of them feel very guilty.

Fumihiko Hinoshita: Okay. In Brazil, there are many new claimers who would be absolutely free of TE, right?

Lavinia Schuler-Faccini: I am sorry? In Brazil?

Fumihiko Hinoshita: In Brazil there are so many new claimers, but in reality, free of TE at all, right?

Lavinia Schuler-Faccini: Yes, very few, I think, although I must say something. There are two different things. One is the medical diagnosis and the other is the law. Okay? So in Brazil, if you cannot prove if it's a compatible case, and if you cannot prove other cause, and it's compatible with TE probably he is going to be recognized. So what I know is that some cases are accepted in Brazil as having TE, while in Germany they have refused to be recognized. But what I am saying is the same. Now, like 60 years later, it's very difficult. If it's not the complete, the characteristic, case, it's very difficult to know whether the mother took thalidomide or not. So, in these less-characteristic cases, if it's not another genetic syndrome, it's difficult to say. But what I am saying is that for those born in the 1970s, 1980s, and even 1990s, it's really, really rare to have a new case. There are many claimants but very few are considered compatible. Now, we have many other opportunities of genetic testing, so we can now rule out Holt–Oram syndrome, which we were unable to do earlier.

So, I know that in this group of 120 there are some patients with Holt–Oram syndrome. They might also have Okihiro syndrome. So, recently, because of oriented genetic screening, not full genetic screening, but oriented by diagnosis, we were able to diagnose more genetic conditions.

Fumihiko Hinoshita: I see. Okay. Do you have any further comment?

Ryoji Kayamori: Excuse me. May I ask Professor Faccini? You mentioned, as an indication for a thalidomide drug, you mentioned the lupus, AIDS, and individual indications besides leprosy and multiple myeloma. So, I wonder if they/ the new claimers complained of AIDS or the other indications.

Lavinia Schuler-Faccini: No. It's interesting. That's interesting. Because of those, among those claimers, no one specified these diseases that you have mentioned. It's not possible-thalidomide is not in the drug stores, it's not in the pharmacies-it's the government. So, to have a patient using thalidomide, the doctor has to fill in a form and say I am going to give this patient this medication. So, if there is now

any claimer, it may be that our patient is related to someone who is registered. But not one of these obscure cases was registered, besides those ones I presented. I was clear.

Ryoji Kayamori: Almost all new claimers include leprosy?

Lavinia Schuler-Faccini: No. That's interesting. It's very important. These cases were not claimers. We diagnosed them. We went there and said "Okay, this is a thalidomide case." The claimers are different. They are in the population, and they enter as a claimant, yeah, for the legal system. It's very important, because these new cases, we ascertain them. It was not true. But the last patient truly obtained thalidomide though, that's the reason why she was certified as a thalidomide victim. There are two realities. The last patient, I saw her only for the past 5 years. She got the compensation. Because she went through the legal system, she got the compensation. But she didn't get the medical attention. That is quite schizophrenic. Double reality. You can receive the compensation yet you are not receiving the proper medical care. But the claimers, the other claimers, none are in these special programs.

Ryoji Kayamori: Could you give us individual indications, what kind of individual indications?

Lavinia Schuler-Faccini: Yes. You know, the number of diseases potentially treatable by thalidomide or its analogs is about 400, including immunological conditions, cancer, and skin disorders. So, the doctor has to show that there is literature evidence, and he can then request medication from the government for a specific patient. The request is going to be reviewed. It's not like its immediately approved. It is a process. But it's possible. Okay?

Fumihiko Hinoshita: Okay. Do we have any comment from the UK side? I mean, Dr. Baple and Ms. Newbronner or Dr. Morrison, comments regarding new claimers in the UK?

Dee Morrison: No. I've just passed on two cases in the last 18 months. So then, we had six in 2016, two accepted in 2017 whom we haven't seen, and the two going forward now.

Fumihiko Hinoshita: So, in the UK you have recognized two thalidomiders? New cases, I mean, recently?

Dee Morrison: Yes. We've had two cases accepted in 2017.

Fumihiko Hinoshita: Just two cases.

Dee Morrison: And then we've got two that we have just passed on to St George's, just recently, that they haven't looked at yet. Previously we may have asked St George's if we weren't sure about the pattern of damage. And that's maybe where the confusion is lying. But we've certainly got two cases that they haven't seen yet, that they are about to see.

The pattern of damage will be looked at but also how much access the mother had to thalidomide, it's not just the pattern of damage. We don't ask for proof, but we do consider the history. The timing is also very important.

Shadi-Afarin Ghassemi: How old are they?

Dee Morrison: They will be in the age range; these are in the age-specific range. Yes. There would have to have extremely good evidence of proof of access to thalidomide if they are outside the age range by about 10 years, because the drug was withdrawn.

Fumihiko Hinoshita: Are there any new claimers in Sweden?

Shadi-Afarin Ghassemi: No. In the beginning, when the government, except the monthly payments that they receive, according to their reports, and it depends on how malformed they are, how many malformations they have. It was also at the beginning of the century that the government paid, well, quite a high amount as one payment.

Then there were some people coming. Actually, a woman born in 1957 was recognized, which is very, very early, because there was no thalidomide in Sweden before 1959. But, as you said Dee, it was because of the history, because the father was a chemist and visited Grünenthal in Germany. So, he took the medicine with him. And I think the mother never told anyone that she actually took it. I mean, the parents probably agreed not to say anything. So after that payment, she submitted a claim, and she was actually approved as well. So, the highest number of TE individuals in Sweden has been 115.

But when we started it was 108. There has been a death and actually one murder, and some that, I mean, I think some just move on and never have any further contact, so they are no longer members. But after that, no, we haven't had any new claimers.

Fumihiko Hinoshita: Okay. Then you have newly diagnosed TE, two people in the UK, and more than 10 people in Germany. Then, your government or the trust would compensate him or her, just after the recognition of TE in Germany and in the UK?

Dee Morrison: Sorry, you are talking about compensation?

Fumihiko Hinoshita: Yes, compensation started.

Dee Morrison: Yeah. Okay. What we'd do is, if they are accepted into the Trust, they would receive compensation from Diageo, a drug company responsible for those who distributed thalidomide in the UK. They would receive a lump sum and they would then receive an annual allowance, the same as everybody else. What they've missed out on is the annual grant every year, up to now. But the lump sum they still get and they still get the annual grant. And in addition, they will then get the health grant every year annually, from the government.

Fumihiko Hinoshita: And in Germany?

Klaus M. Peters: In Germany, we have some medical commission of the proper diagnosis. They decide. And if they decide "no" in the first round, maybe that claimer has to seek justice.

Fumihiko Hinoshita: Okay. The reason why I choose this agenda, for new claimers and new cases with TE, is partly because it's very tough and difficult in some cases to diagnose TE. So, we proceed to the final agenda: How to diagnose TE? Now, we are accepting new panelists this time in this symposium. For example, Dr. Baple and Professor Faccini. Then, let's talk about how to diagnose TE.

Agenda 3

How to diagnose TE?

1. **Can you summarize the essence of DATE again, Dr. Baple?**
2. **How do you diagnose TE in your countries?**
3. **What do you think of DATE proposed from the UK?**
4. **What do you think are the essential and/or important items to correctly diagnose it?**
5. **Are you planning to newly determine how to diagnose TE in Brazil and Germany? We just started to think of how to diagnose it in Japan.**

First of all, can you summarize the essence of DATE again, Dr. Baple? And then. do you think it's a final version of diagnosing TE?

Emma Baple: So, the premise of 'DATE' or 'ValiDATE,' as we are calling it nowadays, is that it can potentially provide a numerical score for the likelihood that an individual's congenital abnormalities were caused by thalidomide. So, that's the premise of it. And what we did to arrive at that weighted score was to look at the different abnormalities that are seen as part of thalidomide, and characterize those as abnormalities that are found very commonly in TE and that are not found commonly outside of TE. Those would get the highest scores.

There are certain abnormalities that are more commonly found together, and they would get an enhanced score. And at the other end of that spectrum, we have abnormalities that we felt are not part of TE. These included isolated unilateral limb defects, as Lavinia mentioned earlier. So, we put the diagnostic aid or algorithm together and presented, at the WHO Conference in 2014, the features that we felt would fall into those different categories, to try and reach a consensus on what we now have included in the manuscript. We want ValiDATE to be available to all clinicians seeing patients with possible TE. So, it will be available through a Web-based interface. There will be a small cost associated with using it, but it's not-for-profit. It will be maintained by an independent trust that's overseen by the Thalidomide Trust. It will be called the 'ValiDATE Trust', so that the algorithm can be revised in the light of any new knowledge and it can also be maintained.

Fumihiko Hinoshita: Good news. Anyway, I should ask the same question to other specialists in other countries. For example, in Brazil, Germany, Sweden, and Japan, how do you diagnose TE in your country? For example, in Germany, do you agree with the proposal of 'DATE' from the UK?

Klaus M. Peters: Yes. I think it's a good new tool. We haven't used it yet because it's relatively new, but I think we will also use it in future because I think it's very helpful. Up till now, we have a criteria catalogue for the damages. We use clinical examination, X-rays, and ultrasound, for example, missing kidney and also gall bladder, and so on. A definitely defined catalogue.

Fumihiko Hinoshita: Okay. What do you think of it, the 'DATE' from the UK? Dr. Ghassemi from Sweden?

Shadi-Afarin Ghassemi: Well, 'ValiDATE' is, I think, going to be a very, very useful tool really. I think it's just amazing. Because I know that at the Ex-Center in Stockholm they also use X-rays. Many individuals actually got their diagnoses during childhood. And those who came later on, as adults, have X-rays. That was very convincing at the time. But then I realized that it maybe shouldn't be so. Even only triphalangeal thumbs have been a reason to be approved as a thalidomider (actually there are a couple).

So, I think these tools are very, very nice. But God forbid if new cases emerge in Sweden. I must say, because it's so, so restricted using, I mean, all the fertile women, and even men, they go through, they have to write a consent how to

use, how to behave. And women who are using thalidomide, especially with some blood cancers, they have to go through pregnancy diagnoses every 6 weeks. So, it's nothing that, we don't have the crime of abortion of course in Sweden.

Fumihiko Hinoshita: What do you think of it, Dr. Schuler-Faccini?

Lavinia Schuler-Faccini: Okay. In Brazil, the diagnosis is stepwise. It has changed over the years, but of course it's mostly clinical. It involves exclusion criteria. First, there are some basic things that it's more likely to validate. Unilateral – out. Ectrodactyly – out. There is a panel of various experts that receive photographs and X-rays. That's the first step: photographs, X-rays, any type of evidence, the history, year of birth, and all. The evidence of exposure is, I must say, useless, because it's very difficult to be confident and reliable. So, I am going to say something that is very interesting; you might say it's true or not. The people who have proven maternal exposure, the guilt from parents, and even from the child that learns as an adult, that says, okay, like open to public, that the mother took or something. Nowadays, it's very, very difficult. So, in the majority of the cases, the claimants are not certain that their mothers took (the drugs). It's like a history that has become repeatedly established, or instructed by the lawyer. And because it's very similar, different claimants come with the same history, without any confirmed evidence.

So, what I mean is the diagnosis is mainly clinical, but it includes which type of exposure, if there is anyone in the family with leprosy or multiple myeloma or AIDS. We begin with X-rays and photographs.

