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早老症の医療水準やQOL向上を目指す集学的研究

令和2年度　総括・分担研究報告書

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総括研究報告書

早老症の医療水準やQOL向上を目指す集学的研究

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研究要旨

早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例としてWerner症候群（以下WSと略）とHutchinson-Gilford Progeria症候群（以下HGPSと略）が知られる。WSは思春期以降に発症し、がんや動脈硬化のため40歳半ばで死亡する早老症であり、国内推定患者数は700～2000名、世界の報告の6割を日本人が占める。平成21～25年度の難治性疾患克服研究事業により 25 年ぶりの診断基準改訂と治療の標準化や世界初の WS 診療ガイドラインが作成され、平成26年度の政策研究事業によりWS重症度分類が作成され、平成26年5月指定難病に指定された。さらに難治性疾患実用化研究として推進されている早老症レジストリー研究と連携し、平成29年度には診療ガイドライン、重症度分類を改訂した。一方、HGPSは1～2歳時に早老徴候が出現し、10歳代でほぼ全例が死亡する重篤な小児疾患である。平成25年度に施行した全国調査により、我が国で6名の患者が新規に同定され、平成29年度には世界初のHGPS診断基準が作成された。

本研究は①WS 診療ガイドラインの普及啓蒙、②早老症レジストリー研究と連携した診療ガイドラインの検証、③その他の早老症研究（Rothmund-Thomson症候群の現状把握、WS類似疾患の診断基準作成）、④HGPSの診療ガイドライン作成、⑤ WS、HGPSの早期診断の実現と小児成人期移行医療（トランジッション）の推進を行う。本研究班では、内科医・外科医・小児科医・臨床研究専門家の連携・融合による集学的な取り組みを通じて、小児から成人までの「早老症」の予後改善を目指す。

A．研究目的

早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner 症候群（以下 WS と略）、Hutchinson-Gilford Progeria 症候群（以下 HGPS と略）や Rothmund-Thomson 症候群（以下 RTS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡し、国内推定患者数は約 700～2,000 名、世界の報告の 6 割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により診断基準改訂と世界初の WS 診療ガイドラインが作成され、平成 26 年度、重症度分類が作成され、平成 26 年 5 月指定難病に指定された。平成 29 年度には診療ガイドライン、重症度分類を改訂し、令和 2 年には診療ガイドラインを英文誌に公表した。HGPS は 1～2 歳時に早老徴候が出現し、10 歳代でほぼ全例が死亡する重篤な小児疾患であり、平成 25 年度に施行した全国調査により、我が国で 6 名の患者が新規に同定され、平成 29 年度には世界初の HGPS 診断基準が作成され、令和元年 4 月指定難病

に指定された。RTS は特徴的な皮膚所見が乳児期から認められ骨格異常や癌腫を合併する。平成 30 年に施行した全国調査により 10 名の患者を同定し、診断基準を改定した。さらに早老症の実態を明らかにすべく難治性疾患実用化研究として推進されている早老症レジストリー研究と連携してきた。これらの研究を推進し、早老症の医療水準や患者 QOL 向上に貢献することを本研究の目的とする。

Ｂ．研究方法

WS研究：①都道府県難病診療連携拠点病院を中心とした、難病医療支援センター、関連学会やナショナルセンター等と連携して診断基準や診療ガイドラインを啓蒙普及する。②関連学会において改訂版 重症度分類の承認を得る、③WS の早期診断のための情報を収集するとともに、小児科と内科の連携により小児成人期以降医療の体制を整える。④早老症レジストリーと協力してAMED「再生医療実現拠点ネットワークプログラム（疾患特異的iPS細胞の利活用促進・難病研究加速プログラム）」「老化メカニズムの解明・制御プロジェクト／個体・臓器老化研究拠点」を支援する。

HGPS研究：①診療ガイドラインの作成へ向け、エビデンス収集を開始する。②関連学会において重症度分類の承認を得る、③患者・家族会の設立を支援する。④小児科と内科の連携により小児成人期以降医療の体制を整える。

その他の早老症：①RTS の我が国おける現状把握のための全国研究を行う。②RTS の全国疫学調査の結果をもとに診断基準を改定する。

Ｃ．研究結果

WS 研究：2012 年に発表した日本語版の診療ガイドラインに 1996 年から 2020 年までの臨床論文のシステマティックレビューや最新の治療経験を加えて、１．脂質異常症、脂肪肝　２．サルコペニア　３．糖尿病　４．骨粗鬆症　５．感染症　６．皮膚潰瘍(皮膚科治療)　７．下肢潰瘍（形成外科治療）8．アキレス腱の石灰化の項目に関してより実臨床に即した診療ガイドライン (management guideline 2020)を作成し英文で発表した。この診療ガイドラインを用いることにより、日本国内のみならず世界中の WS の治療が標準化され、患者の生命予後や QOL 向上に寄与することを期待したい。さらに、「ウェルナー症候群ハンドブック～ウェルナー症候群の皆さんと家族、医療者のためのガイド～」を作成し、1．ウェルナー症候群とは、2．生活で気につけること、3．糖尿病、4．脂質異常症、5．感染症、7.目の病気、8.サルコペニアと骨粗しょう症、9．足の潰瘍（治りにくいキズ)、10.腫瘍の 10 項目に関して平易な言葉で解説した。（分担研究　葛谷、竹本、谷口（俊）、茂木、忍足、谷口（晃））。

HGPS 研究：平成 24～29 年度厚生労働科学研究費補助金(難治性疾患等克服研究事業(難治性疾患克服研究事業))「早老症の病態解明、診断・治療法の確立と普及を目的とした全国研究」(研究代表者：横手幸太郎)により国内の HGPS 症例について全国調査とアジアにおける古典型 HGPS の臨床像をもとに HGPS 診断基準策定を行い、日本小児遺伝学会理事会で診断基準の承認を受けた。さらに指定難病登録のため厚生労働省難病対策課の指示により臨床調査個人票の策定など事務手続きをすすめ、2019 年 5 月に指定難病に告示された。2019 年夏から適用が開始されたとともに、HGPS の診断に不可欠な LMNA 遺伝子検査は公益財団法人かずさ DNA 研究所が受託し保険外検査としての運用が始まった。このように検査法と診断基

準が整備されたことを受け、2020 年（令和 2 年）度診療報酬改定において LMNA 遺伝子検査が保険診療の遺伝学的検査（5,000 点）に追加された。さらにまた HGPS 患者家族と専門研究者・臨床医を結び付ける国際的 NPO 法人である Progeria Research Foundation(PRF)が発行する患者向けハンドブック（The Progeria Handbook 2nd Edition）の日本語訳（プロジェリアハンドブック第２版）を作成し、PRF に提供しホームページに公開された。これまでの診療情報を統合し、広く日本社会に発信するため日本語のホームページを作成し令和 3 年 1 月に公開した。さらに GeneReviews 日本語版に疾患情報を日本語で公開した。（分担研究　井原、小崎、松尾)。

その他の早老症：全国の小児科専門医研修施設、日本皮膚科学会認定研修施設に一次調査を送付し、回答のあった確定例･疑い例 8 例を臨床的に RTS と考え二次調査を行った。記載のない 1 例除き、7 例に多型皮膚萎縮症、眉毛睫毛の異常の皮膚症状認めた。骨症状は 3 例で認めた。骨肉腫で 2 例が死亡していた。白内障は2例に認められた。発達遅滞は 4 例に認め比較的頻度が高かった。RECQL4 遺伝子は 7 例に検索されていたが、異常があったのは 2 例のみであった。重症度は、死亡から無症状まで幅広く分布していた。以上より、本邦における RTS の実態が明らかになった。RECQL4 遺伝子異常の存在しない症例も多く、新規病因遺伝子の探索並びに、診断基準の検討が必要であると考えられた。（分担研究　金子)。

D．考察

ほぼ研究計画に沿って研究が行われた。本研究組織は、全国各地域の大学や国立研究センターに在籍する分担研究者と研究協力者によって構成される。これらのメンバーが WS、HGPS、RTS の症例集積を継続的に実施し、主要なエビデンスを収集、相互に協調しつつ診断基準や診療ガイドラインの作成・改訂や重症度分類の作成、検証が行われた。また、臨床研究中核病院である千葉大学医学部附属病院の臨床試験部に設置された「早老症レジストリー」事務局において症例の登録とフォローアップが継続進行中であり今後、長期的に臨床経過が詳細に観察され、現代の早老症患者の自然史が明らかになることが期待される。さらに本研究の成果(症例情報)をベースとして新規研究課題が採択された、AMED「再生医療実現拠点ネットワークプログラム(疾患特異的 iPS 細胞の利活用促進･難病研究加速プログラム)」(課題名:早老症疾患特異的 iPS 細胞を用いた老化促進メカニズムの解明を目指す研究(研究開発代表者))および「老化メカニズムの解明･制御プロジェクト／個体･臓器老化研究拠点」(課題名:早老症に立脚したヒト老化病態の解明とその制御への応用(研究開発分担者))の研究推進を継続支援してきた。

とくに HGPS、WS は患者・家族用の資材が作成され、患者の日常生活における QOL 向上に貢献するものと思われる。今後も公開講座などを通じて国民へ啓発活動を行ってゆき、最終的に、小児から成人までの「早老症」の予後改善を目指してゆきたい。

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２．学会発表

前澤 善朗 (2020) 第 62 回日本老年医学会学術集会会 シンポジウム３ AMED 老化拠点からの発信「早老症ウェルナー症候群の臨床症候と細胞老化」 8 月 4 日、ウェブ開催

Ｇ．知的財産権の出願・登録状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

ウェルナー症候群:
診療の質および患者 QOL 向上を目指した研究

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研究要旨:早老症は、全身に老化徴候が早発・進展する疾患の総称である。その代表例として Werner 症候群（以下 WS と略）が知られる。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡し、国内推定患者数は約 700～2,000 名、世界の報告の 6 割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により診断基準改訂と世界初の WS 診療ガイドラインが作成され、平成 26 年度、重症度分類が作成され、平成 26 年 5 月指定難病に指定された。平成 29 年度には診療ガイドライン、重症度分類を改訂し、令和 2 年には診療ガイドラインを英文誌に公表した。さらに早老症の実態を明らかにすべく難治性疾患実用化研究として推進されている早老症レジストリー研究と連携してきた。本研究では１．診療ガイドラインの改定を行い、日本語版と英語版を作成し、英語版に関しては英文雑誌に掲載した。２．患者用リーフレットを作成した。これらの試みにより WS の診療の質および患者 QOL 向上に貢献してゆきたい。

A. 研究目的

早老症あるいは早期老化症候群（progeroid syndrome、premature aging syndromes）では暦年齢に比較して加齢現象が促進して観察される。特定の早老徴候が特定の臓器に誇張された形で観察されることより、部分的早老症候群（segmental progeroid syndrome）とも呼ばれる。代表的な疾患としてウェルナー症候群（以下 WS と略）や Hutchinson-Gilford 症候群が挙げられる。それぞれ原因遺伝子は同定されているが、早老機序は必ずしも明らかではなく、根本的な治療法開発には至っていない。WS は思春期以降に発症し、がんや動脈硬化のため 40 歳半ばで死亡する早老症であり、国内推定患者数は 700～2,000 名、世界の報告の6割を日本人が占める。平成 21～25 年度の難治性疾患克服研究事業により 25 年ぶりの診断基準改訂と治療の標準化や世界初の WS 診療ガイドラインが作成され、平成 26 年度の政策研究事業により WS 重症度分類が作成され、平成 26 年 5 月指定難病に指定された。さらに難治性疾患実用化研究として推進されている早老症レジストリー研究と連携し、平成 29 年度には診療ガイドライン、重症度分類を改訂した。本研究の目的はこれまでの研究をさらに発展させ WS の診療の質および患者 QOL 向上に貢献することである。

B. 研究方法

1. 診療ガイドラインの改定と普及

2. 患者用リーフレットの作成と普及

（倫理面への配慮）

本研究では個人情報を収集するため、個人情報保護法、文部科学省・厚生労働省・経済産業省：ヒトゲノム・遺伝子解析研究に関する倫理指針、文部科学省・厚生労働省：疫学研究に関する倫理指針、厚生労働省：臨床研究に関する倫理指針経済産業省：情報システムの信頼性向上に関するガイドライン、民間部門における電子計算機処理に係る個人情報の保護に関するガイドラインなどを順守して研究計画の立案・遂行を行う。調査・研究の実施に際しては、各施設の倫理委員会に諮り、許可を申請する。患者の血液検体解析においては、事前に文書で本人に説明と同意を得ることとし、不参加の場合でも何らの不便・不都合とならないことを伝える。解析にあたっても患者のプライバシーに配慮し、臨床経過が個人と結びつかないようデータを管理した。

C. 研究結果

2012 年に発表した日本語版の診療ガイドラインに 1996 年から 2020 年までの臨床論文のシステマティックレビューや最新の治療経験を加えて、1．脂質異常症、脂肪肝　2．サルコペニア　3．糖尿病　4．骨粗鬆症　5．感染症　6．皮膚潰瘍 (皮膚科治療)　7．下肢潰瘍（形成外科治療）8．アキレス腱の石灰化の項目に関してより実臨床に即した診療ガイドライン (management guideline 2020)を作成し英文で発表した (1－8)。この診療ガイドラインを用いることにより、日本国内のみならず世界中の WS の治療が標準化され、患者の生命予後や QOL 向上に寄与することを期待したい。さらに、「ウェルナー症候群ハンドブック～ウェルナー症候群の皆さんと家族、医療者のためのガイド～」を作成し、1．ウェルナー症候群とは、2．生活で気につけること、3．糖尿病、4．脂質異常症、5．感染症、7. 目の病気、8. サルコペニアと骨粗しょう症、9．足の潰瘍（治りにくいキズ）、10. 腫瘍の 10 項目に関して平易な言葉で解説した。

D. 考察

2009 年 厚生労働省科学研究費補助金 難治性疾患研究事業では、我が国おける WS の現状を調査すべく、2009 年年 9 月には一次アンケート調査を、2009 年 10 月には一次アンケートで明らかとなった症例対する二次アンケート調査を行った。そしてこれらの調査で明らかなった臨床的特徴もとにして、診断基準の改訂が行われた (9)。2012 年 2 月 19 日には東京国際フォーラムにて「遺伝性早老症ウェルナー症候群のこれまでの研究の歩みとこらからの展望」とのタイトルで研究報告会が行われたが、この会では患者・家族の会も同時に行われ、その当時の最新の研究成果を研究者のみならず患者・家族会でも共有した。この年には我が国におけるウェルナー症候群の臨床経験をもとにして世界で初めて「ウェルナー症候群の診療ガイドライン 2012 年版」が発表された。2015 年には WS の重症度分類を作成し発表した (10)。そして、2015 年 7 月 1 日、WS は指定難病に選定された。

その後、2016 年には 2 回目の全国調査が施行され、2020 年にはレジストリー研究の一部が報告されている (11)。また大阪大学の中神らは創修復作用と抗菌活性の両方の特性をもつ SR-0379 液を難治性潰瘍に対する外用薬として開発し、この薬剤の効果が WS においても検証された。その結果、SR-0379 はプラセボに対して有意に潰瘍サイズを縮小（22.9% vs. 0.1%）させたことが報告されている (12)。今後のウェルナー症候群の難治性潰瘍治療に貢献することを期待したい。また最近の WS の臨床的特徴を検討すべく、2009 年の全国 2 次調査の結果と、2020 年のレジストリー研究の結果が比較検討された (11)。その結果、難治性皮膚科潰瘍、狭心症、心筋梗塞、悪性腫瘍の併存率が減少していることが報告されている。狭心症、心筋梗塞に関しては診断を受けた症例の脂質、血圧、血糖管理の成果が奏功している可能性がある。内服薬の比較でもスタチンは両年ともに 65％以上に、ARB は 42.1%、35.3%処方されていた。血糖降下薬に関しては両年で使用トレンドが異なってきているが、SGLT2 阻害剤、GLP-1 受容体作動薬といった一般の糖尿病患者において心血管イベント抑制作用が報告されている薬剤も登場してきており、WS における適応やその効果に関して今後の解析が必要と思われる。下肢潰瘍

や悪性腫瘍の併存率が近年減少している理由は不明であるも、今後も注意深い経過観察が必要と思われる。さらに今回作成されたガイドドラインを用いることにより、日本国内のみならず世界中の WS の治療が標準化され、患者の生命予後や QOL 向上に寄与することを期待したい。さらに、WS 患者向けのリーフレットを作成し、今後我が国おける WS 患者や家族さらに医療者に利用していただくよう周知してゆく予定である。

E. 結論

一般的に老化を進行させる要因として遺伝因子と環境因子が挙げられるが、WS においては遺伝要因がその早老機序に関与することは疑いの余地はない。一方、WS 患者の平均寿命は以前の報告に比し延長しており(13)、WS をより早期に診断し、より早期から合併する代謝性疾患や下肢潰瘍の管理を行うことは寿命延長や QOL の向上の観点から意義は大きい。WS は日本に多いとはいえ、推定 2000 症例であり、希少疾患である。教科書的に、アメリカでは 8000 種類の希少疾患に 300 万人罹患しており、適切な診断までに平均で 7.6 年かかり、多くの不必要な検査がなされること、診断までに 8 人の医師（4 人の家庭医と 4 人の専門医）を受診し 2〜3 の異なった診断をされると記載がある。WS の発症年齢が 26.1±9.5 年であるのに対し、診断年齢は 42.5±8.6 年と報告されており、適切な診断まで実に 16 年の歳月を要している（11)。このギャップを埋めることは喫緊の課題といえよう。また本研究班ではウェルナー症候群に限らず、Hutchinson-Gilford 症候群や Rothmund-Thomson 症候群の臨床研究が行われている。2018 年 2 月 16 日〜18 日には、千葉県のかずさアカデミアパークにて「国際シンポジウム・早老症と関連疾患 2018」が開催され多くの臨床医、研究者による意見交換が行われた（14)。このような活動を通じて早老症全体の ADL、OOL の向上や予後が改善することを今後も期待したい。