If there is enough basic evidence that it's compatible, it is referred to a medical geneticist. These consultations can be paid by the government. So, the government pays because the legal system requires it. Later, they also pay for genetic tests. In Brazil, if you are poor, you have access to a lawyer, free of charge. So even if they don't gain the cost, they won't be paying. If you are richer, you have to pay for these things and if you gain the cost, you refund it. So, what I mean is that it's stepwise, involving mostly clinical criteria, and you are using almost the same algorithm as Dr. Emma presented, more intuitively (but not very strict in the sense). If I cannot prove that there is another genetic condition or another environmental condition, and the case didn't fit any of exclusion criteria, it is going to be accepted. Okay? So if there is doubt, the claimant has the benefit.

Fumihiko Hinoshita: Thank you. In Japan, the Japanese research group has just started to determine the diagnosis criteria or conditions to diagnose TE correctly. By the way, Professor Kayamori, do you have any comments about how to diagnose TE?

Ryoji Kayamori: Yeah. I want to ask Dr. Schuler-Faccini. She showed us an algorithm, a diagnostic algorithm, not DATE, based on the preaxial or morphological characteristics. You showed us one slide. It is very good. In Brazil, it's difficult to use the DATE system because it looks like it is easy to obtain the thalidomide drug. So, in that situation, the DATE system cannot be used. So, we want to know what is the minimum characteristics in TE.

Lavinia Schuler-Faccini: Yes. This flowchart that I showed is what we developed before ValiDATE, before the WHO meeting. So, it has to be bilateral. It has to be preaxial. Or a thumb or radial X-ray needed. But if you don't have the confirmed exposure, only an ear defect, at this moment it's not going to be accepted. You have to have some orthopedic malformation.

But as far as I know, in Brazil, to date, only ear anomalies are not asking for compensation, it's more related to limb anomalies. We now presently carry out molecular testing, for Holt–Oram, Roberts, and SALL4, because it's impossible to make a differential diagnosis and, in some cases, a specific diagnosis. But these three conditions are likely to the basics; they must be present, to qualify for compensation. So, you have to have negative test results for these three genetic conditions before being eligible to receive the compensation.

Ryoji Kayamori: May I ask one more question?

Lavinia Schuler-Faccini: Yes, of course.

Ryoji Kayamori: If you have a patient requiring a differential diagnosis, for instance, for Okihiro syndrome, the absence of radials, and Duane syndrome, is it easy? We don't have any knowledge about genomic diagnosis, so, is it easy, or how long does it take to get the results?

Lavinia Schuler-Faccini: Okihiro, there is one gene, SALL4, and we sequence the gene. We didn't have many patients for differential diagnosis. Presently, there is a student of mine carrying out these tests. When we have one Variant of Uncertain Significance (VUS). If we find a VUS, we don't roll out because we are going to say: "Okay, we have not enough evidence that this VUS is the cause." So, only if you have a pathogenic or possible pathogenic, according to these international criteria, to rule out/to confirm Okihiro.

Ryoji Kayamori: We understand your situation. The important things that make a diagnosis of TE comprehensive with the clinical history and findings, X-ray films, and other imaging. Genetic testing is not indispensable, but a final approach to make a differential diagnosis.

Lavinia Schuler-Faccini: Yeah, the genetic test is done…

Fumihiko Hinoshita: Now, we have the advanced technique of genetic or genomic analysis. So, what or how should we use or utilize the genetic or genomic analysis for the new claimers or the people suspected to have TE?

Lavinia Schuler-Faccini: It was my question to Emma yesterday, and then we agreed. We use the genetic test only if we have a phenotype, then I say it's thalidomide or Okihiro or Holt–Oram or Roberts. So, I never use like a screening test. It's going to be a headache and it's impossible. So first, a very clear clinical description. Because these three syndromes are very much alike in terms of the genetics. Sometimes there are other congenital abnormalities, but it depends, you know, on your medical assessment. It starts with a very good medical consultation, and then you proceed to the other tests. Sorry.

Fumihiko Hinoshita: Is there any other opinion from the specialists in other countries? Okay. Dr. Baple?

Emma Baple: I completely agree with that consensus. I think there is a move to do more complicated genomic testing, so exome or genome testing. Certainly, I know people who have done whole exome sequencing and trawled through all of the variant data, which I think is actually quite dangerous. And some people would argue for an extended panel, but I think that, in reality, you have to get back to your clinical skills, examine the patient, determine a differential diagnosis, and test them for the disorders that you think that they might have. I would probably add in, and I presume you also do, a microarray for some patients.

Lavinia Schuler-Faccini: Yes. Yeah.

Emma Baple: Yeah. So, I would also add in a micro and I would do SALL4, as well as SALL1. Would you agree with that if you had it available, Lavinia?

Lavinia Schuler-Faccini: Yes.

Emma Baple: Yes, I would do SALL1 and SALL4.

Lavinia Schuler-Faccini: Yeah, SALL1, too. Yes.

Emma Baple: Because Okihiro and Townes–Brocks are pretty difficult to differentiate from each other. So, yeah.

Fumihiko Hinoshita: Dr. Schulte-Hillen?

Jan Schulte-Hillen: I just wanted to ask if there is any new test available for Holt–Oram syndrome, because, as far as I know, it has a sensitivity of only 0.3. That means two-thirds of the cases remain undetected. So, the test could not be used to actually rule out the Holt–Oram syndrome. Are there any new developed tests, or is that still the situation?

Lavinia Schuler-Faccini: I am going to ask Emma later, but to my knowledge, no. And we know, that's the reason we say it in doubt, the claimant has the right. So, what I mean is that there might be some Holt–Oram cases that we were not able to diagnose, and then the doubt goes in favor of the claimant. But I don't know if you have more information about the molecular tests for Holt–Oram.

Emma Baple: No. Except that I guess we can do more accurate copy number variant analysis nowadays than probably that number indicates. And I guess the other thing I would say is there are some clinical differentiators. So, I think there are some aspects of Holt–Oram that clinically are slightly different from thalidomide, and that you wouldn't necessarily see in thalidomide, like the particular EKG or ECG abnormalities you sometimes see in the shape of the shoulders is quite characteristic.

Lavinia Schuler-Faccini: Yes. Yes.

Emma Baple: So, whilst saying that any reasonable doubt is in favor of the claimant, I think there are some clinical indicators. And it is a diagnosis that you'd want to get correct.

Lavinia Schuler-Faccini: Yes. You know, that's the question I mentioned when we have a separation between the legal and the clinical sides. I have a patient, rather, I had a patient ("had" because she abandoned me). But I am going to tell you why because I was pretty sure that it was Holt–Oram. There was no evidence. And she was born in a place that had no thalidomide. The phenotype was more Holt–Oram than TE. So, I counseled her as Holt–Oram. But she was really angry, saying "Okay, you are denying me the right I have for this compensation." So, I said "Okay, it's different information. I am your doctor. You have the right to approach the legal system." She went and she was successful, not with my report, because of the legal system she entered. It was before having the test. And now that she has the compensation, she no longer wants to be tested. Sometime, when I met her, I told her "Okay, you are protected by the secrecy of the medical system. So, if you want …?"
But she doesn't want. It's too risky for her to have a test that

might be negative. So, the only thing I said is "Okay when your child is grown up, please tell her that perhaps it's good to have a genetic test or something. That it's protected. But it's a question because it's autosomal dominant." So, for her, okay. But for your grandchildren, there might be a risk. So, okay, that was how our medical doctor–patient relationship ended. But I do think I tried to convey the message. She probably understood. She was a patient with a good education.

Emma Baple: Let's hope so.

Fumihiko Hinoshita: Okay. Thank you very much. Anyway, to diagnose TE correctly and genetically, it is a delicate problem. Anyway, the hot discussion continues, but I think the time is over. Finally, are there any other comments from other specialists or from the floor? Final comments?

Lavinia Schuler-Faccini: I have just one final comment.

Fumihiko Hinoshita: Okay.

Lavinia Schuler-Faccini: I think my final comment is addressed to Dr. Handa who spoke yesterday, and to all the biochemists. We have to find a non-teratogenic drug. Because thalidomide is important. You are on this side, but I have friends with multiple myeloma, and multiple myeloma was a death sentence until some years ago. Now, they are living more than 5 years. Even in Brazil that it's underdeveloped. And when I see these patients with leprosy, they are suffering. So it's not possible to say "Okay, you must not take this medication, but the men can take it."

Regarding the future there is one question here: how to prevent? We need to find a drug that has the therapeutic potential and non-teratogenic potential. But, that's my opinion.

Fumihiko Hinoshita: Okay. Thank you very much for collaborating together with us for the panel discussion here. We have heard many good results and conclusions here in this panel discussion. And, of course, all of us came to mutually know the real situation in other countries regarding TE.

Anyway, thank you very much again to the panelists and to the audience. I would now like to close this panel discussion. Thank you.

Closing Remarks

Fumihiko Hinoshita, MD, Ph.D.

Staff: Dr. Hinoshita, all the panelists, thank you very much. At the very end, we would like to receive closing remarks by Dr. Hinoshita. So, let's continue in this way.

Fumihiko Hinoshita (Chairman): Well, thank you very much for the in-depth discussion on important themes in thalidomide embryopathy or TE over the past 2 days. In fact, investigations and research for the Japanese thalidomide victims have continued since the 1960s, originally by the Teikyo University group and recently by the research group of Ministry of Health, Labour and Welfare (MHLW), first organized in 2011.

However, leading up to the time of the first international symposium on TE in Tokyo, held in 2015, we Japanese group members only knew of a few or several who were engaged in the research activities and support for the thalidomide victims throughout the world.

I believe that our vigorous international activities and the first International Symposium on TE, held in Tokyo in 2015, and in particular the presentations of the invited European speakers have greatly influenced the TE researchers, not only in Japan but also in Europe.

These activities have played a role in promoting international collaboration and exchange of valuable information between the specialists in Europe and Japan. In addition, these international activities might facilitate clarification of more specific TE-associated problems and promote future consideration of specific measures to overcome such problems.

Together, these activities progress clinical research on TE in countries such as Germany, the UK, Sweden, and Japan. Moreover, I feel now that the researchers would be more stimulated, and learn more things from colleagues abroad. Therefore, the present international symposium is very valuable in many senses. We have newly invited guest speakers. Professor Handa spoke on teratogenicity and the pharmacological mechanism of thalidomide. Professor Skinner spoke on total hip joint replacement. Professor Faccini reported new cases with TE in Brazil. Dr. Baple reported on how to diagnose TE. All of the themes they discussed are very important. They are fresh topics that were not included in the previous symposium.

Next slide, please.

Though we have not completely resolved all of the difficult TE-associated problems, all of us continuously work towards a resolution. Importantly, it is imperative that we do not forget that we have great colleagues worldwide, not only in Europe and Japan, but also in Brazil and other countries. And I really hope that this global network on TE will successfully push forward and function well in the future, too.

Finally, I would like to thank you all for joining us yesterday and today. In particular, I would like to thank Ministry of Health, Labour and Welfare for their great assistance, and everyone here. Moreover, I want to wish you safe travels back home. I also welcome those of you who will be touring Japan from tomorrow. Thank you very much again, and so long.



Proceedings of the 2nd International Symposium on Thalidomide Embryopathy in Tokyo

Published on September 1, 2020
Editor: Fumihiko Hinoshita, Department of Nephrology,
Center Hospital of the National Center for Global Health and Medicine (NCGM)
Publisher: The Research Group on on grasping the health and living situation as well as creating
the support infrastructure for thalidomide-impaired people in Japan (Head: Fumihiko Hinoshita)
Grant-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical
Devices from the Ministry of Health, Labour and Welfare, Japan
c/o Department of Nephrology, Center Hospital of NCGM
1-21-1, Toyama, Shinjuku, Tokyo 162-8655

Copyright©2020

Printed in Tokyo, Japan

新型コロナウイルス感染症の
(COVID-19)
基本的知識と生活上の対応

－サリドマイド被害者の皆様へ－





厚生労働行政推進調査事業
「サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築」研究班

目　次

COVID-19 の基本的知識と生活上の対応

－ サリドマイド被害者の皆様へ －

はじめに ..... 日ノ下文彦　1

I.　COVID-19 感染症とは ..... 長瀬　洋之　2

II.　COVID-19 の感染予防策と感染確認 ..... 長瀬　洋之　4

III.　COVID-19 に対する歯科 / 口腔外科からのアドバイス ..... 丸岡　豊　10

IV.　COVID-19 流行期に食事で気をつけるべきこと ..... 田上　哲也　12

V.　COVID-19 の巣ごもり時期にやるべき運動 ..... 藤谷　順子　14

VI.　おわりに ..... 長瀬　洋之　16

はじめに

2019年12月に中国の武漢で初めて確認された新型コロナウイルス感染症（COVID-19）はあっという間に世界中に拡がり、おそらく歴史に残るパンデミック（世界的大流行）となってしまいました。その結果、人類のすべての活動にブレーキがかかり、経済の低迷だけでなく、政治、文化、芸術、研究、国際交流、観光などあらゆることに悪影響が及んでいます。

わが国では、2020年春の第一波に始まり、夏の第二波、さらに同年冬から2021年初頭にかけての第三波に至るまで、COVID-19により国民生活のすべてが大打撃を受け、「ステイホーム（Stay home）」や「巣ごもり生活」が当たり前となってしまいました。おそらくサリドマイド被害者の皆様もマスク着用、三密回避、手洗い、手指消毒、うがいなどを心掛けながら、不安な日々を送っていらっしゃるのではないかと想像しております。

そこで、少しでもCOVID-19感染症とこの病気に対する感染対策を理解していただき、安心して暮らせるよう、研究班で小冊子を作成することに致しました。呼吸器内科の専門家である長瀬先生はもとより、他の研究班員もそれぞれの専門領域におけるアドバイスをまとめております。

最後に、この冊子を皆様の感染対策や健康管理に役立てていただき、COVID-19に罹患しないのはもちろんのこと、日常生活の中でCOVID-19を極端に怖れずにすむよう願ってやみません。

2021年2月

厚生労働行政推進調査事業
「サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築」研究班
研究代表者 国立国際医療研究センター病院腎臓内科　日ノ下　文彦

Ⅰ COVID-19 感染症とは

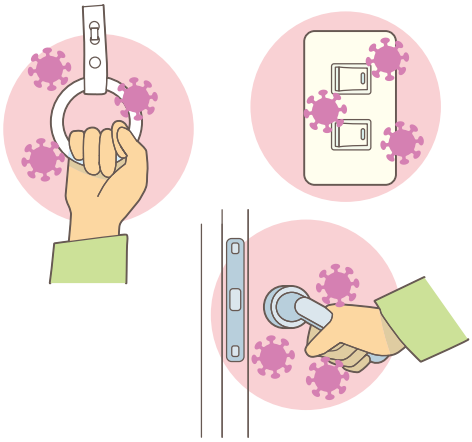
① 新型コロナウイルス感染症とは

ヒト由来のコロナウイルスはかぜ（感冒）の原因の 10 ～ 15%を占める病原体として知られていました。しかし、より重症な肺炎として、2002 年に中国・広東省に端を発した重症急性呼吸器症候群（SARS）、2012 年にアラビア半島で中東呼吸器症候群（MERS）が報告されました。そして、2019 年 12 月から中国･武漢市で発生した肺炎の原因が、新型コロナウイルス（SARS-CoV-2）です。SARS-CoV-2 による感染症を COVID-19（新型コロナウイルス感染症）と呼びます。

② どのようにして感染するか －飛沫感染と接触感染－

感染した人がせきをして飛んだ飛沫に含まれるウイルスを、別の人が口や鼻から吸い込んでしまうのが飛沫感染で、新型コロナウイルス感染の主体と考えられています。

接触感染とは、感染した人がせきを手で押さえた後や、鼻水を手でぬぐった後に、ドアノブなどに触れ、その場所に別の人が手で触れ、鼻、口に再び触れることにより、ウイルスが体内に入り感染することで、これも感染の原因となります。新型コロナウイルスは、プラスチックの表面では最大 72 時間、ボール紙では最大 24 時間生存するとされています。



空気感染とは、小さい病原体が空気中を漂い、広範囲に感染を拡げる状態で、麻しんウイルス（はしか）、結核菌が知られていますが、新型コロナウイルスの主な感染経路とはされていません。



症状が出ている人が感染をうつす主体ですが、発症から間もない時期でも感染性が高いため、感染が拡がる原因となっています。発症 2 日前から発症後 7 ～ 10 日間程度の期間に、感染性があると考えられています。

また、COVID-19 を発症した人の家族内感染率は 11.8%とされています。10 歳代の患者さんの家族内感染率は 18.6%と高く，成人患者さんと同等以上でしたが、0 ～ 9 歳の患者さんからの家族内感染率は 5.3%と低かったとされています。家庭においても、症状がある家族がいる場合、マスク着用、手指衛生などの予防策をとる必要があります。

コロナウイルス感染症は一般に温帯では冬季に流行しますが、COVID-19 も冬季に流行の拡大がみられています。

③ どのような症状が出るか

初期の症状は、インフルエンザや感冒に似ており、COVID-19 を区別することは困難ですが、インフルエンザにおける突然の高熱、COVID-19 における嗅覚・味覚障害などはそれぞれに特徴的とされています。わが国の解析では、COVID-19 に頻度が高い症状は、発熱、咳嗽、倦怠感、呼吸困難で、下痢は約 1 割で、味覚障害 (17.1%)、嗅覚障害 (15.1%) もみられました。

④ どのように診断するか

PCR 法は、新型コロナウイルスの遺伝子配列を検出する検査法です。感度が高く、検査の主体となっています。「鼻咽腔ぬぐい液」で当初検査されていましたが、発症から 9 日以内であれば、「唾液」を用いた場合でも、同等の精度が確認されています。

そのほかに抗原検査があり (インフルエンザウイルス検査でよく用いられている方法)、30 分程度で結果が出るなど、メリットがありますが、キットの種類により感度が異なります。

⑤ どのように治療するか

軽症の場合は、経過観察のみで自然に軽快することが多いですが、発症 2 週目までに急速に病状が進行することがあります。高齢者や、糖尿病、心不全、COPD (タバコ肺)、がん、腎臓病、肝疾患、肥満などの基礎疾患のある方は、重症化する割合が高いとされており、軽症でも入院とする場合があります。

息切れや肺炎のある中等症以上では、入院して治療します。肺炎が進行する場合、ステロイド薬やレムデシビルの使用が考慮され、必要に応じて酸素投与が行われます。重症例では、人工呼吸管理や体外式膜型人工肺 (ECMO) が用いられます。

COVID-19 では、血栓が認められやすく、ヘパリンなどによる抗凝固療法を行うことがあります。そのほかにも、トシリズマブの治験が行われており、ファビピラビル (アビガン®) は、保険承認申請中です。シクレソニドは喘息用の吸入ステロイド薬で、COVID-19 への効果も期待されましたが、最近の研究では、無症状・軽症の患者さんには推奨されない結果が示されました。

II COVID-19 の感染予防策と感染確認

① どのように予防するか

飛沫感染を防ぐために、マスクの着用、「３つの密」の回避を行います。接触感染を避けるために、石けんによる手洗いや、手指消毒用アルコールによる消毒を行います。

A.「３つの密」を避ける

「３つの密」は、感染を拡大させるリスクとなります。人と人との距離をとること (Social distancing; 社会的距離) が重要です。

i) 密閉空間を避けて、十分に換気する

＊２方向の窓を数分間開けて、できれば毎時２回以上換気しましょう。窓が１つしかない場合でも、入口のドアを開ければ、窓とドアの間に空気が流れます。
＊通常の家庭用エアコンは、空気を循環させるだけです。別途、換気が必要です。
＊一般的な空気清浄機は、通過する空気量が少なく、新型コロナウイルス対策への効果は不明です。

ii) 密集場所を避け、隣の人とは互いに手を伸ばして届かない距離を取る

＊レジなどで列に並んでいるとき、前の人に近づきすぎないようにしましょう。
＊飲食店では一つ飛ばしに座る、真向かいに座らない、互い違いに座るなどに留意しましょう。
＊エレベーターで混みあっているときは、一本遅らせましょう。健康のためにも、階の上下には階段の利用に努めましょう。

iii) 密接場面を避ける

＊５分間の会話で、１回の咳と同じくらいの飛沫が飛びます。
＊対面での会議や面談が避けられない場合は、十分な距離を保ち、マスクを着用しましょう。
＊エレベーターや電車の中では、会話や携帯電話による通話を慎みましょう。
＊多人数での会食は、マスクを外す時間が長くなり、大声になりがちなため、慎みましょう。
＊多人数かつ室内で呼気が激しくなるスポーツジム、ライブハウス、カラオケは避けましょう。
＊喫煙の際はマスクを外しており、喫煙所では人との「密」が起こります。喫煙者は重症となる可能性が高いことも報告されています。禁煙する選択肢も考慮しましょう。

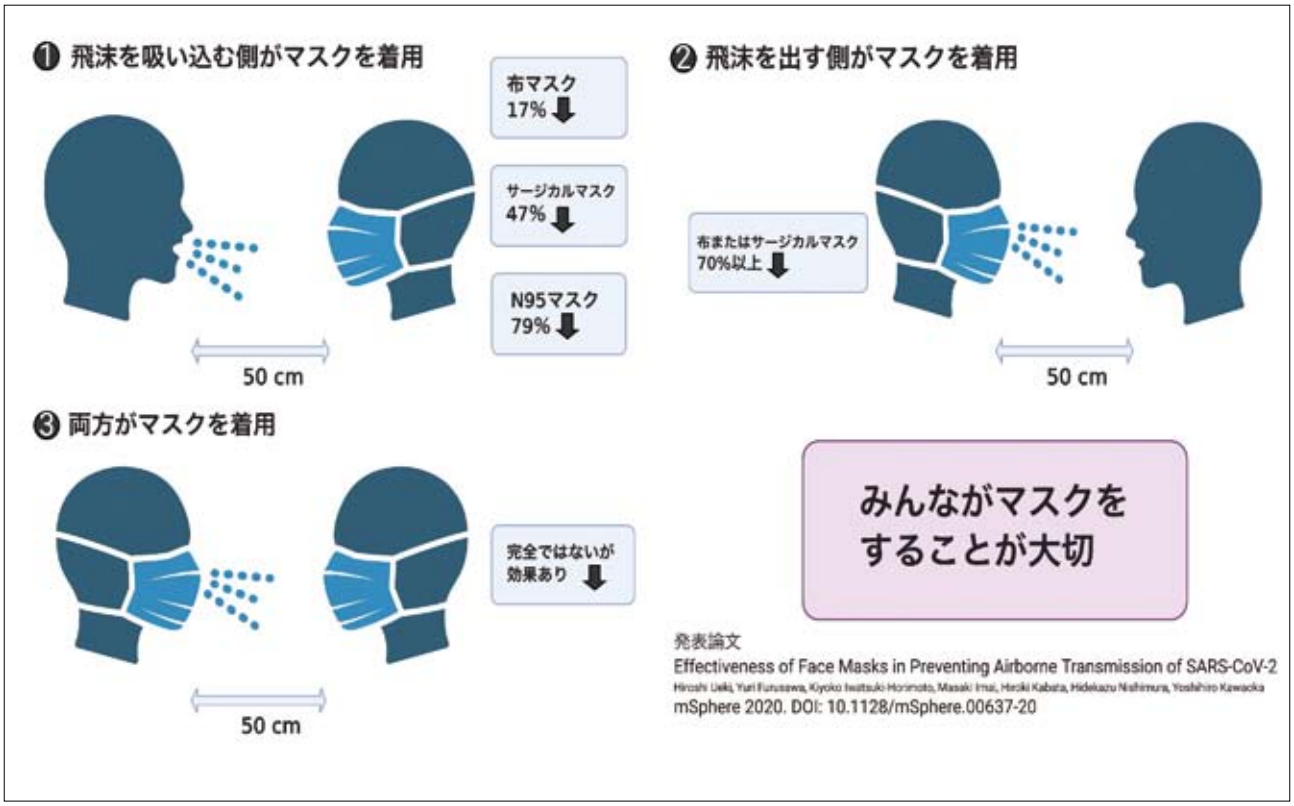
B. マスクを着用する

マスクの素材によって、効果は違います。不織布マスクが最も効果が高く、次に布マスク、その次にウレタンマスクの順です。

マスクは、「飛沫を出す側：自分」「飛沫を吸い込む側：相手」とすると、相手だけがマスクを着用するより、自分だけがマスクを着用する方が効果が高く、7 割以上飛沫を減少させます。自分から相手への感染拡大を防ぐために、話す時はいつでもマスクを着用しましょう。