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F. 健康危惧情報

特になし。

G. 研究発表

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2. 学会発表

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H. 知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得
   無し
2. 実用新案登録
   無し
3. その他
   無し

厚生労働科学研究費補助金（難治性疾患等政策研究事業）
分担研究報告書

ハッチンソン・ギルフォード症候群：日本語ホームページの策定とGeneReviews 日本語版疾患情報の公開

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研究要旨：平成 24～29 年度厚生労働科学研究費補助金(難治性疾患等克服研究事業(難治性疾患克服研究事業)）「早老症の病態解明、診断・治療法の確立と普及を目的とした全国研究」(研究代表者：横手幸太郎)により国内のハッチンソン・ギルフォード症候群（HGPS）症例について HGPS 診断基準策定を行い、日本小児遺伝学会理事会で診断基準の承認を受けた。さらに臨床調査個人票の策定など事務手続きをすすめ、2019 年に指定難病に告示され適用が開始された。HGPS の診断に不可欠な *LMNA* 遺伝子検査は公益財団法人かずさ DNA 研究所が受託し保険外検査としての運用が始まった。検査法と診断基準が整備されたことを受け、2020 年（令和 2 年）度診療報酬改定において *LMNA* 遺伝子検査が保険診療の遺伝学的検査（5,000 点）に追加された。HGPS 患者家族と専門研究者・臨床医を結び付ける国際的 NPO 法人である Progeria Research Foundation(PRF)が発行する患者向けハンドブック（The Progeria Handbook 2nd Edition）の日本語訳（プロジェリアハンドブック第２版）を作成し、PRF に提供しホームページに公開された。2020 年度はこれまでの診療情報を統合し、広く日本社会に発信するため日本語のホームページを作成した（令和 3 年 1 月に公開)。さらに GeneReviews 日本語版に疾患情報を公開した。

Ａ．研究目的

ハッチンソン・ギルフォード症候群(Hutchinson-Gilford progeria syndrome;HGPS)は、遺伝性早老症の中でも症状が特に重篤な疾患であり、出生後より重度の成長障害、脱毛、老化顔貌、皮下脂肪の減少などを呈し、特に動脈硬化性疾患の合併症により平均寿命は 14.6 歳と報告されている難治稀少疾患である。

昨年度は、指定難病登録のため（１）臨床調査個人票と病気の解説と FAQ の策定、（２）*LMNA* 遺伝子検査の保険診療承認に向けた準備と受託解析の確立を行い、また HGPS 患者家族と専門研究者・臨床医を結び付ける国際的 NPO 法人 Progeria Research Foundation(PRF)が発行する患者向けハンドブックの日本語訳を作成した。

本年度はこれまでの情報を統合し広く日本社会に発信するため日本語のホームページを作成した（令和 3 年 1 月に公開)。さらに GeneReviews

日本語版に疾患情報を公開した。

Ｂ．研究方法と結果

（１）日本語のホームページ

（http://square.umin.ac.jp/hgps/）

＜トップページ＞

疾患概要

トピックス

＜2 ページ目＞

疾患についての説明

診断基準と重症度分類

＜3 ページ目＞

プロジェリア・ハンドブックの紹介と

ダウンロード

＜4 ページ目＞

行政情報

＜5 ページ目＞

症例登録

国際患者登録

問い合わせ先

詳細については、参考資料参照。

（２）GeneReviews 日本語版登録

（http://grj.umin.jp/grj/hgps.htm）

今回、我々は、超稀少疾患であり、ニーズが少ないため、今だ GeneReviews Japan 日本語版に登録されてなかった、本疾患 HGPS について GeneReviews 原文全ての和訳を行った。GeneReviews は、米国の NIH および U.S. Department of Energy のサポートを受け，主に University of Washington によって運営されている医療スタッフ向けの遺伝性疾患情報サイトである。遺伝性疾患の症状や診断，遺伝学的検査，遺伝カウンセリングなどについて，専門家による解説が参照でき，臨床遺伝医学に関する総合情報サイト GeneTests のセクションのひとつとして公開されている。Gene Reviews Japan (GRJ) は全国遺伝子医療部門連絡会議の支援をうけ、GeneReviews の内容を日本の医療関係者，当事者向けに重要性の高いと思われる項目を中心に日本語訳を公開しているサイトである（和訳にあたり、GeneTests から許可を得ている)。和訳された原本は、2021 年 1 月 13 日に GeneReviews Japan に「ハッチンソン-ギルフォード プロジェリア症候群」として公開した。信頼性の高いサイトであり、より医療者向けへの検索・認知しやすいことが予測された。Google 検索では、検索順位がすでに上位 2～３位である。超稀少疾患であり、限られた医学的情報・エビデンスの下、Progeria Research Foundation(PRF)が発行する患者向けハンドブックと重複する内容もあるが、有用な情報発信をすることができた。

Ｄ．考察

平成 24 年度に始まった本研究班の取り組みが着実に成果を積み重ね、指定難病の認定と遺伝学的検査の保険検査承認に至った。今後保険診療で実施される遺伝学的検査により HGPS は確実に診断されることになり、また未診断例の発見が増えることが見込まれる。また長期生存例においても、指定難病に認定されたことで社会的、経済的支援が受けることが可能となり、今後は行政側の社会保障体制の整備も進むことが期待される。昨年策定した患者向けハンドブック日本語版とともに

本年度公開した日本語ホームページとGeneReviews 日本語版により本疾患の情報を日本人が日本語で容易にアクセス可能になり、医療現場、学校、行政機関など幅広い利用が期待できる。

Ｅ．結論

日本人向け日本語ホームページと GeneReviews 日本語版を公開した。次年度以降は、①患者・家族会の設立支援、②小児科と内科の連携により小児・成人を一体的に研究・診療できる体制の構築、③患者登録レジストリの運用、④Minds ガイドラインセンター「診療ガイドラインの手引き」に準拠した診療ガイドラインの作成、⑤ファルネシルトランスフェレース阻害薬（FTI）の国内承認に向けて進めていく予定である。

Ｇ．研究発表

1.　著書発表

なし

２．学会発表

なし

３．ホームページ等

1）ハッチンソン・ギルフォード症候群：日本語ホームページ
http://square.umin.ac.jp/hgps/

2）ハッチンソン・ギルフォード症候群：GeneReviews 日本語版
http://grj.umin.jp/grj/hgps.htm

Ｈ．知的財産権の出願・登録状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

ロスムンド･トムソン症候群の重症度の検討

研究分担者　金子　英雄　岐阜県総合医療センター　小児療育内科部長

研究要旨:ロスムンド・トムソン症候群は、多形皮膚萎縮症、骨格の異常を特徴とする常染色体劣性の遺伝形式をとる疾患である。本研究の目的はロスムンド・トムソン症候群の本邦での患者数、臨床症状を明らかにし、以前作成された診断基準の検証を行い、普及させることで、患者の QOL の向上、生命予後の改善を図ることである。全国調査を行い臨床的にロスムンド・トムソン症候群と診断された8名の重症度につき解析した。無症候から死亡まで、重症度は幅広く分布していることが明らかになった。また、本疾患が指定難病であることの主治医の認知度は高かった。今回の調査により、本邦におけるロスムンド･トムソン症候群の重症度が明らかになった。

A. 研究目的

本研究の目的は、ロスムンド・トムソン症候群の患者数,臨床症状等を明らかにし、以前作成された診断基準を検討し修正後、普及させることにより、患者のQOLの向上、生命予後の改善を図ることである。本邦における実態を明らかにするため、二次アンケート調査を実施した。今回、ロスムンド・トムソン症候群の重症度、認知度につき検討した。

B. 研究方法

一定規模以上の病院に調査用紙を送付し、アンケートを実施し、全国の病院からの患者情報、検体の収集を行った。一次調査に、確定例または疑い例ありと得られた 11 例に二次調査を行った。二次調査はロスムンド・トムソン症候群の症例数、皮膚病変、骨病変、重症度について質問した。重症度は、modified Rankin Scale (mRS) にて検討した。

（倫理面への配慮）

臨床情報を収集する場合は、連結可能匿名化した。一次調査、二次調査に関しては「ロスムンド･トムソン症候群の全国疫学調査」として国立病院機構長良医療センター･岐阜県総合医療センターの倫理委員会の承認を得た。

C. 研究結果

11 例のうち 10 例から回答が得られた。2 例は該当する疾患がないとのことであった。8 例について解析を行った。8 例のうち 6 例から mRS に対しての回答があった。

mRS のスケール0:まったく症候がない（自覚症状及び他覚徴候がともにない状態である）**1例**。

スケール1:症候はあっても明らかな障害はない:日常の勤めや活動は行える（自覚症状及び他覚徴候はあるが、発症以前から行っていた仕事や活動に制限はない状態である）**1例**。

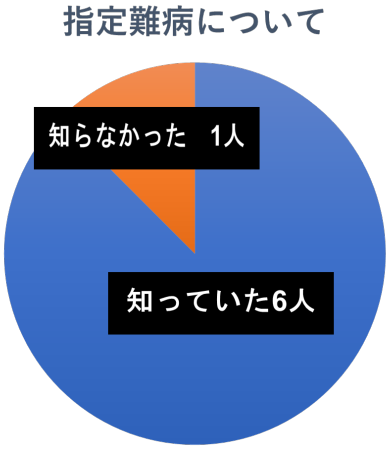
スケール2:軽度の障害:発症以前の活動が全て行えるわけではないが、自分の身の回りのことは介助なしに行える（発症以前から行っていた仕事や活動に制限はあるが、日常生活は自立している状態である）**1例**。

スケール3:中等度の障害:何らかの介助を必要とするが、歩行は介助なしに行える（買い物や公共交通機関を利用した外出などには介助を必要とするが、通常歩行、食事、身だしなみの維持、トイレなどには介助を必要としない状態である）**1例**。

スケール4:中等度から重度の障害:歩行や身体的要求には介助が必要である（通常歩行、食事、身だしなみの維持、トイレなどには介助を必要とするが、持続的な介護は必要としない状態である）**0例**。

スケール5:重度の障害:寝たきり、失禁状態、常に

介護と見守りを必要とする（常に誰かの介助を必要とする状態である）**0例**。
スケール6：死亡**2例**。



また、主治医にロスムンド・トムソン症候群が指定難病であることを知っているか尋ねたところ、7名のうち6名が知っているとの回答であった（図）。

D. 考察

ロスムンド・トムソン症候群は、常染色体劣性の稀な疾患である。全国調査でも8例しか登録がなく、その重症度は明らかではなかった。今回の調査では、無症候から死亡まで、重症度は幅広く分布していることが明らかになった。今後、患者のフォロー行い重症度の変化についての検討が必要と考えられた。また、ほとんどの主治医が、ロスムンド・トムソン症候群が指定難病であることを認識しており、本研究事業や学会発表等で、医師への認知度が高まった可能性が考えられた。

E. 結論

ロスムンド・トムソン症候群の全国調査を行い重症度を解析した。無症候から死亡まで、重症度は幅広く分布していることが明らかになった。

F. 健康危惧情報

特になし。

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本邦におけるロスムンド・トムソン症候群の実態調査
第65回日本人類遺伝学会　Web 開催
2020 年 11 月 18 日～12 月 2 日

H. 知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得
無し
2. 実用新案登録
無し
3. その他
無し

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

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PREFACE

Management guideline for Werner syndrome 2020

Establishing an evidence-based approach for the treatment of Werner syndrome

Werner syndrome (WS) is an autosomal recessive disorder sometimes referred to as "premature aging syndrome" because, beginning in puberty, it presents with symptoms such as cataracts, and loss and graying of hair, which makes individuals look relatively old for their age. Of the world's reported cases to date, 60–80% are from Japan, where the incidence of WS in the population is unusually high. The life expectancy for people with WS is shorter because of its frequent comorbidities, which include diabetes, arteriosclerosis and malignant tumors. Although individuals with this disease "age prematurely," simply referring to it as "accelerated aging" ignores the fact that the incidence of some common aspects of aging, such as dementia, are rare. Moreover, its comorbid malignant tumors are more frequently non-epithelial "sarcomas" than the more common epithelial "cancers". In addition, the disease has a high incidence of intractable ulcers in the legs and feet, which result in pain and infections that can have a major negative impact in the person's quality of life and vital prognosis.

In Japan, in 1984, the Ministry of Health and Welfare Specific Disease Research Group created a guide for the diagnosis of WS, which greatly contributed to the understanding of the disease. Since then, remarkable progress has been made in cellular research at the molecular level. In 1996, a mutation in the DNA helicase Werner syndrome protein (WRN) encoded by the RecQ genes on chromosome 8 was identified as the cause of the disease. Although no fundamental treatment has been developed for the disease, many studies have been published on its clinical features and the treatment of its specific morbidities. Findings of these studies are beginning to suggest that patient life expectancy could potentially be extended with appropriate treatment interventions.

It should be noted that numerous Japanese researchers have played a central role in advancing this research. On the other hand, no systematic survey of the number of patients, their symptoms and outcomes had been conducted in Japan for more than a quarter century. Furthermore, it can be presumed that a considerable number of Japanese individuals suffering from WS are never correctly diagnosed.

With this background, supported by a Health and Labour Sciences Research Grant for Research Projects on Overcoming Intractable Diseases, our research team set out to advance research on this disease with the following goals: (i) conduct a national assessment of the prevalence and treatment of patients with WS, (ii) create highly objective diagnostic standards that could be easily used as part of daily medical care, and (iii) standardize treatments of the syndrome and raise public awareness about the disease and its treatment. For the 2009–2013 Research Projects on Overcoming Intractable Diseases, the diagnostic criteria for WS were revised for the first time in 25 years, treatments were standardized, and the world's first guidelines for its diagnosis and treatment were developed. A WS severity classification system was created by the 2014 Intractable Disease Policy Research Project, and in May 2014, WS was designated as an intractable disease (i.e., eligible for public medical expense subsidy). Regarding international forums, we sponsored a symposium in February 2012 for WS researchers from Japan and overseas in Tokyo, and in February 2018, we sponsored the International Meeting on RecQ Helicases and Related Diseases 2018, held in Chiba Prefecture.

For the 2020 version of the guidelines, we asked the leading WS researchers in all domains (including basic research, clinical research and medical care) for contributions beyond their fields of expertise. In principle, diagnostic and treatment guidelines consist of procedures that can be recommended scientifically and

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objectively based on collections of findings from clinical research backed by a large amount of evidence. However, for a rare disease such as WS, no large-scale treatment intervention studies can be conducted; therefore, the "evidence" available is limited. Thus, rather than being true "guidelines," this management guideline is more of a "consensus guide" to clinical practice. However, we will be flattered if this attempt garners a certain amount of appreciation as "the first guide for the standardized treatment of WS that can be performed anywhere in the world." Furthermore, using this guide as a foundation, it is our responsibility as researchers to make periodic revisions as we work toward the completion of "true guidelines," by trying to increase the amount of evidence available and establish the fundamentals of treatment.

In 2010, our research team started the world's first WS peer support group, the Werner Syndrome Patient and Family Association, building a foundation for patients and their families nationwide to make the most of treatment by sharing their concerns and information with peers. In addition, we were happy that both of the aforementioned symposia were jointly held with association, which enabled researchers to hear patients and their families "live" and provided researchers with the latest research results for their benefit.

Finally, we would like to express our sincere gratitude to everyone who made this management guideline possible, including the doctors and medical facilities nationwide that kindly cooperated with our research team, all the co-researchers and collaborators on this project who worked so hard on the guidelines, all members of the Werner Syndrome Patient and Family Association who really motivated us, everyone at the Japan Patients Association, and everyone involved with the Health and Labour Sciences Research Grant for the Intractable Disease Policy Research Project.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

SOCIAL RESEARCH, PLANNING AND PRACTICE

Management guideline for Werner syndrome 2020 1. Dyslipidemia and fatty liver associated with Werner syndrome

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For the purpose of examining the characteristics of dyslipidemia and fatty liver in patients with Werner syndrome in Japan in recent years, we searched all case reports of Japanese Werner syndrome reported on Medical Online and PubMed since 1996, and collected and examined the data and clinical features described in these reports. In addition, as there are few descriptions of treatment methods in these reports from Medical Online and PubMed, we analyzed 12 cases for which detailed data on treatment methods are available at Chiba University. **Geriatr Gerontol Int 2020; ••: ••–••.**

Keywords: clinical medicine, geriatric medicine, management guideline, Werner syndrome.