さらに、自分と相手の双方がマスクを着用することで、吸い込みを 7 割以上抑えます。皆がマスクをすることが大切です。室内で会話する場合は、特にマスクを着用する必要があります。屋外でも、最低 1 メートルの間隔を確保できない場合もありますので、やはりマスクは重要です。

自分の顔にぴったりとフィットしているマスクを選ぶことが重要です。鼻に留め金がある場合は、鼻の形に合わせて固定します。鼻を出した状態では効果が不十分です。



東京大学医科学研究所のデータをもとに内閣官房が作成
https://corona.go.jp/proposal/pdf/mask_kouka_20201215.pdf

・サリドマイド胎芽症の皆様へ

ひものない、貼るタイプのマスク、マスク固定用のテープ、首にかけるマスクがあります。お示しする製品は、アマゾンなどの通信販売サイトで入手可能です。

価格は 2021 年 1 月現在の実勢価格です。

● 貼るマスク (5 枚 : ¥780)

四隅に粘着テープが貼ってあります。
正面から見ると、ひもつきマスクと同じように見えます。



● 貼りマスクテープ (¥980)

市販のマスクのひもを切って改造し、テープを四隅に貼って装着することができます。



● 首にかけるストラップ (¥980)

マスクのゴムにストラップを装着し、首に回します。ウレタン素材で、ソフトに首に固定できます。



● フェイスシールド・マウスシールド

フェイスシールドはマスクと併用し、眼からの飛沫感染防止のために用いるものですので、マスクと併用しましょう。マウスシールドは、マスクに比べて予防効果が弱く、単独での使用は、できる限り避けましょう。透明のシールドを使用する場合は、フェイスシールドを鼻先から垂直に、あごの下まで隠れるように装着します。

また、マスクを外して飲食せざるをえない場合、フェイスシールドやレイン用サンバイザー、ほほの上部で固定する紙のマスクなどを着用した上で、あごの下からストローを使って飲むように工夫します。

フェイスシールド　10 枚 ￥1,340



ハレマス　貼るマスク 50 枚 ￥4,235



レインバイザー　￥849



サンバイザー　￥599



C. 手洗いと消毒

接触感染を予防するために、手洗いや手指消毒を行います。

i) 手洗い

ウイルスは水で洗い流すことで、かなり数を減らすことができます。手指に付着しているウイルス量は、流水による 15 秒の手洗いだけで 1 /100 になります。さらに、石けんで 10 秒もみ洗いし、流水で 15 秒すすぐと、1 /10,000 に減らすことができます。

石けんやハンドソープを使った
丁寧な手洗いを行ってください。



手洗いを丁寧に行うことで、
十分にウイルスを除去できます。
さらにアルコール消毒液を
使用する必要はありません。

手洗い		残存ウイルス
手洗いなし		約 100 万個
石けんやハンドソープで 10 秒もみ洗い後流水で 15 秒すすぐ	1 回	約 0.01%（数百個）
	2 回 繰り返す	約 0.0001%（数個）

（森功次他：感染症学雑誌、80:496-500,2006 から作成）

ii) 手指消毒

手洗いがすぐに出来ない状況では、アルコール消毒液（濃度 70%～ 95%のエタノール）も有効です。60%台のエタノールによる消毒でも一定の有効性があります。

・サリドマイド胎芽症の皆様へ

ポンプ式の消毒液のほかにも、以下のような自動種手指消毒器があります。

手や足をかざすだけで消毒液が噴霧されます。



A：YTA
￥2,280



B：VEEAPE
￥2,680



C：ハイスト
￥2,990

● 自動手指消毒器

また、さまざまな固定器具があり、
高さや角度を変えることができます。

● 粘着テープ

扉の取っ手の横に粘着テープ式のフックを装着すると、開閉時に、すぐ消毒が可能。





アスクル粘着テープ
￥808

● マグネット式スタンド

ドアノブの下にマグネット式スタンドを装着すると、ドア開閉時に自動的にアルコールが噴霧される。







アスクルマグネット式スプレースタンド
￥968

● 三脚

高さを調節し、玄関などよく使う場所に、使用しやすいように整える。





三脚
￥5,691

iii) 身の回りのものの消毒・除菌

熱水、次亜塩素酸ナトリウム（いわゆる塩素系漂白剤）、アルコール消毒液による消毒をおすすめします。これ以外では、界面活性剤（いわゆる住宅用･台所用洗剤）でも、効果が期待できます。新型コロナウイルス感染症や疑われる患者さんがトイレを使用時に、下痢症状などでトイレが汚れた場合には、次亜塩素酸ナトリウムまたはアルコール（70％）による清拭を推奨します。

D. 新型コロナウイルス接触確認アプリ

新型コロナウイルス接触確認アプリ（略称 COCOA）は、陽性者と接触した可能性をいち早く知ることが可能となります。感染者と、「過去 14 日間に」、「概ね 1 メートル以内で」、「15 分以上の近接した状態」の可能性があった方のスマートフォンに通知が送られます。アプリの通知画面では、接触者外来等の連絡先などが案内されます。通知を受けた方が検査を受ける場合は、行政検査となるため、検査費用の自己負担はありません。新型コロナ対策に非常に有効な手段のひとつですので、スマートフォンへのダウンロードをおすすめ致します。

E. ワクチン

ワクチンの接種は、海外で開始されていますが、わが国では準備段階です（2021 年 1 月現在）。日本政府は、製薬企業 3 社から合計 2 億 9,000 万回分（1 人に 2 回接種を行うとした場合 1 億 4,500 万人分）の供給を受ける合意をしています。ワクチンが国内で承認され、供給できる準備が整った際は、無料で受けることができます。

F. 新型コロナウイルス感染症にかかっていないか調べたいとき

発熱等の症状のある方は、まずは、かかりつけ医等の身近な医療機関に直接電話相談し、医療機関を受診してください。感染が疑われると判断された場合には検査を受けることができます。

かかりつけ医で検査ができない場合や、かかりつけ医がない場合は、「受診・相談センター」に電話相談してください。

地域により、受付方法が異なりますので、お住いの自治体の情報をご確認ください。

【帰国者・接触者相談センターページ】

https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/covid19-kikokusyasessyokusya.ht

III COVID-19 に対する歯科 / 口腔外科からのアドバイス

① お口の中と COVID-19

COVID-19 に感染したときの初期症状としては嗅覚障害や味覚障害が知られていますが、これは舌に存在する味蕾（みらい：味を感じる器官）や神経へのウイルスそのものによる傷害のほか、嗅覚も影響を受けることにより、食べ物の匂いや風味がわからなくなるためといわれています。このウイルスは全身の様々な細胞が持っている ACE2 受容体に結合し、感染することが知られていますが、口の中の粘膜（口腔粘膜）、特に唾液腺管（唾液を運ぶ管）の上皮や気道全体に豊富に存在することがわかっています。類似のウイルスである SARS ウイルスの早期標的であることがすでに実証されていますので、COVID-19 についても同じ状況である可能性が高いと思われます。つまり、感染した人の唾液には生きた COVID-19 のウイルスが存在するのです。そのため 2020 年 7 月から発症してから 9 日以内であれば、唾液からの PCR 検査にも健康保険が適用されるようになりました。

② 歯科受診は「不要不急」か？



「不要不急」の外出を避けるように、といわれていますが、歯科受診はどうでしょうか。

歯科の疾患の中で代表的なものは、むし歯（う蝕）や歯周炎ですが、これらも細菌により起こされる「感染症」です。初期の段階では自覚症状はありませんが、違和感や痛みを感じたときにはかなり進行してしまっています。加えて家の中にいる時間が長いため、生活のペースも乱れ気味であり、つい歯みがきなどを忘れてしまうことも少なくないでしょう。「痛くないからいい」ということではないのです。

口の中には大量の COVID-19 ウイルスがいると思われるため、緊急事態宣言の際はエアロゾルを発生させるという理由で歯を削る器械が使えず、ほぼ全ての歯科治療ができませんでした（現在では感染予防対策をしっかり行いながら診療を行っています）。特に歯の神経の痛み（歯髄炎）には薬の効果が届きにくいため、辛い日々を過ごされた方も少なくはなかったと思います。また歯周病などの重症化は生活習慣病のリスク因子にも影響を与え、誤嚥性肺炎の発症など日々の生活と健康に悪影響を及ぼす可能性が極めて高いと考えられることから、予防のための定期管理が重要であると考えられます。

つまり継続的な歯科受診は「不要」などでは決してありません。（なお、歯科治療を通じての患者さんへの感染の報告は 2020 年 12 月現在まで確認されていません。）

③ 最近の知見

口の中のウイルス量を減らす試みは色々なされています。

３種類の市販のうがい薬の有効性を調べたランダム化比較試験の研究があります[1)]。ポビドンヨード（PI)、グルコン酸クロルヘキシジン、および塩化セチルピリジニウム（CPC）と水とでうがいの効果を比較したところ、水でのうがいと比較して、CPC と PI のうがいによるウイルス減少の効果は、使用後 5 分以内に唾液中のウイルスを低下させ、6 時間の時点で持続することが観察されました。

うがい薬を使わない他の方法がダメだということではありません。唾液を用いた PCR 検査の検体採取には、「歯みがきやうがいなどの後は最低 10 分、可能であれば 30 分ほど空けること」と示されていますので、しっかりとした歯みがきが大事なのはいうまでもありませんが、単純な水うがいでも唾液中のウイルス量を減らす効果はありそうです。ただ、ウイルスの一般的な感染経路には，直接感染（咳，くしゃみ、飛沫吸入）および接触伝染（口、鼻、および目の粘膜との接触）などが考えられていることから、むやみに目や鼻や、口などに手を触れないように気をつけることが大事であろうと思われます。



手洗い、うがい、マスク着用とともに「歯みがき」も励行しましょう。

1) Zhou, P. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature https://doi.org/10.1038/s41586-020-2012-7 (2020).

Ⅳ COVID-19流行期に食事で気をつけるべきこと

① 食事場所について

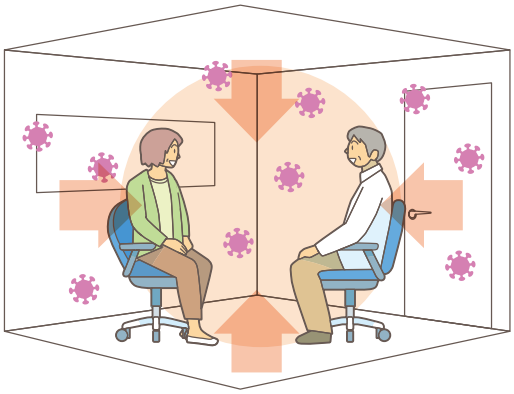
新型コロナウイルスの感染経路はインフルエンザと同じく，飛沫感染と接触感染です。したがって、飛沫と接触を避けることが重要です。

① 換気の悪い密閉空間、

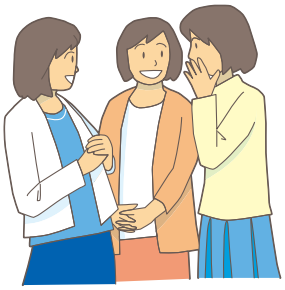
② 人が密集している、

③ 密接した近距離での会話や発声が行われる、

という 3 つの条件が同時に重なった場合に特に感染が広まりやすくなることが知られています。食事に限らず、普段の生活では、このような場所には立ち入らないようにしましょう。







② マスク・フェイスシールド

症状が出現する数日前から周囲の人にうつしてしまうことが判っています。体調に問題ない方を含めて、すべての皆さんが人と会話をするときには必ずマスクをしましょう。他の人と 2m 以内に近づく可能性のある場合には、屋内外を問わずマスクを着用しましょう。小耳症でマスクをかけづらい方には、長いゴムのついたマスクや医療用シリコンテープで頬に貼付して装着する「ひもなし」マスク、あるいは、かぶるタイプのフェイスシールドが市販されています。

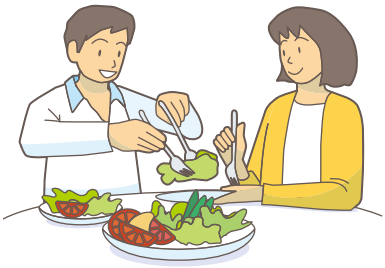
③ 食事前には

石鹸をつかった 20 秒以上の手洗い（足を手の代わりに使っている方は足の洗浄）を徹底することが重要です。こすりあわせての洗浄が困難な場合はアルコール消毒が有効です。スプレータイプやジェルタイプがあります。接触感染が起きる可能性のある場所は周囲にたくさんあります。付着したウイルスは数時間から 3 ～ 5 日程度生存すると言われています。ウイルスが付着している部分に触った後で、目や口に触れる、調理をする、食事をすることで感染します。不特定多数の方が触った物に触れた後は、必ず正しく洗浄・消毒しましょう。外出先から戻ったとき、食事の直前（外食時は会計後）、料理の前が特に大切です。

④ 食事中は

多人数で長時間（5 人以上、2 時間以上が目安です）の会食は避けましょう。特に，新型コロナウイルス感染症が増加中の現在は、家族以外との飲食は、茶菓のような簡単な場面も含め、やめておきましょう。家族でも、向かい合っての飲食は避けましょう。会話をしながらの飲食、大皿から取り分けること、お互いに食べ物や飲み物をシェアすることもやめましょう。飲食用にデザインされたフェイスシールドが市販されていますので、活用してください。







⑤ 食生活について

重症化しやすいのは、高齢者と基礎疾患のある方です。重症化のリスクとなる基礎疾患には、慢性閉塞性肺疾患（COPD）、慢性腎臓病、糖尿病、高血圧、心血管疾患、肥満，ステロイドなどの免疫抑制剤の使用中，がんの治療中，血液疾患などがあります。また、喫煙歴のある方なども、重症化しやすいかは明らかでないものの、COPD や心疾患の原因ともなり、注意が必要です。基礎疾患のある方は、主治医から処方されている治療薬を継続して下さい。生活習慣病では、食事療法や運動療法も重要です。特に、不摂生やお薬の自己中断による血圧上昇、高血糖、体重増加は禁物です。コロナが怖いと言って､勝手にかかりつけ医の受診を控える方がときどきおられます。基礎疾患の悪化につながり、コロナ感染の有無に関わらず大変危険ですので、電話再診でいいかどうかを含め、主治医と相談の上、その指示に従って下さい。日頃からの体調管理が、万一感染しても重症化することの予防につながりますので、普段から規則正しい食生活を心がけましょう。

V COVID-19 の巣ごもり時期にやるべき運動

① 散歩はしましょう！

感染症は心配ですが、自宅周囲など、人に会わないところを歩くぶんには、感染の危険はありません。家の周り 1 ブロックからでも良いですので、できれば毎日、外に出る機会を作りましょう。普通に歩くだけでなく、少し膝を高く上げて歩く、大股で歩く、など変化をつけると、より運動になります。

② 家庭内でも運動しましょう！

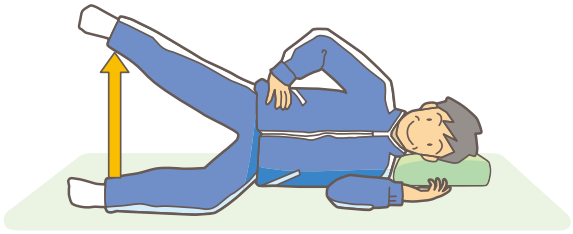
すでに何か運動をされている方はそれを続けてください。特に運動習慣のない方に、簡単で、歩行能力を維持するのに効果的な体操をご紹介します。おすすめの時間帯は食事の前です。

回数も、時間も自由ですが、複数組み合わせて、短い休憩も含めつつ、20 分以上、運動の時間を持つようにすると、動脈硬化の予防にもなります。

特に、最後の二つの自重トレーニングは総合的な下半身の運動でもあり、大きな筋肉を使うために、全身運動としての生活習慣病への効果も期待できます。

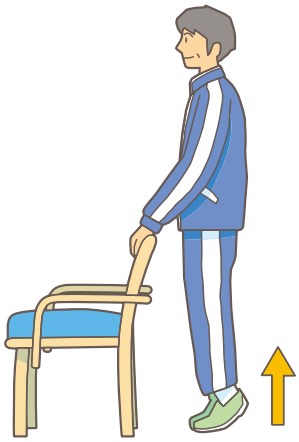
＜脚の横上げ＞

* 脚を横に挙げる筋力は、歩行バランスに重要な役割を果たします。
* 立位で行えば、それ自体がバランス訓練になります。
* 立位でも、側臥位でもできます。
* 10 回から開始し、できれば 20 回くらいまで行いましょう。



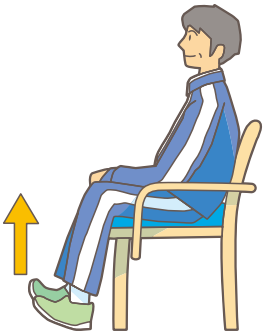


＜ふくらはぎの運動１．つま先立ち＞



＊ 転ばないように、どこかにつかまってください。
＊ 膝と腰を伸ばして、身体全体が空のほうに持ち上がるように、つま先立ちをしてください。
＊ バランスが良い人は、上がったところで３秒から７秒くらい、キープしてください。転びそうになる時にはすぐにかかとを下ろしましょう。
＊ 少しずつ回数を増やして、10 - 20 回くらいできるようになりましょう。

＜ふくらはぎの運動２．つま先上げ＞



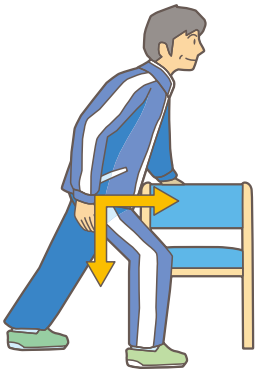
＊ 椅子に腰かけて、かかとをつけ、つま先をできるだけ上にあげます。数秒間キープします。
＊ ふくらはぎの前側の筋肉が固くなるのを感じてください。
＊ 左右交互に、左右同時に、やってみましょう。10 - 20 回がめやすです。
＊ 布団の中で膝を伸ばした時にも、やってみてください。

＜スクワット＞



＊ 脚を肩幅に開き、腰を落としていき、また立ちます。
＊ 膝が前に出すぎないようにしましょう。
＊ 深く沈みすぎるときついので、はじめは浅く腰を落とすだけで結構です。
＊ 繰り返す際に、立ったところでいったん休憩してからまた腰を落とすようにしましょう。
＊ 繰り返して何回も行いましょう。10 回以上できるような、軽い・ゆっくりしたスクワットから開始しましょう。

＜前方ランジ＞



＊ 脚を前後に広げて立ち、前の脚の膝を曲げて、前の脚に重心を載せるように、身体を少し沈ませ、そしてまた戻りましょう。３回程度行ったら、広げた脚を戻します。
＊ 上半身はまっすぐたてたままが良いですが、むつかしければ少し前に傾けてもいいです。
＊ 後ろの脚のかかとはあがってかまいません。
＊ 沈めすぎるときついので、はじめは軽く沈めるようにしましょう。
＊ 慣れてきたら、脚の広げ方を広くする、上半身の沈め方を深くする。沈めた位置でのキープを長くする、などしていきましょう。

VI おわりに

このパンフレットは、主として「新型コロナウイルス感染症 (COVID-19) 診療の手引き第 4.1 版」(2020 年 12 月 25 日発行) の内容に準拠して作成しました。

以下の厚生労働省の HP にも、有用な情報が多数掲載されていますので、ご参照ください。

新型コロナウイルスに関する Q&A （一般の方向け）

https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/dengue_fever_qa_00001.html

新型コロナウイルス感染症 (COVID-19) の基本的知識と生活上の対応
－ サリドマイド被害者の皆様へ －

発行日　2021 年 3 月 31 日

発行者　厚生労働行政推進調査事業
「サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築」研究班
研究代表者　日ノ下　文彦
国立国際医療研究センター腎臓内科
〒 162-8655　東京都新宿区戸山 1-21-1　TEL 03-3202-7181

48th Annual Meeting, 2020, Virtual One-Day Meeting

Published: 04 August 2020

04 August 2020

Category: Annual ETS Meetings

Annual ETS Meetings

Tuesday September 15th from 10.00 am to 5.00 pm (CEST)

Download: ETS Invitation Letter / Flyer Register here

The ETS council regrets not being able to celebrate this year's ETS meeting in Madrid, but we are happy to partially replace it by a virtual one-day event in order for our members and collaborators to share their current findings in the field of reproductive and developmental toxicity.

Therefore, we would like to invite you all to the 1st virtual one-day event of the European Teratology Society (ETS), to be celebrated on the 15th of September online from 10:00 am to 5.00 pm (CEST).

Sign up for this exciting program, a great opportunity for sharing your knowledge with colleagues and discuss hot topics in a virtual environment.

With warmest regards, keep safe and healthy!