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Introduction

Arteriosclerosis is one of the two leading causes of death in Werner syndrome patients, along with malignancy.[1] Among the various forms of arteriosclerosis Werner syndrome patients develop, coronary artery diseases and peripheral arterial disease have a high incidence, and the latter plays a role in making skin ulcers in Werner syndrome patients refractory.[2] Arteriosclerosis in Werner syndrome patients is considered to be one of the features of disease-specific premature aging, whereas disorders of carbohydrate metabolism and lipid metabolism associated with Werner syndrome also act as promoting factors. Insulin resistance associated with a fatty liver (non-alcoholic fatty liver disease [NAFLD]) and accumulation of visceral fat has been considered to be greatly involved in these metabolic abnormalities.[3–5] Recently, the ratio of hepatocellular cancer caused by NAFLD or non-alcoholic steatohepatitis (NASH) in all hepatocellular cancers has reportedly risen in the general population, thus the management of these diseases in Werner syndrome patients is also important.[6,7]

It has been said that Werner syndrome patients develop dyslipidemia/fatty liver at a high rate. The previous guidelines showed that hypercholesterolemia occurred in 53% of 15 Werner syndrome patients.[2] However, there have been no data obtained by an extensive literature screening on the incidence of dyslipidemia and characteristics of dyslipidemia/fatty liver in Werner syndrome patients. To address this issue in the current edition of the guidelines, we screened cases reported on PubMed and Medical Online from 1996 to 2016 (98 articles, 119 cases), from which 44 cases (26 men with a mean age of 45.6 years) including some descriptions or data relating to either lipid or fatty liver in the articles were selected for analysis (reports before 2005: 26 cases).[8–43] The detailed literature search method and process were as follows.

Medical Online: We searched Medical Online with the search term "Werner Syndrome" and publication year "since 1996". A total of 186 papers were hit, and 49 case reports were confirmed to be appropriate and picked up.

PubMed: We searched PubMed by search formula "Werner syndrome" [All Fields] AND (Case Reports [ptyp] AND ["1996/01/01" (PDAT): "3000/12/31" (PDAT)]). With this screening, 151 case reports were hit, and 49 Japanese documents were picked up from them.

Considering that Werner syndrome is likely to be associated with malignant diseases, and that an onset of a malignant disease would possibly affect the lipid metabolism or fatty liver, the participants were divided into 13 Werner syndrome patients with a malignant disease (6 men; mean age 50.4 years) and the remaining 31 Werner syndrome patients with either no malignant diseases or no descriptions of malignant diseases (20 men; mean age 43.6 years) for analysis. As to these data, the Werner syndrome patients with a malignant disease and the other Werner syndrome patients are represented as a group with M and a group without M, respectively, in the guidelines.

Meanwhile, the case reports obtained through the aforementioned literature search included neither adequate description on the treatment nor records on any treatment effect/rates of achieving control target values. Additionally, an antihyperlipidemic drug has shown remarkable progress in recent years. Under such circumstances, we researched treatments for dyslipidemia/fatty liver and their effects in 11 patients with no malignant diseases at the time of data acquisition (4 men and 7 women; mean age 50.7 years [range 39–60 years]) among 12 patients (5 men and 7 women; mean age 50.1 [range 39–60 years]) under follow up at Chiba University whose detailed data on their lipid levels and fatty livers from 2010 were available. We also examined patients with data of a liver-to-spleen attenuation ratio (L/S ratio), which was considered to reflect the degree of fatty liver.

The results obtained through literature search are represented as SR, and the results of case examination at Chiba University are represented as CS in these guidelines.

Dyslipidemia

Q1. How frequently does dyslipidemia occur in Werner syndrome? What type of dyslipidemia appears in these patients?

A1. The incidence of dyslipidemia in Werner syndrome patients is high, at 85%. The most common type of dyslipidemia is hypertriglyceridemia, occurring in 76% of

patients, followed by hyper-low-density lipoprotein (LDL) cholesterolemia/non-high-density lipoprotein (HDL) cholesterolemia in 68% of patients and hypo-HDL cholesterolemia in 32% or patients (SR; Table 1**).**

Descriptions on the presence or the absence of dyslipidemia were found in 41 (the group with M: 13 patients, the group without M: 28 patients) of 44 patients, and 35 of whom (85.4%) developed dyslipidemia (the group with M: 84.6%, the group without M: 85.7%). Data on lipid were confirmed in 25 patients (the group with M: 7 patients, the group without M: 18 patients); hypertriglyceridemia (TG) accounted for 76.0% (the group with M: 57.1%, the group without M: 83.3%), hyper-LDL cholesterolemia/non-HDL cholesterolemia f accounted or 68.0% (the group with M: 42.9%, the group without M: 77.8%) and hypo-HDL cholesterolemia accounted for 32.0% (the group with M: 14.2%, the group without M: 38.9%).

Q2. What are the characteristics of Werner syndrome with dyslipidemia?

A2. Werner syndrome patients with dyslipidemia develop diabetes at a high rate (≥90%). The mean body mass index (BMI) of Werner syndrome patients with TG was 18.2, showing a lack of association with obesity (SR;Tables 1,2)

Records on the presence or the absence of diabetes were found in 33 out of 35 Werner syndrome patients with dyslipidemia, and 31 patients (93.9%) of whom developed diabetes (the group with M: 88.9%, the group without M: 95.8%), showing an extremely high incidence of diabetes. Complications of arteriosclerosis were found in four Werner syndrome patients with dyslipidemia; they developed atherosclerosis at a mean age of 41 years, indicating premature arteriosclerosis in Werner syndrome.

A total of 19 Werner syndrome patients with hypertriglyceridemia had a mean BMI of 18.2 (the group with M: 17.6, the group without M: 18.4), a maximum BMI of 22.8 and a minimum BMI of 12.49. There were nine underweight patients who had a BMI <18.5 (47.3%; the group with M: 7 patients, 46.7%; the group without M: 2 patients, 50%). The mean BMI of nine patients with normal triglyceridemia was 16.5, and eight of whom (88.9%) had a BMI not >18.5; there was no significant difference in BMI among normo- and hypertriglyceridemic patients, but was a tendency to be more "underweight" in normotriglyceridemic patients than those with hypertriglyceridemia. Thus, Werner syndrome patients with hypertriglyceridemia tended to have a higher BMI than patients with normal triglyceridemia in Werner syndrome; however, its characteristics were different from those in hypertriglyceridemic patietns in the general population, who are strongly complicated with obesity.

Q3. What are the rates of achieving the lipid control target values in patients with Werner syndrome? Which drugs are effective?

A3. The rates of achieving the lipid control target values are high, at 91% for LDL cholesterol, 91% for HDL cholesterol and 82% for TG. Strong statin is mainly used as an antidyslipidemic drug, and contributes to achieving the control target values (CS).

Of 12 Werner syndrome patients with CS, diabetes was documented in six, glucose intolerance in one, lower leg ulcer in nine and peripheral arterial disease in three (all developed diabetes and lower leg ulcer), but none had a history of myocardial infraction. Thus, there were six patients who were classified as the high-risk group according to the categorization in the Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular diseases 2017.[44]

Among 11 Werner syndrome patients who did not have malignant disease, five were taking antidyslipidemic drugs, one was neither taking a statin nor achieved the LDL cholesterol control target value based on risk factors, one had HDL cholesterol <40 mg/dL and two had TG levels of ≥150 mg/dL; thus, taken all together, eight were diagnosed with dyslipidemia (a patient who met either criterion; 73%). All patients who were taking statin achieved the LDL cholesterol control target value, and the achievement rates for LDL cholesterol, TG and HDL cholesterol reached markedly high levels of 91%, 82% and 91%, respectively. Antidyslipidemic drugs administered to the patients were all strong statins (atorvastatin, rosuvastatin and pitavastatin).

The LDL cholesterol level of Werner syndrome patients complicated with diabetes, which is classified as a high-risk condition in the JAS guidelines, was 84.5 ± 21.4 mg/dL (minimum 51.0 mg/dL, maximum 105.4 mg/dL), showing successful control compared with the mean LDL cholesterol level of diabetes patients in the general population who received special health checkups (men 114.0 mg/dL, women 122.9 mg/dL).[45] Similarly, the LDL cholesterol level of Werner syndrome patients with peripheral arterial disease, also a high-risk condition in the JAS Guidelines, was 75.1 ± 23.2 mg/dL (minimum 51.0 mg/dL, maximum 97.4 mg/dL), which was a better outcome compared with special health checkup results of patients with a history of cerebral vascular disorder, a high-risk condition, as with peripheral arterial disease (men 115.7 mg/dL, women 123.2 mg/dL).[45] As such, the rates of Werner syndrome patients achieving the lipid control target values reached 100% in high-risk conditions, suggesting that the lipid was quite successfully controlled in high-risk Werner syndrome patients, compared with the approximately 60% achievement rate of

Table 1 Characteristics of dyslipidemia among Werner Syndrome

Malignant disease		No. cases	Dyslipidemia		DM among dyslipidemic patients			Cases reported with precise lipid data			
			present	Absent	Present	Absent	Not reported	Reported	High LDL-C/ non-HDL-C	High TG	Low HDL-C
Asent or not reported	No. cases (*n*)	28	24	4	23	1	0	18	14	15	7
	%		85.7	14.3	95.8	4.2			77.8	83.3	38.9
Present	No. cases (*n*)	13	11	2	8	1	2	7	3	4	1
	%		84.6	15.4	88.9	1.1			42.9	57.1	14.3
Total	No. cases (*n*)	41	35	6	31	2	2	25	17	19	8
	%		85.3	1	93.9	6.1			68.0	76.0	32.0

DM, diabetes mellitus; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglyceride.

Table 2 Characteristics of Werner syndrome patients with hypertriglyceridemia

Malignant disease		No. cases	Mean BMI	BMI <18.5	
				No. cases	%
Absent or not reported	High TG	15	18.4	7	46.7
	Normal TG	6	16.4	5	83.3
Present	High TG	4	17.6	2	50.0
	Normal TG	3	16.7	3	100
Total	High TG	19	18.2	9	47.3
	Normal TG	9	16.5	8	88.8

BMI, body mass index; TG, triglyceride.

Table 3 Characteristics of Werner syndrome patients documented with fatty liver

Malignant Disease	No. cases (*n*)	Mean BMI	Max BMI	BMI >22		BMI <18.5		No. cases with lipid data	Complicated with dyslipidemia		No. cases with GI data	Complicated with GI
				No. cases	%	No. cases	%		No. cases	%		No. cases
Absent or not reported	10	19.3	22.6	2	20.0	4	40.0	10	9	90.0	10	9
Present	2	18.7	19.3	0	0.0	0	0.0	2	2	100.0	1	1
Total	12	18.8	22.6	2	16.7	4	33.3	12	11	91.6	11	10

BMI, body mass index; GI, glucose intolerance.

LDL cholesterol control target value in the general population with high-risk conditions (with a history of diabetes or cerebrovascular disorder) based on special health checkup data.[45]

Fatty liver

Q4. What are the characteristics of fatty liver in patients with Werner syndrome?

A4. Werner syndrome with fatty liver had a mean BMI of 18.8 and a maximum BMI of 22.6, and 83% of these patients are underweight (SR; Table 3**.)**

Descriptions of fatty liver were found in 12 (the group with M: 10 patients, the group without M: 2 patients) of 44 Werner syndrome patients, with a mean BMI of 18.8 (the group with M: 18.7, the group without M: 19.3). Among them, just two patients had a BMI of ≥22 (in the group without M), and the maximum BMI was 22.6. In contrast, the prevalence of fatty liver (NAFLD) in the general population is approximately 30% and increases with the degree of obesity. The reported incidences of NAFLD in individuals with a BMI of ≥28, 25–<28, 23–<25 and <23 are approximately 85%, 60%, 40% and 10%, respectively. Accordingly, the main characteristic of fatty liver in Werner syndrome patients would be that even "underweight" patients develop fatty liver at a high rate. Additionally, 91.6% of these 12 Werner syndrome patients with fatty liver had concomitant dyslipidemia (the group with M: 90.0%, the group without M: 100%), and 90.9% had disorders of carbohydrate metabolism (the group with M: 90.0%, the group without M: 100%), showing that they also developed other metabolic disorders at a high rate.

Q5. Are there any differences in biochemical data between Werner syndrome patients with fatty liver and those without fatty liver?

A5. The L/S ratio showed a positive correlation with HDL cholesterol levels and a negative correlation with TG levels. It does not correlate with the liver enzyme levels (CS).

The following are analytical results of nine patients with data on L/S ratios and without malignancy in CS. Four patients (44%) had concomitant fatty liver (L/S ratio not >1.0). The mean BMI of these patients was 16.7 (maximum BMI 17.8, minimum BMI 15.5), consisting only of "underweight" patients (the mean BMI of non-fatty liver patients 17.1). When individual laboratory test values (LDL-C, HDL-C non-HDL-C, TG, aspartate transaminase, alanine transaminase, γ-glutamyl transpeptidase, cholinesterase and aspartate transaminase/alanine transaminase ratio) of the fatty liver group were compared with those of the non-fatty liver group (*t*-test), the HDL cholesterol levels stood at 46.0 ± 8.1 mg/dL in the fatty liver group and 64.6 ± 13.3 mg/dL in the non-fatty liver group, showing a significantly low value in the fatty liver group ($P < 0.05$). As to the correlation of the L/S ratio with each laboratory value, it showed a positive correlation with the HDL cholesterol levels ($R^2 = 0.609$, $P = 0.013$) and a negative correlation with the TG levels ($R^2 = 0.509$, $P = 0.031$).

Q6. Have there been any Werner syndrome patients with hepatocellular cancer?

A6. One of the 44 Werner syndrome patients reportedly developed hepatocellular cancer, although no specific description of a relationship with fatty liver was found (SR).

One report out of 44 showed that hepatocellular cancer occurred in a 40-year-old male patient.[30] Although we cannot say for certain due to a lack of description on a non-cancerous hepatic tissue, he tested negative for hepatitis B and C viruses and autoimmune hepatic disease, and thus it cannot be denied that hepatocellular cancer might have been originally caused by NAFLD or NASH in this case.

Discussion

As described in the review article by Epstein *et al.* in 1966[46] and in the report by Yokote *et al.* in 1989,[47] Werner syndrome is likely to be accompanied with dyslipidemia. We comprehensively collected recent relevant case reports (from 1996) and examined them according to the diagnostic criteria specified in the JAS Guidelines for Prevention of Atherosclerotic Cardiovascular diseases 2017.[44] The results showed that: (i) dyslipidemia occurred in 85% of Werner syndrome patients, ≥90% of whom developed diabetes; (ii) all types of dyslipidemia (i.e. hyper-LDL cholesterolemia/non-HDL cholesterolemia, hypertriglyceridemia and hypo-HDL cholesterolemia) were observed in Werner syndrome, although hypertriglyceridemia was relatively common; and (iii) Werner syndrome patients developed hypertriglyceridemia without obesity; the mean BMI of affected patients was 18.2. Mori *et al.* examined abdominal computed tomography images of three male patients and one female patient,which showed that two male patients had a visceral fat area of >100 cm^2 and the other two patients showed a high visceral fat area/subcutaneous fat area ratio.[21] There remain many unclear points about the molecular mechanism of accumulated visceral fat in Werner syndrome, but the accumulation of visceral fat is considered to increase insulin resistance, leading to dyslipidemia or disorder of carbohydrate metabolism. From another point of view, Werner syndrome is a condition that has not only visceral fat accumulation observed in metabolic syndrome, but also an imbalance between visceral fat mass and subcutaneous fat mass and subcutaneous fat reduction, which are observed in lipodystrophic patients[48] and metabolically unhealthy normal-weight individuals.[49] In any of these pathological conditions, the cardiometabolic phenotype, such as dyslipidemia, diabetes, insulin resistance and ectopic fat accumulation, such as fatty liver, is observed. In particular, in recent years, great attention has been paid to the contribution of a decrease in subcutaneous fat to fatty liver and cardiometabolic phenotype, and this contribution is thought to be compatible with Werner syndrome.[50] The assumed mechanism for cardiometabolic phenotype in Werner syndrome is summarized in Figure 1.

As to hyper-LDL cholesterolemia, Yokote and Mori *et al.* reported that thickened Achilles tendon and hypercholesterolemia occurred in six out of 10 Werner syndrome patients in their facilities,[47] and five of them showed a decrease in the LDL receptor activity;[51] thus, it might be plausible that Werner syndrome itself possesses some sort of mechanism to decrease the LDL receptor activity. Given that an increased LDL cholesterol level is a disease-specific postnatal feature in Werner syndrome, it might be possible to assume that hypercholesterolemia in Werner syndrome patients has a risk equivalent to familial hypercholesterolemia considering the notion of cumulative LDL cholesterol, which has recently been proposed.

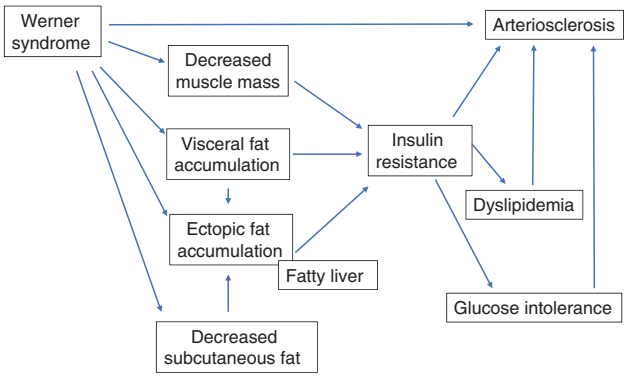

Figure 1 Schematic flow of metabolic disorder that causes arteriosclerosis in Werner syndrome.