Arantza Muriana

Meeting Organisation
Solution office e.K.
Pia Schröder
Bergstr. 2
29646 Bispingen
Germany
Tel.: +49 5194 97449-0
Fax: +49 5194 97449-4
E-mail: pia.schroeder@solution-office.de

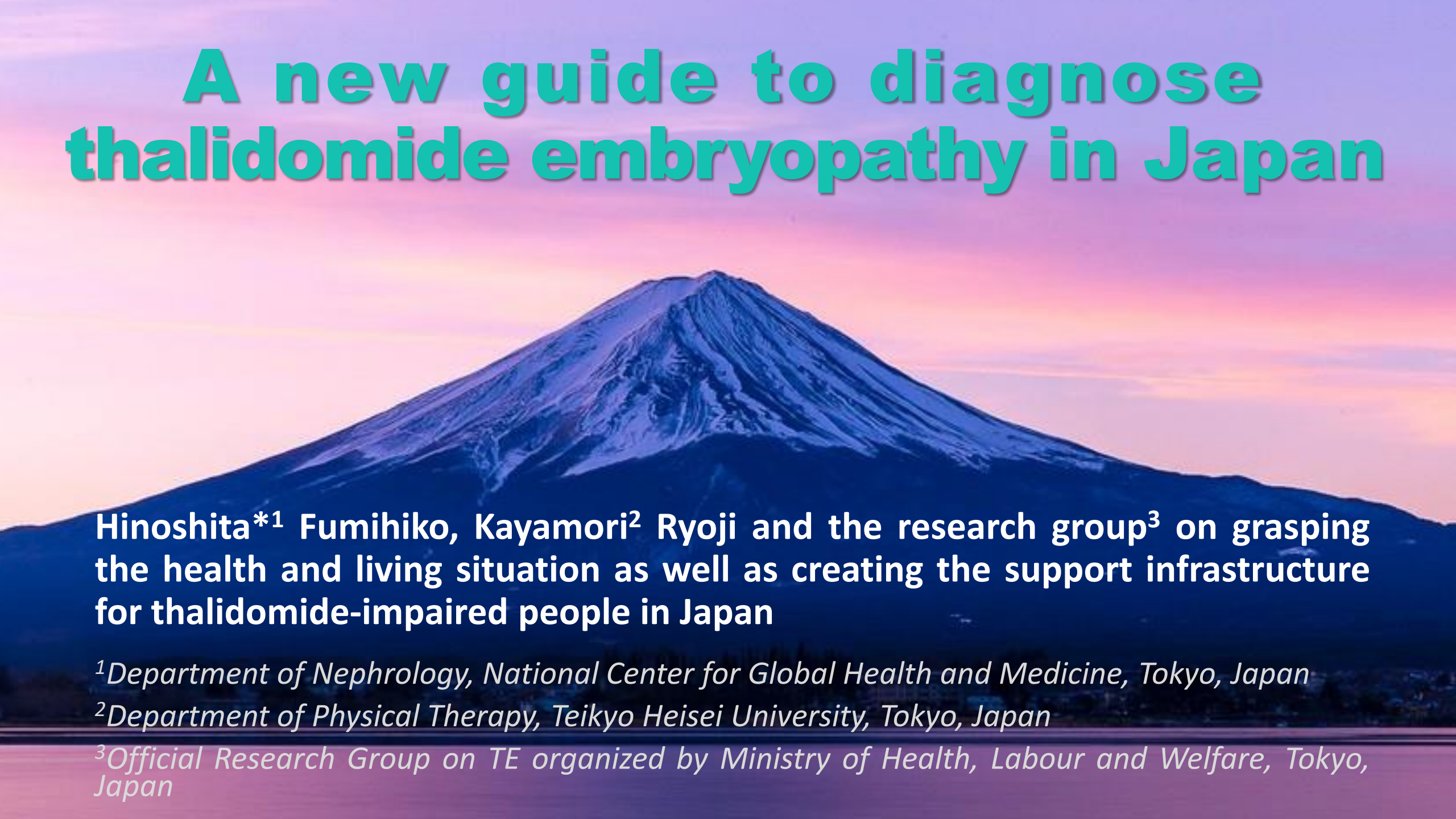
Programme Overview

10:10 am	Welcome by Arantza Muriana, Nicola Powles-Glover and Steven Van Cruchten
10:30 – 12:00 pm	Short communications Chairs: Arantza Muriana & Elena Menegola
10:30 am	Screening of multi-endocrine disruptors in zebrafish María José Mazón- Biobide, Spain
10:45 am	In vitro biotransformation of proteratogens in different laboratory animal models, including the zebrafish Chloé Bars, Comparative Perinatal Development, University of Antwerp, Belgium
11:00 am	Assessment of neurodevelopmental adverse effects induced by Intrauterine growth restriction and testing of future therapies. Application in an in vitro rabbit neurosphere model Britta Kühne- GRET, INSA-UB and Toxicology Unit, Faculty of Pharmacy, University of Barcelona and BCNatal-Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital lClínic and Hospital Sant Joan de Déu), Fetal i+D Fetal Medicine Research Center, IDIBAPS, Spain

11:15 am ✓	A new guide to diagnose thalidomide embryopathy in Japan Fumihiko Hinoshita, Department of Nephrology, National Center for Global Health and Medicine, Japan
11:30 am	ZNF48 and ZNF84 are potentially involved in the regulation of genes affected by thalidomide Thayne Kowalski, Universidade Federal do Rio Grande do Sul, Porto Alegre; 2CESUCA, Brazil
11:45 am	Challenges when designing juvenile animal studies that meet global regulatory expectations Luc De Schaepdrijver, Janssen Research & Development, Belgium
12:00 – 1:00 pm	BDRP and European Teratology Society Exchange Lecture Early Principles of Teratology: Does Karnofsky's Law Still Apply Chairs: Susan L. Makris, US Environmental Protection Agency and Nicola Suzanne Powles-Glover, AstraZeneca Dr. David Karnofsky: The First 50 Years European Teratology Society Derek R Newall, European Teratology Society Past-President Dr. David Karnofsky: Can He Rest in Peace or Do We Have a Way to Go? BDRP Alan M. Hoberman, Charles River
1:00 – 2:00 pm	Lunch

以下、午後の部は略。　書式は✓も含め一部改変。

A new guide to diagnose thalidomide embryopathy in Japan



Hinoshita*[1] Fumihiko, Kayamori[2] Ryoji and the research group[3] on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan

[1]Department of Nephrology, National Center for Global Health and Medicine, Tokyo, Japan

[2]Department of Physical Therapy, Teikyo Heisei University, Tokyo, Japan

[3]Official Research Group on TE organized by Ministry of Health, Labour and Welfare, Tokyo, Japan

Background

The history of thalidomide embryopathy (TE) started back in 1958. About 60 years have passed since thousands of babies, exposed in utero to thalidomide, were born with a variety of visceral disorders and birth defects such as limb deformities, phocomelia, and hearing loss or impairment.



Package of real Contergan®
at Deutsches Apotheken-Museum in Heidelberg

In fact, however, TE still continues to make history. Some specific problems remain unresolved, including new claimers for TE. Many persons with congenital birth defects have newly claimed to be thalidomiders in European countries as well as a few in Japan. New claimers have emerged with the reintroduction of thalidomide or by saying they were overlooked 50 years ago. Based on the present situation regarding new claimers for TE, a UK group showed a diagnostic algorithm for TE (DATE) in 2019*. We also felt the necessity to determine any new diagnostic criteria which are unique to Japan.

** S. Mansour, E. Baple, C.M. Hall . A Clinical Review and Introduction of the Diagnostic Algorithm for Thalidomide Embryopathy (DATE). J Hand Surg Eur 44 (1): 96-108, 2019*

Method

1) Six members were selected for the Diagnostic Criteria Development Committee of TE from the members of the Official Research Group on TE in Japan. The committee consisted of the research group head, 2 rehabilitation doctors, a radiologist, an oto-rhinolaryngologist and an ophthalmologist. The staff in charge of the Ministry of Health, Labour and Welfare also attended the committee as observers.

2) The committee met four times in 2019 to establish a guide to diagnose TE. Mr. Sato, the chairman of the Ishizue Foundation, the public interest incorporated foundation of thalidomide victims in Japan, also attended the committee as an observer for the last two meetings. We finally held a consensus meeting in which some other members of the research group and pharmaceutical companies' staff as well as thalidomide victims and general citizens participated. At the consensus meeting, a tentative guide or diagnostic flowchart to diagnose TE which had been suggested by the Diagnostic Criteria Development Committee was shown and freely discussed.

3) A tentative guide with diagnostic flowchart was made as follows:

* Each member suggested indispensable and primary conditions to diagnose TE based on objective references and past experiences as well as on radiological findings. These conditions were shown to the committee from their own specialized points of view.
* Each member also examined previous reports and documents associated with the diagnosis of TE.
* We further read and studied a diagnostic algorithm for TE (DATE) a UK group had reported in 2019 [J Hand Surg Eur 2019, 44:96–108].
* We seriously discussed how to diagnose TE at the 2nd International Symposium on TE in Tokyo held on Jul 14 and 15, 2019, where many specialists on TE got together from Germany, UK, Sweden, Switzerland, Brazil as well as Japan. There were some specialists on TE who were knowledgeable about diagnosis of TE, such as Prof. Lavinia Schuler-Faccini from Brazil, Prof. Ryoji Kayamori from Japan and Ms. Emma Baple from UK, a member of the group determining DATE.
* We also examined many congenital diseases which are similar to TE and listed for candidates for the differential diagnosis.

Diagnostic procedure

Results

New Claimers

Definite case

1) Born in 1958 to 1964
2) Mother's positive history of thalidomide intake during pregnancy
3) Congenital disorder of bilateral limbs or congenital hearing disorder, or both (See major conditions in Details)

Suspected case

Essential conditions

1) Born in 1958 to 1969; Or examined given a possible situation of TE just in case even if born after 1970
2) Mother lived in a country where thalidomide was sold during pregnancy
3) Negative family history
4) Evidence of at least one congenital disorder in upper limbs, lower limbs, face, eyes, ears and congenital hearing impairment which are typical of TE (See major conditions in Details)
5) No unilaterality of upper limb deformity

Incompatible with essential conditions above → **Exclude TE**

Check clinical characteristics and results of diagnostic imaging

Confirming 3, or more than 3, major conditions (at least 2 major conditions in addition to abnormal image findings)

Yes → **Thalidomide Embryopathy (TE)**

No

Evaluation by multiple specialists on TE

1) Differential diagnosis for similar congenital disorders
2) Genetic testing if necessary

#Prerequisite

Mother's negative history of taking specific drug such as anti-epileptic drugs causing congenital limb deformities and hearing impairment as well as of viral infection such as rubella during pregnancy

Major clinical conditions

General findings

1) Upper and lower reduction defects are longitudinal dysplasia. Preaxial longitudinal dysplasia (radial side) or hypoplasia including thumb hypoplasia is recognized in the upper limb deformity type which is often found in Japan.

2) Hypoplasia and deformity of the limbs are basically bilateral (not always symmetric). Upper limb deformity is not unilateral.

3) No family history of similar congenital malformation.

4) Congenital hearing impairment is found, and there are multiple deformities of temporal bones, inner, middle or outer ears. Moreover, other diseases or syndromes to cause these deformities can be excluded. Crocodile tears syndrome and Duane syndrome from infancy are characteristic of TE.

Image findings

1) X-ray examination and CT reveal deficits or hypoplasia of upper limbs (humerus, radius, ulna, carlpals and finger bones), namely dysmelia. Pointed shoulder is also characteristic of TE.

2) X-ray examination, CT and MRI reveal sacrococcygeal hypoplasia.

3) X-ray examination, CT and MRI reveal that multiple vertebrae (cervical or upper thoracic vertebrae) are fused, becoming block vertebrae.