Of course, it remains unclear whether dyslipidemia occurs before the diagnosis of Werner syndrome. However, considering that macrophages are likely to become foamy in Werner syndrome, and that Werner syndrome is characterized by overlapping risk factors including disorders of carbohydrate metabolism and accumulated visceral fat, it is necessary to proactively and adequately control dyslipidemia.[52] The analyses of 12 Werner syndrome patients in CS showed that an intensive treatment using strong statin might possibly achieve the lipid control target values. The rate of achieving the LDL cholesterol control target value of high-risk patients in the special health checkup was approcimately 60%, whereas that in Werner syndrome patients was ≥90%, which might be because both healthcare professionals and patients have recognized the association between Werner syndrome and arteriosclerosis, and proactively treated dyslipidemia in Werner syndrome.

According to the questionnaire investigation of 102 Werner syndrome patients carried out by Imura *et al.* in Japan in 1985, 35.4% of these patients had mild hepatic dysfunction, and fatty liver was suggested as its cause.[53] The analysis on 12 Werner syndrome patients in CS confirmed that approximately 40% of them developed fatty liver. Unlike common fatty liver disease, both the SR and CS analyses showed that fatty liver occurred in normal-weight and underweight Werner syndrome patients, and that the rates of developing dyslipidemia and glucose intolerance were extremely high in them. A similar mechanism for the onset of fatty liver in the general population; that is, excessive free fatty acids inflow into the liver from the accumulated visceral fat, would underlie athe onset of fatty liver in Werner syndrome, although a Werner syndrome-specific mechanism might be involved in the onset of fatty liver.[54]

Recently, an onset of hepatocellular cancer caused by NAFLD or NASH has become the focus of interest. Hepatocellular cancer observed in a 40-year-old Werner syndrome patient of SR might have occurred in association with Werner syndrome, but the possibility of its occurrence in association with fatty liver or NASH cannot be excluded. Therefore, a treatment to ameliorate fatty liver also needs to be established. There is evidence about treatments with pioglitazone,[55,56] vitamin E[57] and ursodeoxycholic acid[58] in the general population, whereas Takemoto *et al.* reported that astaxanthin, a kind of carotenoid, improved fatty liver in Werner syndrome patients.[43] Another study also showed an effect of resveratrol to improve fatty liver in a Werner syndrome-model animal.[59] Further therapeutic drug development is expected.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

SOCIAL RESEARCH, PLANNING AND PRACTICE

Management guideline for Werner syndrome 2020. 2. Sarcopenia associated with Werner syndrome

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Aim: Sarcopenia is defined as a condition that combines decreased skeletal muscle mass with weakness or decreased physical function. It is well known that in older adults, the presence of sarcopenia is a risk of frailty, falls and physical dysfunction. Patients with Werner syndrome are characterized by visceral fat accumulation and thin limbs, but the prevalence of sarcopenia in patients with Werner syndrome has not been investigated.

Methods: A literature search was conducted using Werner syndrome and skeletal muscle as keywords. We also analyzed data from our 7 Werner syndrome patients.

Results: A literature search on the relationship between Werner syndrome and skeletal muscle yielded only one article reported from Japan. According to this paper, a decrease in skeletal muscle mass (appendicular skeletal muscle index) was observed in all 9 Werner syndromes investigated. On the other hand, in our 7 Werner syndrome patients, their appendicular skeletal muscle indexes were below the standard value except for one male patient who had continued resistance exercise.

Conclusion: The decrease in skeletal muscle mass frequently occurs in patients with Werner syndrome. However, resistance exercise may prevent the appearance of sarcopenia and requires early intervention in patients with Werner syndrome. **Geriatr Gerontol Int 2020; ••: ••–••.**

Keywords: clinical medicine, Werner syndrome, geriatric medicine, management guideline, others.

Introduction

Werner syndrome is frequently associated with a decrease in extremity skeletal muscle mass in adults (below the age of 40 years).

Although its contributing factors are still unclear, there are some cases where habitual resistance exercise has prevented a decrease in skeletal muscle mass. Therefore, appropriate intervention with habitual resistance exercise may be a useful preventive measure.

Sarcopenia

Sarcopenia is characterized by a significant decrease in skeletal muscle mass and muscle weakness or a decline in the physical function with age.[1] It is generally known that the skeletal muscle area decreases by 25–30% and muscle strength by 30–40% by the age of 70 compared with those in the 20s, and muscle mass decreases by about 1–2% every year after the age of 50.[2] The age-related decrease in skeletal muscle mass is caused by a reduction in skeletal muscle fibers and atrophy of each muscle fiber. A decrease in skeletal muscle fibers has been known mainly to represent a reduction in type IIa muscle fibers (fast-twitch fibers, white muscle).[2] Sarcopenia is a term coined from "sarco" denoting "flesh" and "penia" representing "poverty" in Greek.[1,2] Sarcopenia is classified into primary (age-related) sarcopenia caused only by advancing age and secondary sarcopenia marked by decreases in skeletal muscle mass, muscle strength, and physical function associated with inactivity (disuse), diseases (progressive malignancy and organ failure), or malnutrition.[1]

Sarcopenia is known to be associated with risks of falling, physical function impairment, needing nursing care and frailty in the elderly, and this condition has recently been taken seriously in light of care prevention in Japan.[3]

Sarcopenia in patients with Werner syndrome

A literature search on the relationship between Werner syndrome and skeletal muscle yielded only one article reported from Japan in 2017.[4] According to that report, nine patients with Werner syndrome (four men and five women) with the mean age of 48 ± 8.8 years (range: 39–60 years) underwent a diagnostic test for sarcopenia based on indexes including decreases in the appendicular skeletal muscle mass index and the grip strength using the diagnostic criteria for sarcopenia (appendicular skeletal muscle index obtained by dual-energy X-ray absorptiometry [appendicular skeletal muscle mass, kg/body height, m^2: <7.0 kg/m^2 [male], <5.4 kg/m^2 [female] and grip strength: <26 kg [male], <18 kg [female])[5]suggested by Asian Working Group for Sarcopenia.

As to the grip strength, two of four male patients did not meet the diagnostic criteria for sarcopenia, whereas none exceeded the cutoff value of appendicular skeletal muscle indexes. The researchers also assessed the accumulation of visceral fat (evaluated by abdominal computed tomography) in the nine patients. An age-adjusted evaluation revealed that the decrease in skeletal muscle mass had been observed before the accumulation of visceral fats. All had decreased motor functions. The analysis based on the presence or absence of diabetes indicated that patients with Werner syndrome with diabetes had higher body mass indexes and more visceral fat than those without diabetes, while there was no difference in the skeletal muscle index between the two groups.

In our study, the appendicular skeletal muscle index was examined by the bioimpedance method in seven patients with Werner syndrome (four men and three women) with the mean age of 49.1 ± 6.8 years (range, 39–70 years). The results revealed that their appendicular skeletal muscle indexes were below the standard value (the cutoff values of the skeletal muscle indexes obtained by the bioimpedance method suggested by the Asian Working Group for Sarcopenia are <7.0 kg/m^2 for males and <5.7 kg/m^2 for females)[5] except for one male patient. He was 43 years old and had continued resistance exercise with dumbbells and bodyweight squats from his school days.[6]

As described above, age-related sarcopenia is generally associated with a decrease in skeletal muscle fibers (particularly, fast-twitch fibers) and atrophy of each muscle fiber, whereas it is still unclear whether similar changes appear in patients with Werner syndrome, because of the lack of detailed muscle biopsy findings in this patient population. Additionally, sarcopenia is diagnosed by low extremity skeletal muscle mass, as mentioned above, as an obligatory symptom and accompanied by a decline in muscle strength or physical function (e.g., walking speed).[1–3,5] Patients with Werner syndrome are likely to develop refractory plantar ulcers, which makes it impossible to measure their walking speed in some cases. Hand deformity also occurs in some cases, making it difficult to measure grip strength, and thus it is not always easy to make a diagnosis of sarcopenia.

Discussion

The decrease in skeletal muscle mass, as discussed above, frequently occurs in patients with Werner syndrome before the age of 40. Although the mechanism is still unclear, various potential factors including aged skeletal muscle, metabolic abnormality, and inflammation, or a decreased amount of activity due to low physical function are considered, which are expected in the future progress of the research. On the other hand, a patient with Werner syndrome who was not diagnosed with sarcopenia, as in the above example, has also been observed, suggesting possible prevention of sarcopenia by appropriate intervention (e.g., resistance exercise).

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

SOCIAL RESEARCH, PLANNING AND PRACTICE

Management guideline for Werner syndrome 2020. 3. Diabetes associated with Werner syndrome

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Aims: To evaluate the characteristics of diabetes associated with Werner syndrome.

Methods: A literature search was done with search term "Werner syndrome" and "Diabetes".

Results and Conclusions: Prevalence of diabetes is extremely high in Werner syndrome. Diabetes associated with Werner syndrome is classified as "accompanied with other diseases and conditions and the one occurring mainly in association with other genetic syndromes." This type of diabetes is marked by accumulated visceral fat and high insulin resistance, despite low body mass index. Thiazolidine derivatives and metformin are effective for glycemic control. New antidiabetic drugs, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, could be potentially beneficial for patients with Werner syndrome. Furthermore, the establishment of diet therapy as well as exercise therapy is warranted. **Geriatr Gerontol Int 2020; ••: ••–••.**

Keywords: clinical medicine, geriatric medicine, others.

Introduction

Werner syndrome is a disease representing progeria. The clinical finding that is first observed, is loss of the pubertal growth spurt, followed by geriatric symptoms including atrophy and hardening of the skin, partial loss of the subcutaneous fat, changes in hair such as graying and balding, and cataract. Glucose metabolism disorders are also seen at a high rate, making this a typical metabolic disorder in patients with Werner syndrome.[1,2]

Q1. How frequently do patients with Werner syndrome develop diabetes?

A1. Approximately 55% of them develop diabetes.

The review article published by Epstein *et al.* in 1966 indicates that diabetes was observed in 55 (28 males and 27 females) of 125 patients diagnosed with Werner syndrome.[1] In Japan, the results of the research on domestic patients with Werner syndrome were reported by Imura *et al.*, of the Health and Welfare Ministry's specific disease hormone receptor mechanism research group (Etsurou Ogata Group) in 1984. These researchers conducted a questionnaire survey consisting of 1930 questions to domestic hospitals equipped with at least 200 beds, and 181 patients participated in this survey. Furthermore, a glucose tolerance test was conducted in 90 patients, 50 of whom (55.6%) developed diabetes.[3]

Goto reported that about 70% of patients with Werner syndrome developed type 2 diabetes or borderline diabetes based on the results of the literature review from 1966 to 2004.[4] Goto *et al.* further extended the target year of review to 2008 to review the articles by year and reported that the incidence of diabetes in patients with Werner syndrome remained unchanged regardless of year and that the mean age of onset of diabetes was 33.7, 39.7 and 39.3 years in 1966, 2004 and 2008, respectively, which revealed a delay in onset over time.[5]

As a nationwide epidemiological survey in 2011, a questionnaire survey consisting of 6921 questions was conducted in medical institutions with at least 200 beds, through which 396 patients with Werner syndrome were newly confirmed, and clinical findings of 196 patients were obtained. The results revealed that 55.7% of these patients developed diabetes and 6.5% had borderline diabetes.[6] As described by Goto *et al.*, the incidence of diabetes in patients with Werner syndrome in Japan was comparable with that reported by Imura *et al.* in 1984.

Q2. What type of diabetes do the patients with Werner syndrome develop?

A2. Diabetes associated with Werner syndrome are classified into "one accompanied with other diseases and conditions and one occurring mainly in association with other genetic syndromes." Such diabetes is marked by accumulated visceral fat and high insulin resistance despite low body mass index (BMI).

Epstein *et al.* reported that diabetes occurring in association with Werner syndrome is characterized by a gradual rise in blood sugar levels leading to prolonged hyperglycemia after the glucose tolerance test and less effective insulin therapy for such hyperglycemia despite normal blood sugar levels in many patients with Werner syndrome. His study also indicated that although dead branch-like extremities and fat atrophy are observed in Werner syndrome, fat atrophy is not involved in an onset of diabetes.[1]

According to the report from Imura *et al.*, the researchers measured the serum insulin levels of 53 patients with Werner syndrome in the glucose tolerance test, observing hyperinsulinemia in 33% with basal insulin levels at 20 μU/mL and overreaction to insulin in 67% with the peak level at the glucose tolerance test showing 200 μU/mL. They suggested that a decrease in endogenous insulin secretion have been rarely seen and insulin secretion from the pancreatic β cells has been relatively maintained even though insulin resistance is higher in patients with Werner syndrome. The report also indicates pathogenesis of high insulin resistance in which expression of insulin receptors on the erythrocyte surface is not decreased and malfunction of the insulin receptors expressed is associated with higher insulin resistance in the examination using cultivated dermal fibroblasts.[3]

An onset of diabetes generally correlates with obesity (an increase in BMI), whereas BMIs of most patients with Werner

Table 1 Differences in clinical findings affected by the presence or absence of diabetes

	Non-diabetic	*n*	Diabetic	*n*	*P* value
Age (years)	44 ± 6.9	5	53 ± 9.1	4	0.16
25-question GLFS score	40 ± 31.7	4	43 ± 18.8	4	0.88
Two-step test value	0.73 ± 0.49	5	0.60 ± 0.51	4	0.71
Grip strength (kg)	20.1 ± 7.1	5	12.5 ± 5.1	4	0.11
VFA (cm^2)	56.1 ± 43.6	4	142.6 ± 40.1	3	0.04*
SMI (kg/m^2)	4.2 ± 0.7	5	3.8 ± 0.4	3	0.4
BMD (L) (%YAM)	89.4 ± 13.8	5	83.3 ± 8.4	3	0.47
BMD (F) (%YAM)	75.3 ± 4.6	4	61.7 ± 5.7	3	0.03*
BW (kg)	40.4 ± 7.5	5	42.9 ± 6.6	4	0.61
BMI (kg/m^2)	16.2 ± 1.2	5	18.7 ± 1.3	4	0.02*
Adiponectin (ng/mL)	6.4 ± 2.8	4	6.6 ± 4.1	4	0.95
TNF-α (pg/mL)	1.4 ± 0.6	4	3.0 ± 4.3	4	0.51
Leptin (ng/nL)	7.2 ± 3.6	4	30.0 ± 16.9	4	0.07

*$P < 0.05$, quoted from Yamaga *et al*[10].

Data are expressed as mean ± standard deviation. Comparisons between the two groups were made using Welch's *t*-test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP Pro 12 (SAS Institute Japan, Tokyo, Japan).

BMD (F), bone mineral density (femoral neck); BMD (L), bone mineral density (lumbar spine); BMI, body mass index; BW, body weight; GLFS, geriatric locomotive function scale; SMI, skeletal muscle index; TNF, tumor necrosis factor; VFA, visceral fat area; YAM, young adult mean.

syndrome are <22. Yokote *et al*. reported that accumulated visceral fat, low serum adiponectin levels and increases in tumor necrosis factor α and interleukin-6 were observed in patients with Werner syndrome with diabetes.[7,8] A recent case report has suggested that although it was confirmed in one patient, abnormal glucagon secretion after a food load might be associated with carbohydrate metabolism disorders in patients with Werner syndrome.[9] Recently, the body compositions of Japanese patients with Werner syndrome were examined in detail, and the results revealed that there were no differences in age, sex and skeletal muscle mass between the diabetic (n = 4) non-diabetic (n = 5) groups, whereas they had a predominantly higher BMI and amount of visceral fat (Table 1).[10] Accordingly, not fats in extremities or atrophy of skeletal muscle but insulin resistance accompanied by accumulated visceral fat is associated with an onset of diabetes in patients with Werner syndrome. Diabetes is generally determined by not only genetic background but also changes in environmental factors. Considering that the rate of diabetes occurring in patients with Werner syndrome remains constant, the development of diabetes in patients with Werner syndrome may be greatly influenced by genetic factors rather than environmental factors.

Q3. What is an effective treatment for diabetes in patients with Werner syndrome?

A3. Thiazolidine derivatives and metformin are effective for glycemic control.

As reported by Epstein *et al.*, insulin treatment for diabetes associated with Werner syndrome lacks efficacy. There have been many reports on the effectiveness of a thiazolidine derivative, an agonist, of peroxisome proliferator-activated receptor γ, an insulin sensitizer.[7,8,11–18] On the other hand, although concerns about the effect of thiazolidine derivatives on the bone and the onset of malignancy have been generally reported, no reports have suggested relationships between thiazolidine derivatives and the bone or the development of malignancy in Werner syndrome, which requires further examination. Other than those described above, use of metformin,[19] dipeptidyl peptidase 4 inhibitors[9,20] and glucagon-like peptide-1 receptor agonists[21] have been reported, although are few in number. In patients with Werner syndrome, not only short stature and low body weight but also a reduction in the skeletal muscle mass early in life has been observed.[10] Although dietary instructions to prevent an increase in visceral fat and a decrease in the skeletal muscle mass may be required, no dietary therapy for diabetes occurring in Werner syndrome has been established, which is one of the important subjects to be examined.

Discussion

Diabetes is highly prevalent among patients with Werner syndrome. Reportedly, thiazolidine derivatives increase the risks for weight gain and bone fracture, necessitating clinicians to be wary of the prolonged usage of thiazolidine derivatives. In Japan, thiazolidine derivatives had been widely used in the treatment of patients with Werner syndrome because of the reduced prevalence of biguanide owing to its side effects, such as lactic acidemia. With the growing usage of metformin in Japan and the fact that it reportedly exerts favorable effects on metabolism and acts as an anticancer agent, re-evaluation of the efficacy of metformin in the treatment of patients with Werner syndrome is warranted. In our opinion, new antidiabetic drugs, such as dipeptidyl peptidase 4 inhibitor and/or glucagon-like peptide-1 receptor analog, could be potentially beneficial for patients with Werner syndrome. Furthermore, the establishment of not only diet therapy[22] but also exercise therapy for patients with Werner syndrome is warranted in the future.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Management guideline for Werner syndrome 2020. 4. Osteoporosis associated with Werner syndrome

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CQ1. What percentage of patients with Werner syndrome develops osteoporosis and which site does osteoporosis appear more commonly?

A1. Osteoporosis has been observed in approximately 41% of these patients. It is likely to be more severe in the femur than in the lumbar spine.

Werner syndrome is a typical genetic progeroid syndrome characterized by pathological conditions similar to age-related various changes that present early in life. Among them, osteoporosis is a characteristic sign of premature aging observed in patients with Werner syndrome.

According to a report summarizing clinical characteristics of 24 patients with Werner syndrome by Murata and Nakashima,[1] the radiographs showed osteoporosis in nine of 24 patients. Although osteoporosis was relatively rare in younger patients, almost all patients at least 40 years of age developed osteoporosis, with its degree being more severe in the lower extremities. Their review of the Japanese medical literature revealed that osteoporosis occurred in 41% of 153 patients with Werner syndrome reported in Japan.

As the above report by Murata and Nakashima was made before bone densitometry (using dual energy X-ray absorptiometry) had become generalized, it was unclear whether the incidence of osteoporosis in patients with Werner syndrome using the current diagnostic criteria for primary osteoporosis[2] was as high as that reported in previous studies. Therefore, a more detailed assessment of osteoporosis was made in 10 patients with Werner syndrome visiting Chiba University Hospital.[3] As shown in Table 1, the patients consisted of five men and five women. Werner syndrome was diagnosed by genetic testing using DNAs extracted from peripheral blood leukocyte as well as the characteristic clinical signs (Table 1). Bone density was measured by dual

Table 1 Bone density in 10 patients with Werner syndrome

Case	Sex	Age	*WRN* mutation	Bone density in the lumbar spine ($L_{2–4}$)			Bone density in the femoral neck		
				g/cm^2	*T*-score SD	%YAM	g/cm^2	*T*-score SD	%YAM
1	M	57	6/6	0.730	−2.7[†]	70[‡]	0.601	−2.1	70[‡]
2	F	60	6/6	0.804	−2.1	78	0.452	−3.1[†]	57[‡]
3	F	57	4/6	0.790	−1.9	78	0.351	−4.0[†]	45[‡]
4	M	40	4/11	1.116	0.6	107	—	—	—
5	F	60	4/4	0.803	−1.8	79	0.533	−2.3	68[‡]
6	F	40	11/11	0.983	−0.2	97	0.582	−1.9	74
7	M	51	4/7	0.971	−0.6	93	0.508	−2.8[†]	59[‡]
8	F	42	4/4	0.892	−1.0	88	0.598	−1.7	76
9	M	43	4/4	0.890	−1.3	85	0.697	−1.3	81
10	M	53	4/–	0.901	−1.1	85	0.606	−2.0	70[‡]

[†]*T*-score ≤−2.5.

[‡]YAM ≤70%.

YAM, young adult mean value.

Table 2 Association between the *WRN* gene polymorphism (rs2230009, 340G>A) and femur fractures

Factor	Odds ratio (95% CI)	*P*
Genotype: AA/AG vs. GG	2.528 (1.194–5.350)	0.0154
Sex: women vs. men	2.983 (1.988–4.776)	<0.0001
Age at autopsy (every 10-year increase in age)	1.746 (1.396–2.185)	<0.0001

CI, confidence interval.

energy X-ray absorptiometry, and ≤70% of the young adult mean value or T-score of ≤−2.5 SD was defined as osteoporosis. Osteoporosis was diagnosed by evaluation of the lumbar spine bone density in only case 1. Spine radiographs had positive findings in six patients but with no specific osteoporosis-related fragility fractures. In contrast, osteoporosis was identified in six patients (cases 1, 2, 3, 5, 7 and 10) when assessed by the bone density of the femoral neck. The above results suggested that osteoporosis accompanied by Werner syndrome is more severe in the femur than in the lumbar spine.

CQ.2 Has the pathogenesis of osteoporosis been elucidated?

A2. It is considered that osteoporosis occurs because bone formation is inhibited while bone resorption is normal in Werner syndrome.

Osteoporosis has long been considered to be caused by the imbalance between osteogenesis by osteoblasts and bone resorption by osteoclasts. For example, hyperfunction of osteoclasts mainly due to a decrease in estrogen levels has been known to be involved in the development of typical postmenopausal osteoporosis. From this perspective, Rubin *et al.*, have reported examination results related to the pathogenesis of osteoporosis in patients with Werner syndrome.[4]

The researchers examined osteoporosis in a 43-year-old white female patient. The spine radiograph showed fragility compression fractures in almost all thoracolumbar spines. Her bone density stood at 0.776 g/cm^2 in the lumbar spine and 0.441 g/cm^2 in the femoral neck, which was equivalent to −2.38 and −3.93 SD, respectively, compared with the mean values in women of the same age. Hematological parameters were unremarkable, except for insulin-like growth factor-1 (IGF-1), which showed a low level of 86 ng/mL (normal range for age: 142–389 ng/mL). However, the basal serum growth hormone level was within the normal range, and the load tests using arginine and L-dopa showed a normal somatotropin secretory response pattern. The iliac bone of the patient was also biopsied, which showed low cortical bone mass and thinning of the cortical bone. More important findings included a significant decrease in the osteoid mass and absence of osteoblasts in sampled tissues. To sum up these findings, it was considered that while bone resorption was normal, osteogenesis was inhibited in patients with Werner syndrome.

Furthermore, Rubin *et al.*, reported results obtained when Werner syndrome was treated with IGF-1.[5] They measured changes in bone density and the bone metabolism marker of patients with Werner syndrome with osteoporosis before and after daily subcutaneous injection of recombinant human IGF-1 for 6 months. Serum type I procollagen C-peptide and serum osteocalcin, the osteogenesis markers, had increased, while urinary pyridinoline crosslinked products and urinary hydroxyproline, the bone resorption markers, had also risen during the treatment. The post-treatment bone density of the lumbar spine increased by 3%, showing an increment exceeding a variation coefficient in the testing. Given these results, they concluded that supplementation of IGF-1 might possibly relieve inhibition of osteogenesis in patients with Werner syndrome with osteoporosis displaying low IGF-1 levels.

Generally, age-related osteoporosis occurs more commonly in the bony skeleton, including proximal sites of the vertebra and the femur, whereas osteoporosis in Werner syndrome tends to be more severe in the distal extremities, particularly in the lower extremities. As arthrogryposis associated with dermal sclerosis in the lower extremities or ulcerative lesions in the foot region often occur in Werner syndrome, the bones of the lower limbs are susceptible to disuse and inflammatory changes. This is considered one reason why osteoporosis in Werner syndrome tends to be more severe in the lower extremities.

CQ3. Is osteoporosis related with *WRN* gene polymorphism?

A3. Research results showing the relation between the *WRN* gene polymorphism and osteoporosis suggested that genetic factors might also be involved in osteoporosis associated with Werner syndrome.

Osteoporosis is included as one of the premature aging signs in Werner syndrome, which, however, does not immediately indicate a direct relationship between a genetic abnormality causing Werner syndrome and the bone metabolism. Werner helicase, a

Table 3 Association between the *WRN* gene polymorphism (rs2230009, 340G>A) and each clinical indicator

	GG (n = 236)		AG (n = 15)		Difference (95% CI)	P
	Mean	SD	Mean	SD		
Age (years)	70.9	8.09	71.7	6.83	0.76 (−3.43–4.94)	0.724
Body weight (kg)	48.0	6.81	44.7	5.00	−3.33 (−6.97–0.32)	0.074
Body height (m)	150	11.4	140	38.5	−11.2 (−32.6–10.1)	0.279
Body mass index (kg/m^2)	21.0	2.88	20.1	2.51	−0.92 (−2.46–0.61)	0.240
Muscle mass in extremities (kg)	12.7	1.52	12.4	1.48	−0.24 (−1.18–0.71)	0.620
Skeletal muscle mass index (kg/m^2)	5.51	0.54	5.55	0.52	0.03 (−0.31–0.37)	0.850
Bone density in the lumbar spine (g/cm^2)	0.79	0.14	0.73	0.17	−0.07 (−0.14–0.00)	0.068
Bone density in the femoral neck (g/cm^2)	0.63	0.08	0.59	0.08	−0.04 (−0.08 - −0.00)	0.041*
Serum calcium (mg/dL)	9.65	0.41	9.53	0.31	−0.12 (−0.33–0.09)	0.270
Serum 25-OH vitamin D (ng/mL)	21.5	6.45	19.4	5.15	−2.02 (−5.35–1.30)	0.230

*P < 0.05.

CI, confidence interval; SD, standard deviation.

product of the gene responsible for Werner syndrome, has been considered to play a role mainly in the DNA repair process. It has been observed that the *WRN* gene is expressed in human dermal fibroblasts,[6] whereas it has not been confirmed whether it is expressed in osteoblasts or osteoclasts, leading to difficulty in inferring a functional relationship between the *WRN* gene and bone metabolism. Lately, research providing a new insight concerning this topic has been reported.

It has been known that there are single nucleotide polymorphisms at eight positions in the *WRN* gene: four of them involve amino acid substitution, while the other four do not.[7] Some researchers have already reported examination results of a relationship particularly with rs1346044 (T>C, Cys1367Arg), i.e., a polymorphism with the 1367th cysteine residue being replaced with an arginine residue, and osteoporosis.[8] They examined 377 healthy postmenopausal women with a mean age of 65.6 years. The genotype frequencies were 87.5% for T/T, 12.2% for T/C and 0.3% for C/C. The subjects were classified into two groups of non-carriers of C (T/T) and carriers of C (T/C and C/C) for comparison, which resulted in the carriers of C having significantly low bone density in the lumbar spine (P = 0.037).

We also conducted genotyping of rs2230009 (340G>A, V114I) of the *WRN* gene to examine the association with the prevalence of femoral fracture using DNAs obtained from 1632 consecutive autopsy cases (mean age: 81; 924 men and 708 women) in Tokyo Metropolitan Geriatric Hospital.[9] Table 2 shows the results of multiple logistic regression analysis adjusted for sex and age. The odds ratio of femoral fracture in rs2230009 with the AA or AG genotype was significantly high, standing at 2.528 times as frequently as that with the GG genotype. In addition, the study found that the above odds ratio in women was 2.983 times as high as that in men, and a risk of femoral fracture increased by 1.746 times for every 10-year increase in age. Furthermore, we performed validation of rs2230009 that was found to have a significant association with the femoral fracture by analyzing its relationship with the bone density using DNAs taken from 251 patients with postmenopausal osteoporosis (mean age: 71 years) in Tokyo Metropolitan Geriatric Hospital.[9] Table 3 shows the relationship between the genotype of rs2230009 and each clinical indicator in these patients. A Student's t-test was employed for age, body weight and body height, and a linear regression analysis (adjusted for age) for the others to conduct a significance test. Therefore, it revealed that the AG genotype had a significantly lower bone density in the femoral neck than did the GG genotype.

The results obtained from a series of studies on the association between the *WRN* gene polymorphism and osteoporosis suggests genetic factors are potentially involved in the onset of osteoporosis associated with Werner syndrome.

CQ4. How should osteoporosis in patients with Werner syndrome be treated?

A4. No clear evidence to date regarding treatment for osteoporosis associated with Werner syndrome has been found at present, and thus it is considered appropriate to treat osteoporosis according to the guidelines for the treatment of osteoporosis.[10]

As a typical drug to decrease the risk of osteoporosis-related fractures, bisphosphonates have been widely used. A report indicated that etidronate, one of the bisphosphonates, has ameliorated painful soft tissue calcification,[11] which provides a helpful perspective to select drugs. On the other hand, there has been a report suggesting that osteoporosis in Werner syndrome is caused mainly by inhibition of osteogenesis, for which parathyroid hormone (teriparatide) is considered effective. As sarcoma frequently develops in patients with Werner syndrome, the use of parathyroid hormone requires special attention to the development of osteosarcoma.

Discussion

Werner syndrome is often accompanied by osteoporosis. Age-related osteoporosis generally occurs more commonly in the bony skeleton including proximal sites of the vertebra and the femur, whereas osteoporosis is more severe in the distal extremities, particularly in the lower extremities in patients with Werner syndrome. As arthrogryposis is associated with dermal sclerosis in the lower extremities or ulcerative lesions in the foot region occur in patients with Werner syndrome, the bones of the lower limbs are easily influenced by disuse and inflammatory changes. These are considered one of the reasons that osteoporosis associated with Werner syndrome may become more severe in the lower extremities. On the other hand, the research results indicating the association between *WRN* gene polymorphism and osteoporosis have also been reported, suggesting that an onset of osteoporosis might be genetically promoted in Werner syndrome.

As no specific evidence has been found to date regarding treatment for osteoporosis associated with Werner syndrome, it is considered appropriate to follow conventional treatment for this bone disease. Given that disuse may possibly be involved in the pathogenesis of osteoporosis, prevention against disuse through active rehabilitation is also important.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

SOCIAL RESEARCH, PLANNING AND PRACTICE

Management guideline for Werner syndrome 2020. 5. Infection associated with Werner syndrome

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Introduction

Werner syndrome is characterized by symptoms such as atrophy of subcutaneous tissues, decreased blood flow[1] and lower activity of fibroblast cells[2] due to metabolic disorders in connective tissues,[3] which may easily cause refractory skin ulcers.[4] Furthermore, it may occur with type 2 diabetes,[5] which is likely to cause skin and soft tissue infections and osteomyelitis at an ulcer site. Generally, such symptoms may often become more severe than in patients with diabetes, leading to failure of conservative treatment and necessitating surgical excision of the infected site. It is considered that the goal to treat an infection caused by refractory skin ulcers in patients with Werner syndrome is to minimize exacerbation of the ulcerated skin lesion by detecting signs of infection early and treating it.

Treatment guidelines for infections in dermal ulcers

The bacterial etiology of skin ulcers in Werner syndrome is nearly identical to that observed in a diabetic foot infection. However, skin ulcers are poorly healed in patients with Werner syndrome compared with those of patients with diabetes, thereby raising a risk of long-term and chronic infection. Prolonged infection could cause the emergence of a drug-resistant strain, resulting in a limited choice of antimicrobials capable of treating the lesion. Therefore, it is important to identify the bacterial etiology causing an infection in the skin ulcer and treat with an effective antimicrobial. For poorly controlled infection, debridement and surgical excision are needed at an appropriate time. Thus it is essential to work with plastic surgeons and orthopedists.

Laboratory examination and diagnosis

When treating diabetic foot infections, we recommend a microbiological diagnostic method. To assess the severity of a diabetic foot infection, it is recommended by the Infectious Diseases Society of America (IDSA) to collect samples in the following way.[6]

1. Clean area of the wound, perform debridement and biopsy a deep tissue or take samples by curettage.

Table 1 Examples of antimicrobials for mild or long-term/chronic cases

Antimicrobial drug†	Comments
Oral administration of cephalexin (500 mg) every 6 h	Covers Gram-positive bacteria
Oral administration of amoxicillin (250 mg)/clavulanate (125 mg) + amoxicillin (250 mg) every 8 h	Cover anaerobic bacteria
Oral administration of two sulfamethoxazole (400 mg)/trimethoprim (80 mg) Tablets every 12 h	Cover MRSA
Oral administration of minocycline (100 mg) every 12 h	Covers MRSA
Oral administration of clindamycin (300 mg) every 8 h	Covers anaerobic bacteria and some MRSA
Oral administration of levofloxacin (500 mg) every 24 h	Covers *Pseudomonas aeruginosa*. Often used in combination with clindamycin

MRSA, methicillin-resistant *Staphylococcus aureus*.

†Dosage and dose regimen need to be adjusted according to renal function.

Table 2 Examples of antimicrobials for moderate to severe cases

Antimicrobial drug†	Comments
Intravenous injection of 3 g of ampicillin/sulbactam every 6 h	Covers Gram-positive bacteria and anaerobic bacteriaFirst-line drug in cases of no drug-resistant strains
Intravenous injection of 4.5 g of piperacillin/tazobactam every 6 h	Covers Gram-positive bacteria, anaerobic bacteria and *Pseudomonas aeruginosa*
Intravenous injection of 2 g of cefepime every 12 h and 500 mg of metronidazole every 8 h	Covers drug-resistant Gram-negative bacteria except *Pseudomonas aeruginosa* as well
Intravenous injection of 1 g of meropenem every 8 h	Covers ESBL-producing Gram-negative bacteria and anaerobic bacteria as well
Vancomycin‡	Covers Gram-positive bacteria and MRSA
Daptomycin§	Covers Gram-positive bacteria and MRSA In cases where vancomycin cannot be used

ESBL, extended spectrum beta lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*.

†Dosage and dose regimen need to be adjusted according to renal function.

‡Dosage and frequency based on body weight and drug blood level.

§Dosage and frequency based on body weight.