4) Ultrasonography, CT and MRI cannot identify gallbladder (gallbladder agenesis).

5) Ultrasonography, CT and MRI reveal abnormal lobulation of medial and lateral segments in the left lobe of liver.

6) CT reveals malformation in auditory organs such as in the semicircular canals, auditory ossicles, vestibule, cochlea, inner ear canal, facial canal and outer ear canal.

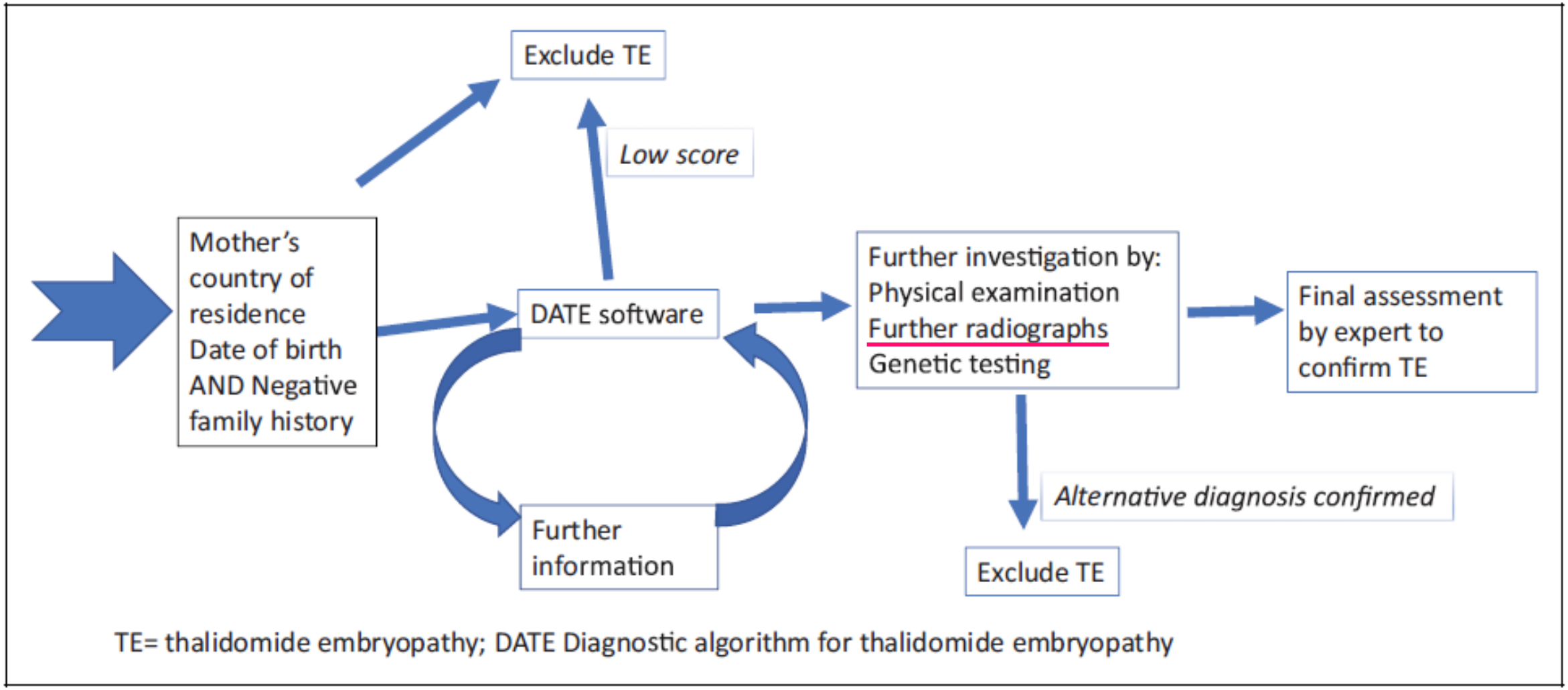
7) MRI reveals deficits or hypoplasia of cranial nerves such as auditory and facial nerves.

8) CT and MRI reveal microphthalmia.

Major congenital malformations to be excluded from the differential diagnosis

1) Okihiro syndrome (Duane-radial syndrome)
2) Holt-Oram syndrome
3) VATER/VACTERL association
4) Townes-Brocks syndrome
5) Thrombocytopenia-Absent Radius syndrome (TAR)
6) Fanconi anemia (Fanconi pancytopenia syndrome)
7) Roberts syndrome

Pathway for the assessment of a patient with possible TE
suggested by Mansour S, Baple E and Hall CM



J Hand Surg Eur 44 (1) : 96-108, 2019

Discussion

1) We newly determined the guide to diagnose TE, which is applied to the Japanese thalidomiders and new claimers for TE born in Japan.
2) The guide was determined based on clinical findings, past experiences, radiological findings as well as objective references. In particular, the guide for Japan is characterized by emphasizing the clinical findings and particulary adopting **image findings of CT, MRI and ultrasonography** in addition to simple X-ray examination as major conditions.
3) We have the main flowchart for diagnosing TE, but we have neither scored the likelihood of TE nor adopted any diagnostic software in this guide for Japan, in part because we thought it is difficult to do precise grading or weighing of abnormalities and malformations in new claimers. We already know the great variety of congenital deficits or malformations in thalidomiders.
4) Finally, it was stressed that this guide is not suitable to diagnose TE in new claimers in other countries because the dose and frequency of thalidomide intake by mothers, and the race and phenotype of TE might differ in different countries.

Conclusion

The Guide to Diagnose TE was newly determined and officially published in Japan on March 31, 2020.

We believe that this guide will be used when new claimers for TE request a differential diagnosis, and that it will persistently become the cornerstone for every clinical practice, support and care as well as for research associated with TE in Japan.


Thank you for your attention

第445号　2021年3月号

いしずえニュース

発行 公益財団法人 いしずえ サリドマイド福祉センター
〒153 - 0063 東京都目黒区目黒1- 9 -19　TEL 03 (5437) 5491 FAX 03 (5437) 5492
E-mail ishizue@qa2.so-net.ne.jp ホームページ http://www008.upp.so-net.ne.jp/ishizue/

「サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築」研究班長 退任のご挨拶 －過去7年間を振り返って－

「サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築」研究班
研究代表者　日ノ下 文彦

この度、２０２１年３月をもって「サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築」研究班の研究代表者（研究班長）を退任することになりました。通算７年間、代表者を務めさせていただき、佐藤理事長はじめサリドマイド薬禍者の皆様、いしずえ職員の皆様、全国にいらっしゃる相談員の方々にはとてもお世話になり感謝しております。本当にありがとうございました。

思えば、月日が経つのはすごく速く、ちょうど7年前の今頃、元研究班長の吉澤先生が辞められるので、是非 班長の仕事を引き受けてくれと言われたのが、つい先日のように思い起こされます。その後、サリドマイド胎芽症について不案内であった私どもに吉澤先生から資料をいっぱい渡されたり、関連情報をメールで矢継ぎ早に送っていただいたりして、当初は戸惑ってしまった覚えがあります。実際、とても重要な任務を託されましたので、正直なところ「大丈夫かな」「無事に務まるだろうか」と思いました。そして、「先生ならやっていけますよ」「兎に角、数多くのサリドマイド薬禍者の方々に会うところから始めて下さい」と吉澤先生に後押しされ、研究班の活動計画を練り始めました。

まずは、吉澤時代から数えると第2次研究班である「サリドマイド胎芽病患者の健康、生活実態の諸問題に関する研究班」（平成26年度からの3年間）の活動骨子を考え始めました。吉澤班の頃の報告書や資料を読み進めながら、まずは吉澤先生が確立された「人間ドック健診」を継続させ、活動の軸に据えることにしました。さらに、ドック受診者の利便性を高め研究班としてのデータ集積も兼ね、耳鼻咽喉科領域の検討も健診内容に盛り込むことにしました。その後、国立国際医療研究センター病院では、頭部・顔面領域の眼科診察や耳鼻咽喉科診察のみならず、希望者には歯科・口腔外科領域の診察、リハビリテーション相談も選択できるようにしました。また、人間ドック健診では身体的問題だけにとどまらず、精神面や生活レベルの問題にも配慮し、精神科スタッフによるアンケート調査も並行して実施させていただき、一定の成果を得ることができました（Imai K, Sone H, Otomo K, Nakano Y, Hinoshita F. Quality of life and pain in patients with thalidomide embryopathy in Japan. Mol Genet Genomic Med. 2020 Nov;8(11):e1464. doi: 10.1002/mgg3.1464.）。

次に、研究班の研究活動をさらに活発化し次元の高い方向へ導く為、国際展開に心血を注ぎました。というのも、サリド

マイド胎芽症は本邦だけで起こった問題ではなく、世界中で生じた問題であり、薬物による先天性障害という意味ではどこの国であろうがどのような人種であろうが、同じ土俵で考えられる（考えるべき）医学的問題であると理解したからです。また、本邦のサリドマイド薬禍者数はある程度多いですが、３００名以下であり、ドイツのような２，０００名以上といわれる薬禍者が生活している国から学ぶことが多いだろうと考えました。そして、ドイツのみならず、同じ問題を抱える英国、スウェーデン、スイスなど他国も交え、国際交流し情報交換し合うことは絶対に意義があるはずだと考えたわけです。吉澤班の頃も、一部スタッフがドイツへ勉強の為、派遣されましたが、私の研究班では私自身や栢森先生、志賀先生、その後は芳賀先生や藤谷先生等、研究班の中心で働く班員がなるべく多く欧州に赴いて様々なことを学び、逆に本邦の情報を先方に供与して、研究者同士の絆を深めるようにしました。そして、普段からメールでサリドマイド胎芽症に関する問題点や新しい情報、質問などが、欧州と日本の間でやり取りされるようになり、まさにサリドマイド胎芽症の研究・臨床の国際的な仲間を増やすことができました。

国際交流という点では、サリドマイド胎芽症の国際シンポジウムを２０１５年と２０１９年に2回開催させていただきました。その結果、世界各国の内科系研究者やリハビリテーション・整形外科の専門家のみならず、基礎研究者や遺伝学者、手術に秀でた臨床医らとも交流することができたほか、当初 本邦、欧州、豪州に限られていたグローバルネットワークがついにはブラジルにも拡がりました。人的な交流以外にも、「サリドマイド胎芽症診療ガイド」の英語版や「国際シンポジウム」の proceedings（議事録）を英語で作成し、諸外国のサリドマイド胎芽症専門家やドイツのコンテルガン財団（Conterganstiftung für behinderte Menschen）、英国サリドマイド財団（The Thalidomide Trust）等に配布しました。

このような国際的な活動、交流を継続した結果、今ではサリドマイド胎芽症に関する強固なグローバルネットワークが確立できたと思います。実際、どこどこで研究会を開くとか、コロナ禍におけるマスク着用はどうしているか、ブラジルで補償金が打ち切られそうになったがどうしたものか、など学術的なことから被害者の悩みに至るまで、わが国に相談が寄せられるようになりました。そして、そうした問題は世界中のネットワーク仲間とすぐに共有して、知恵を絞ったり解決策を練ったり、それぞれの国の情報を提供し合ったりして、まさにグローバルに仕事ができる環境が整いました。