2. Puncture fluid of purulent discharge.
3. Obtain bone biopsy tissue in cases of suspected osteomyelitis.

When a sample is obtained from a wound without clinical symptoms of infection (obtained from an area of the wound without debridement, or obtained simply by swabbing an area of the wound), normal bacterial flora, which may not be the cause of infection can be detected, which poses the risk of administering unnecessary broad-spectrum antimicrobials. In cases of a deep ulcerated lesion with a symptom of infection, a Probe to Bone test (to check whether a probe inserted into the lesion reaches the bone) is performed.[7] If the bone is exposed, osteomyelitis is suspected, which necessitates a culture from biopsied bone tissue.[8]

Selection of therapeutic drugs

As with treatment for diabetic foot infection, a skin and soft tissue infection occurring with an ulcerated lesion in Werner syndrome is treated by targeting Gram-positive bacteria, which includes *Streptococcus* spp. and *Staphylococcus aureus*.[9] To determine if any other bacteria should be covered, the following four items should be checked.

1. Risk of methicillin-resistant *S. aureus*.
2. History of antimicrobial use within a month; if present, Gram-negative bacteria need to be covered.
3. Risk of *Pseudomonas* infection.
4. Determination of the severity.

Example of antimicrobials for (i) mild or long-term/chronic, and (ii) moderate to severe cases are shown in Tables 1 and 2 respectively.

Treatment duration

The goal of treatment is to ameliorate symptoms of infection (red flare, pain and swelling). Treatment duration corresponds to that for diabetes foot infection,[6] but if the infected skin tissue is poorly healed, it should be determined on a case-by-case basis.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Management guideline for Werner syndrome 2020. 6. Skin ulcers associated with Werner syndrome: Prevention and non-surgical and surgical treatment

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Aim: To provide guidelines on the diagnosis, treatment, and prevention of skin ulcers in Werner syndrome.

Methods: This article was based on literature from 1996, when WRN was identified as a gene responsible for Werner syndrome, and we evaluated several authentic clinical cases of genetically diagnosed patients. There were 63 patients with Werner syndrome in the Japanese reports retrieved from Medical Online between January 1996 and December 2017. There were 56 patients with Werner syndrome in English reports written by Japanese authors and retrieved from PubMed during the same period.

Results: Records on skin ulcers were found in 27 (43%) out of 63 patients and 22 (40%) out of 56 patients from the Japanese and English reports, respectively. The reported ulcers were often located at the distal one-third of the lower legs. There were 8 patients with callosities in the foot in the Japanese reports and 9 patients in the English reports. A skin ulcer in Werner syndrome is generally intractable. Weight-bearing ulcers or callosity should be critically assessed in surgical procedures because they have effects on patient pain and gait. By adopting a recently advanced technique to facilitate wound healing, the cases of ulcers that were difficult to treat and those requiring major operations can be closed with minimally invasive surgery.

Conclusions: Skin ulcers in Werner syndrome are refractory, and they lead to reduced quality of life of patients. A callosity in Werner syndrome is an important therapeutic target for the prevention of ulcers. **Geriatr Gerontol Int 2020; ••: ••–••.**

Keywords: callosities, foot ulcer, osteomyelitis, shoes, werner syndrome.

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Introduction

Skin ulcers are commonly observed in Werner syndrome (WS). This article explores the epidemiology, diagnosis, treatment and prevention of ulcers in WS from a surgical perspective.

Skin ulcers in WS are refractory, and they lead to a reduced quality of life for patients. Foot ulcers in WS require special care because its clinical presentation is similar but not identical to that of ischemic limb ulcers or diabetic ulcers, both of which have recently increased in prevalence. As WS is an extremely rare disease, it is difficult to gain adequate experience in treating it. It is also difficult to create evidence-based guidelines based on clinical trials involving several patients. Nonetheless, it is necessary to make an appropriate diagnosis and provide treatment tailored to the skin ulcer in each patient with WS. In addition, ulcers in these patients are refractory, which necessitates prevention. Based on these observations, guidelines on the diagnosis, treatment and prevention of skin ulcers in WS based on case reports, including ours, are important. This article also explores elbow ulcers, as well as other lower-limb ulcers, which occur commonly in WS.

Literature

Most studies on WS are case reports; there are only a few case series. This article was based on literature from 1996, when *WRN* was identified as a gene responsible for WS, and we evaluated several authentic clinical cases of genetically diagnosed patients.

There were 63 patients with WS in the Japanese reports retrieved from Medical Online between January 1996 and December 2017. There were 56 patients with WS in English reports written by Japanese authors and retrieved from PubMed during the same period. Both reports were used in this study. However, these Japanese reports included abstracts of conference presentations; thus, some cases overlapped. Similarly, cases reported in Japanese could overlap with those in English.

Overview of skin ulcers

Q1. What is the complication rate of skin ulcers in patients with Werner syndrome?

A1. Approximately 40% of patients with Werner syndrome have skin ulcers.

WS is a very rare disease, and it is difficult to determine accurately the morbidity and prevalence of complications of skin ulcers. Records on skin ulcers were found in 27 (43%) of 63 patients and 22 (40%) of 56 patients from the Japanese and English reports, respectively (Table 1). The reported ulcers were often located at the olecranon of the elbow joint in the upper limbs; ulcers were observed at sites below the distal one-third of the lower legs in several cases. There have also been reports of ulcers in the extensor surfaces of the knee joints.

Q2. Which part of the lower limb is typically affected in patients with Werner syndrome?

A2. The distal one-third of the lower leg and the foot are typically affected.

Patients with WS often have thin lower limbs and dry skin. Poikiloderma and scleroderma-like changes occur on the foot, particularly on the distal one-third of the lower legs (Fig. 1). The distal one-third of the lower legs and foot will be discussed subsequently. The skin is often poorly extensible and shiny. The contraction of the ankle often limits the range of motion with the pes equinus position. Flat foot is a typical symptom of WS. Flame-like calcification in the Achilles tendon shown on radiographs is a typical symptom in WS, and skin ulcers are sometimes observed. In addition, WS may be associated with lateral and medial malleoli on the ankle and multiple leg ulcers. Callosities are also frequently observed. Even on an ulcer-free foot in relatively good condition, a callosity is often observed when critically assessed. Toe deformities frequently occur and sometimes progress rapidly.

Q3. What are the underlying diseases that can cause lower-limb ulcers?

A3. Glucose metabolism disorders are present in many cases.

Table 1 Number of reported skin ulcers by body part in Werner syndrome

Body part	No. of cases in the Japanese reports (n = 63)	No. of cases in the English reports (n = 56)
Elbow	11 (17%)	1 (2%)
Knee	1 (2%)	2 (4%)
Lower leg	2 (3%)	4 (7%)
Achilles tendon	4 (6%)	5 (9%)
Medial and lateral malleoli in the ankle	2 (3%)	6 (11%)
Sole	4 (4%)	3 (5%)
Heel	6 (10%)	4 (7%)
Toe	4 (6%)	3 (5%)
Foot	1 (2%)	1 (2%)

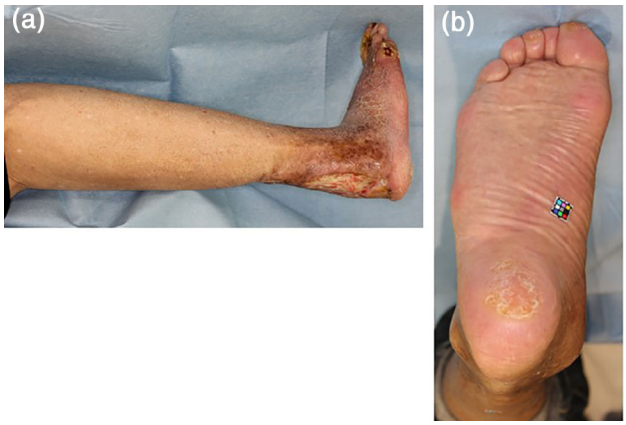

Figure 1 (a) Typical images of lower limbs in Werner syndrome. Significant hardening and atrophy of the skin and soft tissue are observed below the distal one-third of the lower extremities. (b) Foot is in relatively good condition without ulcers yet with a callosity on the heel region.

The incidence of carbohydrate metabolism disorders in patients with WS was high at 43% and 39% in the Japanese and English reports, respectively (Table 2). The clinical presentation of a foot ulcer in WS is partly similar to, but not necessarily identical to, that in diabetes or hypertension, which has been increasing in prevalence recently. This requires attention. Hypertension was not necessarily found in several cases. Lower limb ischemia was also not observed in several WS cases. In WS, a decrease in sensation is not common unless there is diabetes. It should be noted that the ulcers in WS are caused by multiple factors; among them, scleroderma-like changes and foot deformities are the most common. Furthermore, defective wound healing may also contribute to the development of foot ulcers in WS.

Q4. Are there ulcers associated with malignancy?

A4. Yes, such ulcers are occasionally seen.

Malignancy is prevalent in WS. The incidence of a non-epithelial tumor in patients with WS has also been reported to be higher than that in the healthy population. Regarding the association with skin ulcers, a study reported that calcaneal osteosarcoma was observed in a patient with a heel ulcer.[1] Malignancies should be considered as differential diagnoses for skin ulcers in patients with WS.

Q5. Are callosities frequently observed?

A5. Yes, they are frequently observed.

Callosities occur frequently on the feet of patients with WS. There were eight patients with callosities in Japanese reports and nine patients in English reports. Callosities cause pain and decrease quality of life, and an ulcer may occur at a site of callosity. Moreover, pain caused by a callosity worsens gait, which contributes to an increased load on the other sites, and subsequent development of new callosities or ulcers. Accordingly, a callosity in WS is an important therapeutic target for the prevention of ulcers.

Table 2 Underlying diseases that can cause a lower extremity ulcer

	Japanese reports (n = 63)	English reports (n = 56)
Carbohydrate metabolism disorders	27 (43%)	22 (39%)
Hypertension	3 (5%)	1 (2%)
Lower limb ischemia	1 (2%)	2 (4%)

WS is characterized by hardened and poorly extensible skin. In addition, symptoms, including flat foot, toe deformity and ankle contracture, may progress. These conditions cause high callosities in WS.

As mentioned above, a callosity may become the origin of a skin ulcer. Thus, for patients with WS who have a callosity without a skin ulcer, prevention is necessary, considering the risk of developing an ulcer. Such cases have been reported in two patients from Japanese reports and five from English reports. The importance of interventions for preventing or treating callosities in ulcer-free patients with WS is underscored by the following among others: (i) several patients do not take preventive measures, including the use of a foot orthosis and shoe orthosis because they have never developed an ulcer or experienced refractory ulcers; and (ii) patients with mild symptoms are quite active, and therefore high pressure is applied to the callosities over a long period. In our patient, a load on a callosity on the heel ruptured the calcaneal bony cortex, leading to calcaneal bone osteomyelitis (Fig. 2). Although this patient presented with changes typical of WS, including poikiloderma, scleroderma-like skin changes, and ankle contracture of the distal one-third of the lower legs to the foot, the skin on the lower legs and feet were in relatively good condition. The causes of a heel ulcer were considered to include failure to treat a callosity on the heel, use of commercial shoes, and repeated and continuous pressure applied to a callosity on the heel due to the patient's activities.

These observations demonstrate that a callosity is a prodrome of skin ulcers in WS. The interventions for callosities may prevent severe and difficult-to-treat conditions such as skin ulcers and osteomyelitis.

Diagnosis

Q6. Are macroscopic evaluations of ulcers important?

A6. Yes, they are important.

As macroscopic findings, the records of sites and characteristics of ulcers are important. It is useful to keep records, with the items included in DESIGN-R®(edited by the Japanese Society of Pressure Ulcers)[2] in mind, to reduce the number of omissions. DESIGN-R® provides criteria for evaluating pressure ulcers, yet it can also be used to assess ulcers other than pressure ulcers. The evaluation items are depth, amount of exudate, size, inflammation/infection, granulation tissue, necrotic tissue and pocket.

DESIGN-R is a detailed evaluation method that can be utilized for therapeutic effect determination and assessment of time-dependent changes. Its limitations include slightly cumbersome records.

The following are points that are considered important in the assessment of ulcers in WS.

1. Depth of an ulcer: an ulcer in WS easily reaches the bone or the articular cavity. It is necessary to consider the possibility of osteomyelitis in case of the rupture of the ulcer and extension to the bone marrow, osteomyelitis and purulent arthritis in case of an ulcer reaching the articular cavity.
2. Amount of exudate: in cases of purulent exudates, the possibility of osteomyelitis or purulent arthritis should be considered.
3. Size: it is important to determine the condition of an ulcer and the therapeutic effects.

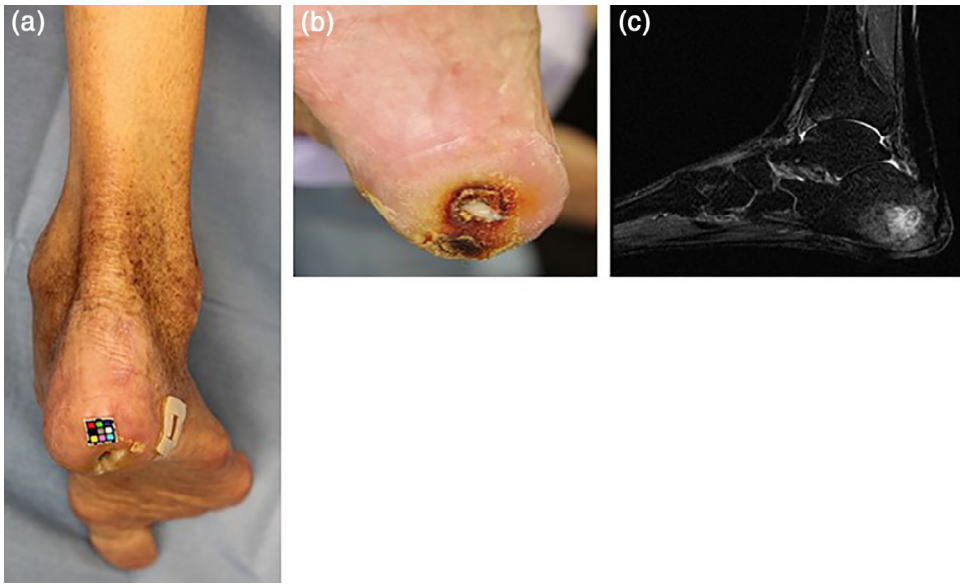

Figure 2 A case of a calcaneal callosity developing into possible calcaneal bone osteomyelitis. (a) Skin is generally in good condition from the distal one-third of the lower extremities to the foot region. (b) Pus from the ulcer on the heel region. (c) Magnetic resonance imaging: sagittal section of the foot. Fat-suppressed T2-weighted image shows high signal intensity in the calcaneal bone marrow, which reflects osteomyelitis.

4. Inflammation/infection: it is important to identify the focus of the infection, which may be the skin and soft tissue, bone marrow, or articular cavity.
5. Granulation tissue: generally, granulation is poor at the site of an ulcer in WS. In cases with poorly formed granulation tissue, it is necessary to investigate the cause, which may include poor blood flow, infection and necrotic tissue, and provide treatments to eliminate these conditions.
6. Necrotic tissue: the following should be determined, i.e., nature, depth and range of necrotic tissue.
7. Pocket: in several patients with WS, the formation of a pocket in a foot ulcer may become a problem.

Q7. Are plain radiography and computed tomography of the foot region useful?

A7. Plain radiography and computed tomography are helpful for examining the shape of the entire foot and the conditions of individual bones of the foot.

It is important to understand the time-dependent changes because the shape of the foot and the state of each bone may change rapidly in WS.

Q8. Is magnetic resonance imaging examination useful?

A8. Magnetic resonance imaging examination is useful for a suspected case of osteomyelitis (Fig. 2).

Q9. Is vascular evaluation necessary?

A9. Yes, it is necessary.

In cases of lower-limb ischemia, it is necessary to assess the possibility of revascularization. Lower-limb ischemia should be considered in patients with a history of hypertension or diabetes, cold feet, or non-palpable dorsalis pedis and posterior tibial pulses. There were suspected cases of lower-limb ischemia in one patient from the Japanese and two from the English reports. One of these patients reportedly showed revascularization after a femoropopliteal artery bypass surgery using a saphenous vein.[3]

Treatment

Q10. Is the combination of surgical treatment and wound bed preparation important in treating skin ulcers?

A10. Yes, it is important to combine these treatments.

A skin ulcer in WS is generally intractable. Weight-bearing ulcers or callosity should be critically assessed in surgical procedures because they have effects on patient pain, gait and quality of life. Even if a wound is finally closed surgically, using procedures such as skin grafting and flap surgery, preparation before wound closure can influence the outcomes. By adopting a recently advanced technique to facilitate wound healing, the cases of ulcers that were difficult to treat and those requiring major operations can be closed with minimally invasive surgery. The attempt to improve the condition of an ulcer preoperatively is called wound bed preparation, and its importance cannot be overemphasized. In addition, progress in regenerative medicine may introduce other treatment options in the future, which may include cultured tissue grafting. This section discusses the progression from wound bed preparation to surgery in patients with WS, incorporating our experience.

Debridement and curettage

In the management of skin ulcers, the removal of necrotic tissue and cleaning of the wound surface are important. Thus, daily cleaning of wound surfaces by patients is necessary. At the same time, curettage and surgical debridement are desirable every time they visit medical institutions. In addition, chemical debridement, which involves the enzymatic removal of necrotic tissue, is one of the options for daily debridement.

For obviously infected wounds, incisional drainage or debridement should be performed immediately. Lately, ulcers with no obvious symptoms of infection but increased bacterial volume, called critical colonization, has attracted attention. The critically colonized bacterial mass forms a biofilm of glycocalyx and other components, disrupts host immunity and affects the effectiveness of external medicine, and inhibits wound healing. A soft yellow- to white-colored tissue attached to the surface of an ulcer (sometimes called a slough) may include a biofilm, which is suggestive of critical colonization. In addition, NERDS has also been reported as a clinical finding suggestive of critical colonization[4] (Table 3). It is considered effective, as a countermeasure against critical colonization, to remove soft yellow- to white-colored tissue attached to the bottom of an ulcer using a sharp spoon or other

Table 3 Signs suggestive of critical colonization

English terms	Meaning
N: Non-healing wounds	Treatment-resistant ulcers
E: Exudative wounds	Heavy effusion
R: Red and bleeding wound surface and granulation tissue	Red granulation tissue with bleeding
D: Debris	Existence of necrotic tissue, etc.
S: Smell or unpleasant odor	Odious smell

Signs suggestive of critical colonization are termed NERDS; an acronym using the terms shown above (quoted from Woo and Sibbald[4]).

instrument when the ulcer in WS is examined; this procedure removes the biofilm and reduces bacterial volume.

Debridement is useful for the diagnosis because it facilitates the determination of the range and depth of an ulcer. During the procedure, it is also important to collect samples for bacterial cultivation from wounded surfaces, necrotic tissue or pus. Some ulcers extend to the bone marrow, and osteomyelitis may be found during debridement. In such cases, pus should be obtained from the bone marrow for bacterial cultivation.

Pain is the most common hindrance in performing debridement for patients with WS. They frequently develop carbohydrate metabolism, yet have less perceptual decline than patients with diabetic ulcers and stronger pain than healthy people during the procedure. This often makes debridement without anesthesia difficult. In the case of local infiltration anesthetic injection, the hardening of tissue worsens the pain caused by the injection and prevents the injected anesthetic agent from penetrating the tissue, which increases the dose requirement and decreases the effectiveness of analgesia. One of the measures is block injection to sites with soft skin away from an ulcer such as the center of the lower thigh (Fig. 3). In any case, the significance and necessity of debridement in WS should be explained to patients, followed by adequate preparations before applying this procedure.

Topical medication

It is important to use an appropriate topical medication for an ulcer. The basic idea of moist wound healing in ulcer treatment is to maintain an adequately moist environment and facilitate wound healing. However, ulcers in WS rarely heal with drugs that directly promote a moist environment and wound healing (Vaseline ointment, prostaglandin-containing ointment and basic fibroblast growth factor [bFGF] spray) alone. The critical colonization of bacteria is often addressed with iodine preparation or silver preparation. Heavy exudation exceeding the range of moist wound healing inhibits this process, and thus preparations with a water-absorbing base (cadexomer iodine and iodine-sucrose preparations) are often used to absorb exudates.

Washing

Washing a wound surface is considered effective. There is little evidence on the effectiveness of washing, but a clinical consensus on efficacy is considered to have been reached. Wound irrigation with a shower by a patient acts as self-care and is one of the desirable personal hygiene measures. Accordingly, washing the foot in the shower just because an ulcer should be avoided, despite the lack of reason, to control a wound.

On the other hand, the following risks caused by washing should be considered, i.e., (i) multidrug-resistant bacteria in the environment are attached to a wound surface, and (ii) multidrug-resistant bacteria on a wound surface may spread to the environment.

Water-related equipment (e.g., water faucets, showerheads, bathtubs, perineal irrigation bottles) may be contaminated by various bacteria in medical institutions. Wound irrigation is likely to cause contamination of the environment by splatter. In light of the

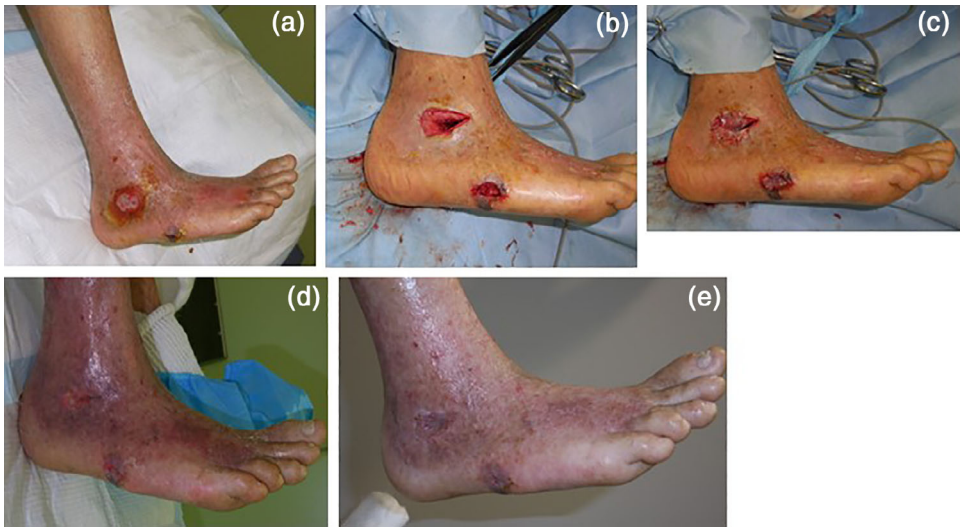

Figure 3 (a) Ulcers are observed on the lateral malleolus in the ankle and the lateral aspect of the foot. (b) Post-debridement. Anesthesia is administered at a site with the soft skin slightly distal from the center of the lower limb for a sural nerve block. Ulcer on the lateral malleolus reaches into the bone marrow, and the ulcer on the lateral aspect of the foot to the fifth metatarsal bone. (c) After artificial dermis was attached on to the ulcers, negative pressure wound therapy (NPWT) started. (d) Post-NPWT: granulated and reduced-size ulcers are observed. They were determined applicable to skin grafting, and split-thickness skin grafts for meshing was performed. (e) Post-skin grafting: successful engraftment and ulcer closure are confirmed.

above risks in (i) and (ii), a wound should be irrigated following standard preventive measures.

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) has been widely used to treat refractory ulcers in recent years. It promotes neovascularization and granulation by continuous negative pressure and facilitates ulcer healing by controlling exudates. It was effective to an extent in our cases (Fig. 3), and it should be proactively employed in the future. General precautions for NPWT include (i) not using infected wounds, and (ii) paying attention to skin diseases around ulcers, which should also be followed accordingly in WS. Skin ulcers associated with purulent arthritis frequently occur in WS. Infected ulcers are not an indication for NPWT monotherapy, but a combination with continuous irrigation may be effective.

Caution should be exercised when administering NPWT for the foot in WS because the tissue is severely indurated and the skin and soft tissue are thin and close to the bone, leading to the likelihood of developing skin and soft tissue disorders following pressure from a foaming agent. A foaming agent should be cut into an appropriate width and thickness for effective use.

Surgical procedure

Attachment of artificial dermis
The skin and soft tissues in WS become thin and indurated, which likely causes loss of all layers of the bone and tendon. The artificial dermis is essential for treating foot ulcers in WS (Fig. 3). In WS, the bony cortex is often ruptured, leading to exposure of the bone marrow, but an artificial dermis can also be attached to the exposed bone marrow. Dermis-like tissue is constructed on the surface of the exposed bone marrow to prevent osteomyelitis and enable epidermization.

Skin grafting
Several skin ulcers in WS had previously been accompanied by bone exposure at the regions of loss of periosteum and aponeurosis, and it is difficult to perform skin grafting. However, the advent of the artificial dermis, bFGF preparation and NPWT has increased the number of cases that can have a base bed for skin grafting for ulcers in WS; patients undergoing skin grafting may also be on the increase. Descriptions of skin grafting were found in one case from the Japanese report and two cases from the English reports. Figure 3 shows the cases of skin grafting on the lateral malleolus in the ankle.

Flap surgery
With or without WS, the percentage of comparatively major surgeries, such as flap surgery, has decreased for the treatment of intractable ulcers, and their roles have been relatively declining. This is attributable to drug advances, including topical medication and bFGF preparations, advent of the artificial dermis, which has made skin grafting possible even in previously contraindicated situations, and a powerful granulating effect and reduction of ulcers by NPWT. On the other hand, flap surgery can close ulcers that could not be closed by other therapeutic procedures; ulcers can be closed using thick skin and soft tissue, and the duration of treatment shortens.

Elbow ulcers
The olecranon bone is curved, and highly flexible soft tissue is required because of the elbow flexion–extension movements. Furthermore, the articular cavity is often exposed in elbow ulcers of patients with WS. For these reasons, flap surgery may be appropriate in several cases instead of skin grafting. Regarding flap surgery for elbow ulcers, there have been reports on the use of radial recurrent flaps,[5] flexor carpi ulnaris muscle flaps,[6] and radial forearm flaps.[7] Other than those above, skin grafting[8] and partial ostectomy[9] have been reported.

Knee ulcers
Flap surgery is highly applicable to ulcers with an exposed knee-joint cavity. There are reports on cases of anterior tibial artery flap, sartorius muscle flap and free latissimus dorsi myocutaneous flap.[10,11]

Heel ulcers
A free serratus anterior muscle flap has been reported for a heel ulcer associated with osteomyelitis.[12]

Ulcers in the Achilles tendon
Calcification with a flame-like shape in the Achilles tendon observed on radiographs is a characteristic finding of WS. The infection of calcification often causes ulcers in the Achilles tendon. It has been reported to be treated with a lateral supramalleolar flap.[13]

Amputation
Amputation of the affected parts cannot be avoided in some refractory ulcers. Records on amputation were found for one case each of the foot and toe from Japanese reports and one case below the knee and another case of the toe from English reports. A case of below-the-knee amputation caused by calcaneal osteosarcoma has also been reported.[1]

Others

Hyperbaric oxygen therapy
Hyperbaric oxygen therapy for calcaneal ulcers accompanied by calcaneal osteomyelitis has been reported.[14]

Lumbar sympathetic ganglion block
There are reports on the lumbar sympathetic ganglion block for foot ulcers and pain.[15,16]

Skin care

Moisture retention
In WS, skin dryness is frequently observed, particularly in the lower leg and foot. It may become a predisposing factor for callosities and the exacerbation of skin ulcers. Desquamation or rash caused by cutaneous dryness is considered to induce contamination in surgical wounds and inhibit wound healing. The application of a moisturizer may be effective.

Management

Q11. Is the management for a callosity necessary?

A11. Yes, it is necessary.

Callosities frequently occur in the foot in WS (Fig. 1b), and they may induce skin ulcers, rupture of the bony cortex in the calcaneal bone, and osteomyelitis (Fig. 2). Special attention should be paid to the callosity in the weight-bearing portion of the foot. Once an ulcer or osteomyelitis occurs in WS, it may become

Figure 4 Samples of shoe-shaped orthoses: (a) outdoor type shoes; (b) indoor type shoes.

intractable, and preventive measures against these symptoms are implemented when a callosity is observed. Therefore, proactive intervention for callosities is important.

Prevention against callosities

A callosity occurs when excessive pressure is prolonged. It is important to avoid excess pressure on the feet to prevent callosity formation.

Use of an appropriate foot orthosis or shoe-shaped orthosis, which is tailored to each patient's foot, may prevent a callosity and an ulcer. An article reported the use of foot orthosis and a shoe-shaped orthosis for two patients with WS.[17] According to the report, it was challenging to make orthoses for both cases, yet one patient was satisfied with it. In our cases, shoe-shaped orthoses were proactively made (Fig. 4). There are outdoor shoe types and indoor shoe types, which are tailored to the lifestyle of each patient by a prosthetist. These shoes are more comfortable than commercial shoes made for healthy people, and they relieve pain. We are currently examining the effects of these orthoses on callosities and ulcers. A toe deformity may progress rapidly in WS, which often renders a prepared orthosis unsuitable after a brief period.

Orthoses can be applied to the lower and upper extremities, such as the elbow joint.

Treatment of callosity

Proactive treatment of a callosity is desirable in WS., Treatment should be continued, given that a callosity recurs unless continuous excessive pressure, the cause, is eliminated. The specific methods include the following.

Shaving of a callosity
The thickness of a callosity may be reduced with a razor, and the shape of a callosity may be smoothened. This makes it possible to prevent extremely heavy pressure from being applied to the narrow range of the skin.

Attachment of salicylic acid preparation
By attaching a salicylic preparation, keratin can be macerated and manually exfoliated.

Use of an appropriate foot orthosis or shoe-shaped orthosis
A foot orthosis or shoe-shaped orthosis tailored to each patient's foot may be effective not only for the prevention of callosity and ulcer but also for their treatment.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Management guideline for Werner syndrome 2020. 7. Skin ulcer associated with Werner syndrome dermatological treatment

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Skin ulcers in Werner's syndrome often arise from hyperkeratotic lesions and trauma to pressure points such as the plantar region, and are more difficult to treat than wound healing in healthy individuals. Multiple factors contribute to the intractable skin ulcers in Werner's syndrome, including skin thinning, sclerosis, fatty tissue loss, impaired blood flow, calcification, and excessive pressure due to osteoarticular deformity. Treatment includes topical application of a keratolytic agent for keratosis around the ulcer. Treatment of ulcers is the same as for normal ulcers, and if the ulcer is associated with infection and necrotic tissue, surgical debridement with a scalpel or scissors should be performed as much as possible after washing with saline or mildly warm water or with an antibacterial agent. Topical medications that promote softening and debridement of the necrotic tissue are used with careful control of moisture in the wound. Topical agents that promote granulation should be used in wounds where necrotic tissue has been removed without infection. Dressings to maintain a moist environment in the wound may also be useful. If the wound does not improve with conservative treatment, surgical treatment should be considered. **Geriatr Gerontol Int ••; ••: ••–•• Geriatr Gerontol Int 2020; ••: ••–••.**

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Introduction

A skin ulcer in Werner syndrome is caused by various factors. It has been said that impaired metabolism of the connective tissue component is involved.[1] In addition, the following factors are considered concurrently associated with ulcer development: greater weight bearing on the distal extremities due to thin limbs for the body trunk, a deformed bone and joint such as hallux valgus and a flat foot, localized hyperkeratosis on the sole of the foot, physical pressure on dermal connective tissue due to subcutaneous calcification, thinning or hardening of the skin, decreased adipose tissue, delayed wound healing due to decreased fibroblast proliferation capacity, occurrence of diabetes and hematogenous disorder accompanied by an arteriosclerotic lesion.[2]

A skin ulcer occurs more commonly at sites on which pressure is exerted, including the Achilles tendon, ankle, elbow and plantar region.[3] It sometimes presents with prodromal symptoms of a corn, callus and trauma. Owing to the atrophied skin and decreased subcutaneous adipose tissue at sites of predilection for skin ulcers, formation of an ulcer causes a tendon or bone to be projected easily.[2] Patients with Werner syndrome often develop tumors, and thus, it is desirable to consult a dermatologist when in doubt to consider the possibility of a refractory skin ulcer attributed to squamous cell carcinoma or a malignant melanoma. In particular, careful attention is needed, as patients with Werner syndrome can develop acral lentiginous malignant melanoma, occurring commonly on the sole of the foot, at a high rate.[4]

Treatment guidelines

A skin ulcer in Werner syndrome is attributed to the above factors, which makes it intractable. It is conservatively treated with topical medications and wound dressings first, while systemic treatment including diabetic control needs to be performed concurrently. For hyperkeratosis around a skin ulcer, keratin softeners such as salicylic acid Vaseline and urea ointment are used topically. Treating a corn and callus with keratin softeners is important to prevent the occurrence of a skin ulcer as well. In cases where a skin ulcer is not improved with conservative medical treatment, surgical treatment should be considered.

Local treatment

A skin ulcer in Werner syndrome is a chronic cutaneous wound. Prolonged inflammation caused by various cytokines and increased activity of protease that plays a role in breaking down necrotic tissue protein cause an extracellular matrix acting as a scaffold of tissue to be breaks down, leading to failure to reconstruct tissues in the chronic cutaneous wound.[5] In addition, impaired molecular composition in the effusion lowers the division potential of the cell that is involved in tissue reconstruction.[5] To facilitate the healing process of a chronic wound, topical medications to eliminate causes that interfere with healing, and topical medications or wound dressings that accelerate the repairing process need to be appropriately selected before use.[6]

In cases where a skin ulcer is associated with infection or necrotic tissue

The skin ulcer is washed with saline or lukewarm water, followed by surgical debridement of the necrotic tissue using a scalpel and a scissor as much as possible. If it is in the process of being infected or already infected, the ulcer is disinfected with povidone iodine, chlorhexidine gluconate or benzalkonium chloride to control infection.[6] In case of failure to perform debridement, chemical debridement is conducted using necrotic tissue removers including CADEX OINTMENT®, Isodine gel® and Bromelain ointment®. GEBEN cream® containing more water facilitates softening and dissolving of necrotic tissue, which is effective treatment for a wound site with a small effusion. In cases with heavy exudate from a wound site due to infection or intense inflammation, CADEX OINTMENT® and U-Pasta® KOWA are effective in absorbing the exudate. As to an ulcer associated with infection or necrotic tissue, closure of an ulcer can worsen infection, and thus it should not be treated with wound dressings (closed dressings) but mainly using antibacterial therapy available in topical preparations.[6]

Granulation/epithelium formation stage

At an infection-free wound site after necrotic tissue has been removed, granulation is generally formed, whereas it is not easily

formed in most skin ulcers occurring in patients with Werner syndrome. Therefore, a wound site should be washed with saline or lukewarm water, followed by application of granulation promoting drugs, including Olcenon Ointment®, Prostandin Ointment® and Reflap Ointment®. A basic fibroblast growth factor (Fibrast spray®) is also effective, but attention is required because skin ulcers in a patient with Werner syndrome are often associated with malignancy.