国内では、各研究班員が行っている研究や活動を発表し議論する場を設ける為、「サリドマイド胎芽症研究会」を創設し、研究会（講演会）を既に３回開催しました。同じく、本邦のサリドマイド胎芽症の研究班の活動やお知らせを国の内外に発信する目的で、サリドマイド胎芽症研究会ホームページも新設しました。これらは、国内のサリドマイド胎芽症研究班員や関係者の結束を固め、研究班の活動を無事に継続させるエンジンになると思うので、是非次の班長や班員には引き継いでいただきたいと考えております。

そして、東京のようにサリドマイド胎芽症に関わっている医師や医療従事者が多い大都市だけでなく、地方でも進んでサリドマイド薬禍者の診療や医療活動に従事するスタッフを確保する目的で、「サリドマイド胎芽症関連医療者ネットワーク」も構築しました。

約1年前には、懸案であったサリドマイド胎芽症の新しい診断指針を「サリドマイド胎芽症診断の手引き」として示すことができました。これは、まだまだ医学が発達していなかった（ＣＴすらありませんでした）１９６０年代

に考えられたサリドマイド胎芽症の認定基準は現代にマッチしない面があり、もう一度見直そうという動きもありましたし、「自分はひょっとしたらサリドマイド胎芽症だったのではないか」と申し出られる方も稀にいらっしゃるので、そうした要請に研究班が応えなければならないという側面もありました。また、サリドマイド胎芽症に対する診療や医療は、次の世代の若手医師や研究者、医療従事者に引き継がねばなりませんが、その際、基軸となるサ症の診断基準が曖昧だとサリドマイド薬禍者（被疑者も含む）にしっかり向き合えないと考えました。さらに、いしずえや厚生労働省からも要請がありましたので、２０１９年にサリドマイド胎芽症診断基準策定ワーキンググループを組織し、十分吟味し議論したうえで、２０２０年3月、「サリドマイド胎芽症診断の手引き」を発効させました。これができたことにより、私が引退しても次の世代に安心して引き継ぐことができ、肩の荷がぐっと軽くなったように感じております。

さて２０１８年度には、サリドマイド薬禍者の皆様の健康・生活実態調査も自ら実施させていただきました。その節は１７３名（回収率63・1％）という大変多くの方にご協力いただきありがとうございました。重ねて御礼申し上げます。お蔭さまでとても貴重な資料を収集することができ、論文化して世界に発信いたしました（Hinoshita F, Beppu H, Shioji S, Fujitani J, Imai K, Tajima T, Tagami T, Ohnishi S. A nationwide survey regarding the life situations of patients with thalidomide embryopathy in Japan, 2018: First report. Birth Defects Res. 111(20):1633-1642, 2019）。また、皆様にとって重要な結果を抜粋し、いしずえ経由でフィードバックさせていただきました。

ここまでに述べてきたこと以外にも、実に様々な活動・研究を行わせていただきました。すべてを書き尽くすとキリがないのでこの辺で止めておきますが、この7年間に数多くのサリドマイド薬禍者の皆様にお会いすることができたのは大きな財産です。何回かのいしずえ全国交流会や40周年記念講演会などで多くの方々にお会いできました。また、２０１７年度には各地域ブロックの交流会に他の班員とともにお邪魔して、健康ミーティングも実施しました。この健康ミーティングでは、全国的な行事に参加されない（できない）地方の薬禍者の皆さまにもお会いして、日常生活における日々の悩みや問題についてお聞きしたほか、内科の健康相談も行いました。

こうした講演会やいしずえの正式行事以外にも、国立国際医療研究センターで何名かの患者さんを定期的に診察したり、他科・他院にご紹介したりすることができました。そうは言っても、残念ながらサリドマイド薬禍者全員にはお会いできていませんが、吉澤先生から伝授された「なるべく多くの方にお会いする」というアドバイス通り、個別に接触するという地道な作業もある程度できたかなと自負しています。

最後に、ご報告したくてもなかなかできないでいた健診結果に基づく健康管理の要点について記しておきます。

①サリドマイド薬禍者の皆様においては、体重がそれほど重くなくても、また見た目に太っていなくても、体脂肪率の高値や内臓脂肪の蓄積、脂肪肝が数多く確認されています。コロナ禍ではありますが、適切に体を動かしたり、過食に陥らないよう努力していく必要があります。

②総コレステロールや悪玉のＬＤＬ－コレステロールが加齢とともに高くなっていく傾向があり、耐糖能異常（糖尿病もしくはその傾向）も含め、注意していく必要があります。

これは、血液検査を受け近くの医師に治療を受けるだけでよいので、是非実行して下さい。

③腎機能低下が認められる方がいるほか、高尿酸血症の方が大勢います。いずれも、ひどくならないうちは症状が出にくいので、定期的に血液検査を受け、問題があれば、腎臓内科医もしくは近くの家庭医に相談して治療を受けましょう。

④上部消化管内視鏡（胃カメラ）では、食道裂肛ヘルニアが多く見つかったほか、食道・胃・十二指腸の様々な問題が数多く認められました。何か消化器症状がある場合には、早めに消化器内科医に診てもらって必要な治療、アドバイスを受けるようにしましょう。

⑤加齢とともに、骨密度の低下傾向がありました。原因は特定できませんが、腰椎（背骨）よりも大腿骨で骨密度低下が顕著であり、今後は下肢の骨（大腿骨近位部や股関節、膝周辺など）などが骨折に陥ったり脆くなったりしないよう考えていく必要があります。特に骨粗しょう症の傾向が著しい方は、お近くの整形外科医に相談されるといいでしょう。また、現在の第4次研究班には多くのリハビリテーション医学の専門家がいるので、相談していただけばいいと思いますし、股関節の外科的治療も安心してできる体制を整えていますので、必要に応じご活用下さい。

以上、私が毎年すべての健診結果を総括して報告書を作成するときに痛感していたことを箇条書きにまとめました。手前味噌になりますが、一般的な健康指南書「老い楽のすゝめ」（文芸社）を3月初めに出版しましたので、もしよろしければ今後の健康管理の参考になさって下さい。この拙著にも書いておりますが、医師としては是非 皆様にいつまでも健康長寿であって欲しいと願っております。そして、シルバーエイジ（高齢者）となっても、充実した人生だった（つまり「老い楽」）と思えるように、これからも健康に留意し、楽しく元気に生活していかれることを願ってやみません。

私はこの3月で研究班長を辞めますが、同じ国立国際医療研究センターの内分泌代謝科医長・田辺晶代先生が班長を務めて下さいます。私も研究分担者として新班長を支え活動を続けますので、研究班が新しい体制になってもどうかよろしくお願い申し上げます。

2021年3月吉日



熱意ある取り組みに感謝

理事長　佐藤嗣道

日ノ下先生には、厚生労働省研究班の研究代表者として、お忙しい中、サリドマイド被害者のために熱意をもって健診、調査などに取り組んでいただきました。感謝しても感謝しきれない思いです。いしずえの交流会等の行事にも何度も足をお運びいただき、貴重なご講演をいただくとともに、被害者に直接ご指導ご助言を賜りました。日ノ下先生をはじめとする研究班の先生方のご助言は本当に有り難く、被害者にとって大きな支えになりました。

日ノ下先生のご尽力により、リハビリテーション、ペインクリニックをはじめ、より多くの先生方にご協力いただけるようになりました。また、日ノ下先生は、「サリドマイド胎芽症診療ガイド」を作成されるとともに、研究会を通じて全国の医療従事者のネットワークを作られ、サリドマイド被害者の特徴を踏まえた診療に関する情報を発信されました。さらに、国際シンポジウム等を通じて海外の医師・研究者との情報交換をされました。サリドマイド被害者の新規認定に関しては、「サリドマイド胎芽症診断の手引き」をご作成いただきました。

これまでの幅広い取り組みに心より御礼申し上げますとともに、引き続きご指導ご助言をいただきたく何卒よろしくお願い申し上げます。

令和　3年　3月　1日

厚生労働大臣
~~(国立医薬品食品衛生研究所長)~~ 殿
~~(国立保健医療科学院長)~~

機関名　国立研究開発法人国立国際医療研究センター
所属研究機関長　職　名　理事長
氏　名　國土　典宏　　印

次の職員の令和２年度厚生労働行政推進調査事業費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　医薬品・医療機器等レギュラトリーサイエンス政策研究事業

２．研究課題名　サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築

３．研究者名　（所属部局・職名）　国立国際医療研究センター病院・腎臓内科　診療科長

（氏名・フリガナ）　日ノ下　文彦　・　ヒノシタ　フミヒコ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　☑	□		□
遺伝子治療等臨床研究に関する指針	□　☑	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　☑	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　☑	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　☑	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ☑　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ☑　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ☑　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ☑　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ☑（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和　3年　3月　1日

厚生労働大臣
~~（国立医薬品食品衛生研究所長）~~ 殿
~~（国立保健医療科学院長）~~

機関名　国立研究開発法人国立国際医療研究センター
所属研究機関長　職　名　理事長
氏　名　國土　典宏　　印

次の職員の令和２年度厚生労働行政推進調査事業費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　医薬品・医療機器等レギュラトリーサイエンス政策研究事業

２．研究課題名　サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築

３．研究者名　（所属部局・職名）　放射線診療部門・部門長

（氏名・フリガナ）　田嶋　強　・　タジマ　ツヨシ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和　3年　3月　1日

厚生労働大臣
~~(国立医薬品食品衛生研究所長)~~ 殿
~~(国立保健医療科学院長)~~

機関名　国立研究開発法人国立国際医療研究センター

所属研究機関長　職　名　理事長

氏　名　國土　典宏　　印

次の職員の令和２年度厚生労働行政推進調査事業費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　医薬品・医療機器等レギュラトリーサイエンス政策研究事業

２．研究課題名　サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築

３．研究者名　（所属部局・職名）　精神科・心理療法士

（氏名・フリガナ）　曽根　英恵　・　ソネ　ハナエ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

令和3年3月31日

厚生労働大臣
~~(国立医薬品食品衛生研究所長)~~ 殿
~~(国立保健医療科学院長)~~

機関名　独立行政法人国立病院機構
京都医療センター
所属研究機関長　職　名　院長
氏　名　小池　薫　印

次の職員の令和２年度厚生労働行政推進調査事業費補助金の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　医薬品・医療機器等レギュラトリーサイエンス政策研究事業

２．研究課題名　サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築

３．研究者名　（所属部局・職名）　健診センター　健診センター長

（氏名・フリガナ）　田上　哲也　・　タガミ テツヤ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	□	京都医療センター	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2021年　1月　26日

厚生労働大臣
~~（国立医薬品食品衛生研究所長）~~ 殿
~~（国立保健医療科学院長）~~

機関名　帝京大学

所属研究機関長　職　名　学長

氏　名　沖永　佳史　印

次の職員の令和元年度厚生労働行政推進調査事業費補助金の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　医薬品・医療機器等レギュラトリーサイエンス政策研究事業

2．研究課題名　サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築

3．研究者名　（所属部局・職名）　医学部内科学講座・教授

（氏名・フリガナ）　長瀬　洋之・ナガセ　ヒロユキ

4．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	国立国際医療センター	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

6．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2/128

令和３年３月１日

厚生労働大臣　殿

機関名　東京大学

所属研究機関長　職　名　総長

氏　名　五神　真　印

次の職員の令和２年度厚生労働行政推進調査事業費補助金の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　医薬品・医療機器等レギュラトリーサイエンス政策研究事業

２．研究課題名　サリドマイド胎芽症患者の健康、生活実態の把握及び支援基盤の構築（20KC2005）

３．研究者名　（所属部局・職名）　医学部附属病院・教授

（氏名・フリガナ）　芳賀　信彦・ハガ　ノブヒコ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	国立国際医療研究センター	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。