Granulation tissue can then fill the ulcer, leading to epithelization. At this stage, epithelization promoters including Prostandin Ointment® and Actosin Ointment® are used. Wound dressings are also effective to maintain a moist environment at the wound site. Hydrocolloid is recommended for wounds with a small amount of exudate, while alginate (Sorbsan®), chitin (Beschitin®), hydrofiber (AQUACEL®), hydropolymer (TIELLE®) and polyurethane foam (HYDROSITE®) are effective with heavy exudate.[6]

Recently, a case has been reported where endothelin receptor antagonist successfully treated a refractory ulcer.[7]

Surgical treatment

In many cases, there are difficulties in healing skin ulcers using skin grafting, while the attachment of artificial dermis[8] and flap reconstruction[9,10] are often more effective. It is also necessary to consider the possibility that debridement may enlarge an ulcer due to decreased fibroblast division capacity.[8]

Discussion

Skin ulcers associated with Werner syndrome are often caused by a corn, callus or trauma occurring at sites on which pressure is exerted, including the Achilles tendon, ankle, elbow and plantar region, and are more refractory than wounds in healthy individuals. This may be attributable to thinning or hardening of the skin, a decrease in adipose tissue, inadequate blood flow, calcification and excess pressure due to a deformed bone and joint. To treat skin ulcers, a keratin softener is used topically for the hyperkeratosis around an ulcer. Treatment for an ulcer associated with Werner syndrome is the same as that for a common ulcer. However, if it is accompanied by infection or necrotic tissue, the ulcer is washed with saline or lukewarm water or disinfected with antiseptic, followed by surgical debridement for necrotic tissue using a scalpel and a scissor as much as possible. Topical medications that promote softening and dissolving of necrotic tissue are used concurrently, with careful attention paid to moisture control at the surgical wound site. For infection-free wound sites after the necrotic tissue has been removed, topical medications for a granulation promoting effect are used. Wound dressings are also effective to maintain a moist environment at the wound site. In cases where a skin ulcer is not ameliorated with conservative medical treatment, surgical treatment should be considered.

Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

SOCIAL RESEARCH, PLANNING AND PRACTICE

Management guideline for Werner syndrome 2020 8. Calcification in tendons associated with Werner syndrome

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Aim: To clarify the diagnostic value of the calcification in the Achilles tendon for Werner syndrome.

Methods: Calcification of the Achilles tendon in the plain radiograph was investigated in 92 patients with Werner syndrome provided from the nationwide secondary survey in 2010. And the same investigation was performed for 2151 feet in 1853 patients without Werner syndrome, who underwent foot and ankle surgeries at the department of orthopaedic surgery in Nara Medical University from 2004 to 2015.

Result and Conclusion: Achilles tendon calcification was observed in 70 (76.1%) out of 92 patients with Werner syndrome, whereas that was observed only in 19 feet (0.88%) without Werner syndrome, accompanied by 1 to 4 calcified masses with a maximum diameter ranging from 9.7mm to 63.2mm. The frequency of Achilles tendon calcification in patients with Werner syndrome is far higher than that of patients without Werner syndrome. Achilles tendon calcification could be included in the diagnostic criteria for Werner syndrome. **Geriatr Gerontol Int 2020; ••: ••–••.**

Keywords: Achilles tendon, calcification, flame-like.

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Calcification in tendons is observed in patients with Werner syndrome

Asymmetrical calcification in ligaments and tendons has been reported in patients with Werner syndrome, the mechanism of which remains unclear.[1] Multiple calcifications of articular capsules and tendinous insertions might be observed in the hand, wrist, foot, knee and elbow.[2] The Achilles tendon might also be calcified,[3] and characteristically shaped calcified substances might be widely observed in some cases.[4] Ectopic calcification has also been previously reported in one-third of Werner syndrome patients,[5] and it has recently been reported in 85.3% of patients.[6] The Na-Pi cotransporter (Pit-1), which plays a vital role in phosphoric acid uptake, has been observed to increase in the fibroblast cells of the skin tissue in patients with Werner syndrome.[6]

Achilles tendon calcification in patients with Werner syndrome differs from that in patients without Werner syndrome

The results of a recent investigation showed that a bone spur on the calcaneus at the insertion of the Achilles tendon, which might be confused with calcified Achilles tendon, is caused by the apoptosis of fibrocartilaginous components on the surface of the Achilles tendon insertion, and subsequent enchondral ossification. This mechanism proves that bony spurs differ from calcified Achilles tendons.[7]

Some studies reported calcification in the Achilles tendon to be found in patients with Achilles tendinitis and Achilles enthesitis,[8,9] whereas another study reported it to be observed after the operative treatment of Achilles tendon rupture.[10] Patients with Werner syndrome develop multiple blocky calcifications in a wide area of the Achilles tendon with a flame-shaped calcification pattern, which clearly differs from Achilles tendon calcification in patients without Werner syndrome.

Calcification of the Achilles tendon found in a plain radiograph is useful for the diagnosis of Werner syndrome

There are clear differences between Achilles tendon calcification in patients with Werner syndrome and those without Werner syndrome in terms of frequency, area and pattern of occurrence. In 2010, a nationwide secondary survey was carried out as part of the Nationwide Study for the Understanding of the Clinical Conditions, Creation of Practice Guidelines and Development of a New Treatment for Werner Syndrome. This survey showed that Achilles tendon calcification was observed in 70 (76.1%) out of 92 patients with Werner syndrome who participated in the survey and submitted their responses regarding calcification of the Achilles tendon. Plain radiographs of 2151 feet belonging to 1853 patients without Werner syndrome, who underwent foot and ankle surgeries at the Department of Orthopedic Surgery in Nara Medical University between 2004 and 2015, showed that Achilles tendon calcification was observed in just 19 feet (0.88%). The finding of calcification in the Achilles tendon was also accompanied by one to four calcified masses with a maximum diameter ranging from 9.7 to 63.2 mm.

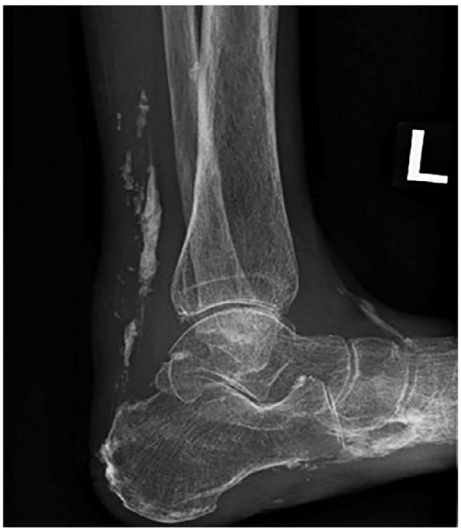

Figure 1 Calcification exceeding 2 cm is observed in the Achilles tendon (a single large segmental calcification).

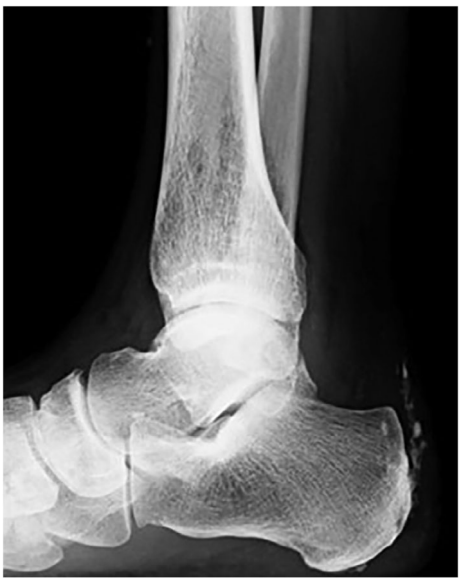

Figure 2 Several calcifications not exceeding 2 cm in length are observed (several small segmental calcifications).

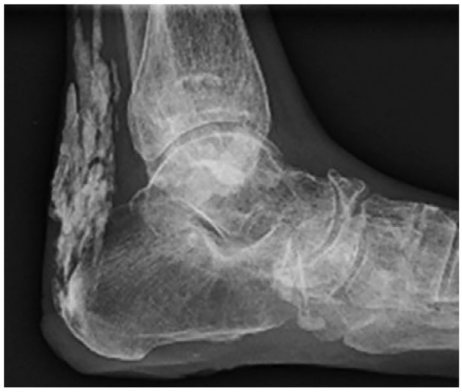

Figure 3 Flame-like calcifications are observed widely in Achilles tendon insertion (flame-like calcifications).

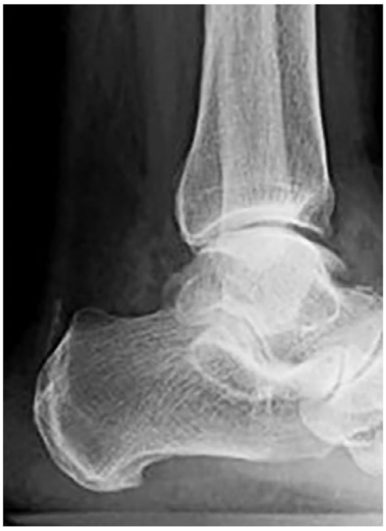

Figure 4 Isolated lesion with 14-mm length in a patient without Werner.

The frequency of Achilles tendon calcification in patients with Werner syndrome is far higher than that in patients without Werner syndrome; thus, it is beneficial to incorporate Achilles tendon calcification into the diagnostic criteria for Werner syndrome.

Achilles tendon calcification includes

1. A calcification seen on a plain radiograph with a length of at least 2 cm that is not contiguous with the calcaneus (a single large segmental calcification; Fig. 1).
2. At least two calcific masses with a length not exceeding 2 cm and not contiguous with the calcaneus (several small segmental calcific masses; Fig. 2).
3. Clearly abnormal flame-like calcification in a large area of the Achilles tendon (Fig. 3).
4. A typical pattern of Achilles tendon calcification in patients without Werner is shown in Figure 4.

In cases where any one of the above items applies, a diagnosis should be made, keeping in mind that a patient might develop Werner syndrome-specific Achilles tendon calcification.

Disclosure statement

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Research Paper

Fibroblasts from different body parts exhibit distinct phenotypes in adult progeria Werner syndrome

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ABSTRACT

Werner syndrome (WS), also known as adult progeria, is characterized by accelerated aging symptoms from a young age. Patients with WS experience painful intractable skin ulcers with calcifications in their extremities, subcutaneous lipoatrophy, and sarcopenia. However, there is no significant abnormality in the trunk skin, where the subcutaneous fat relatively accumulates. The cause of such differences between the limbs and trunk is unknown. To investigate the underlying mechanism behind these phenomena, we established and analyzed dermal fibroblasts from the foot and trunk of two WS patients. As a result, WS foot-derived fibroblasts showed decreased proliferative potential compared to that from the trunk, which correlated with the telomere shortening. Transcriptome analysis showed increased expression of genes involved in osteogenesis in the foot fibroblasts, while adipogenic and chondrogenic genes were downregulated in comparison with the trunk. Consistent with these findings, the adipogenic and chondrogenic differentiation capacity was significantly decreased in the foot fibroblasts *in vitro*. On the other hand, the osteogenic potential was mutually maintained and comparable in the foot and trunk fibroblasts. These distinct phenotypes in the foot and trunk fibroblasts are consistent with the clinical symptoms of WS and may partially explain the underlying mechanism of this disease phenotype.

INTRODUCTION

Werner syndrome (WS) is a rare autosomal recessive premature aging disorder that begins at a young age with graying and loss of hair and cataracts, followed by accelerated aging symptoms such as diabetes, atherosclerosis, and cancer [1–4]. The median life expectancy is in the mid-50s, and most deaths are due to arteriosclerosis and malignancy [5]. Owing to the founder mutation, a high incidence of WS is observed in Japan [6, 7].

The causative gene is WRN, which is located on chromosome 8 and is involved in DNA replication, DNA repair, and telomere maintenance [8]. WS fibroblasts with deficient or dysfunctional WRN proteins show premature cellular senescence *in vitro* [9]. This phenotype is largely dependent on telomere shortening and can be overcome by telomerase overexpression [10, 11].

WS mimics various symptoms of general aging. However, there are also phenotypes specific to WS, such as refractory skin ulcers with severe pain in the extremities, which affect over 80% of patients and may even result in limb amputation [12]. Common sites for ulceration are the heels, soles, toes, Achilles tendons, and elbows. Painful subcutaneous calcification has been reported to precede skin ulcers [13]. The atrophy of subcutaneous fat and muscle when present in the extremities resembles branches of dried trees, which is diagnosed as sarcopenia [14]. In contrast, there is an accumulation of subcutaneous fat in the trunk [15, 16]. While the skin of the extremities, frequently accompanied by ulcers, is atrophic and tight, that of the trunk retains its elasticity and does not develop ulcers. The underlying mechanism behind these differences remains unknown.

To clarify the relationship between the skin properties and the high prevalence of skin ulcers in the extremities, we established fibroblasts from the skin of the trunk and that of the foot from the vicinity of ulceration in two WS patients.

RESULTS

Foot fibroblasts exhibited reduced proliferation compared to the trunk fibroblasts in a telomere-dependent manner

In WS, the skin in the extremities atrophies and hardens, and a skin ulcer develops, while there is no obvious abnormality in the trunk skin. Therefore, plastic surgery is often performed to graft skin from the trunk to the ulcer site in order to treat the skin ulcers. In this study, we established fibroblasts from the foot skin (normal skin adjacent to the ulcer) and trunk skin (graft) of two WS patients (WS1 and WS2) who were admitted to our hospital for plastic surgery. We hypothesized that the difference in skin symptoms between the limb and trunk was related to a reduced proliferative capacity of the limb fibroblasts compared to that of the trunk. As expected, the proliferation rate of foot skin-derived fibroblasts was lower than that of the trunk (Figure 1A). In previous reports, the cause of the reduced proliferative potential of WS fibroblasts was explained by shortened telomere length [10, 11]. Consistent with these reports, there was a significant difference in the telomere lengths between the foot and trunk fibroblasts (Figure 1B, 1C and Supplementary Figure 1). These results suggest that the difference in proliferation ability between skin fibroblasts of the foot and trunk is dependent on the telomere length.

Foot and trunk fibroblasts in WS showed differential expression of genes, especially those involved in embryogenesis and differentiation

Next, transcriptome analysis was performed using RNA sequences to characterize the gene expression profiles of the foot and trunk fibroblasts. In the hierarchical clustering analysis, the WS foot and trunk fibroblasts were classified into different clusters beyond individual differences (Supplementary Figure 2A and Supplementary Table 1). The analysis of differentially expressed genes (DEGs) was performed to identify genes with more than 2-fold differences in expression, and a total of 140 up-regulated and 119 down-regulated genes were identified in the foot (Figure 2A and Supplementary Tables 2, 3). Enrichment analysis of DEGs revealed that their pathways are mainly involved in differentiation and embryogenesis (Figure 2B). Among them, Homeobox A13 (HOXA13) was explicitly expressed in the foot, while Homeobox B5 (HOXB5), Homeobox B6 (HOXB6), Homeobox B7 (HOXB7), and Homeobox D4 (HOXD4) expression were specific to the trunk (Figure 2C), which is consistent with the site-specific gene expression of fibroblasts from normal individuals in previous reports [17, 18]. Intriguingly, the foot fibroblasts showed an elevated expression of genes that relate to the promotion of osteogenesis and suppression of adipogenesis and chondrogenesis, including Stathmin 2 (STMN2), Copine 7 (CPNE7), Protein Tyrosine Phosphatase Receptor Type B (PTPRB), Solute Carrier Family 2 Member 5 (SLC2A5), and HOXA Distal Transcript Antisense RNA (HOTTIP) (Figure 2C) [19–23]. In contrast, in the fibroblasts of the trunk, the expression of the following genes were increased; Clusterin (CLU), Peroxisome Proliferator-Activated Receptor Gamma (PPARG), Insulin-Like Growth Factor 2 MRNA

Binding Protein 3 (IGF2BP3), Cysteine Dioxygenase Type 1 (CDO1), and Zinc Finger Protein, FOG Family Member 2 (ZFPM2) (Figure 2C), which are associated with the promotion of adipogenesis or chondrogenesis and suppression of osteogenesis [24–29]. However, regarding senescence-associated genes, no significant differences were observed in the expression of Cyclin-Dependent Kinase Inhibitor 1A (CDKN1A, p21) and Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A, p16) (Supplementary Figure 2B) [30, 31]. These results suggest that the foot and trunk fibroblasts in WS have distinct gene expressions that regulate mesenchymal-lineage differentiation, but these differences are independent of cellular senescence.

Foot fibroblasts in WS were less capable of adipogenesis compared with the trunk

WS patients present with subcutaneous lipoatrophy in the extremities, while subcutaneous fat tends to accumulate in the trunk. Several reports have previously shown that human dermal fibroblasts can differentiate into mesodermal lineages *in vitro*, including adipocytes [32–34]. Taken together with the above results, we hypothesized that the adipogenesis potential is lower in foot fibroblasts than in the trunk. Thus, we investigated the adipogenic capacity of WS fibroblasts by culturing them in the adipogenic differentiation medium. After induction of adipogenesis, Oil red O staining results

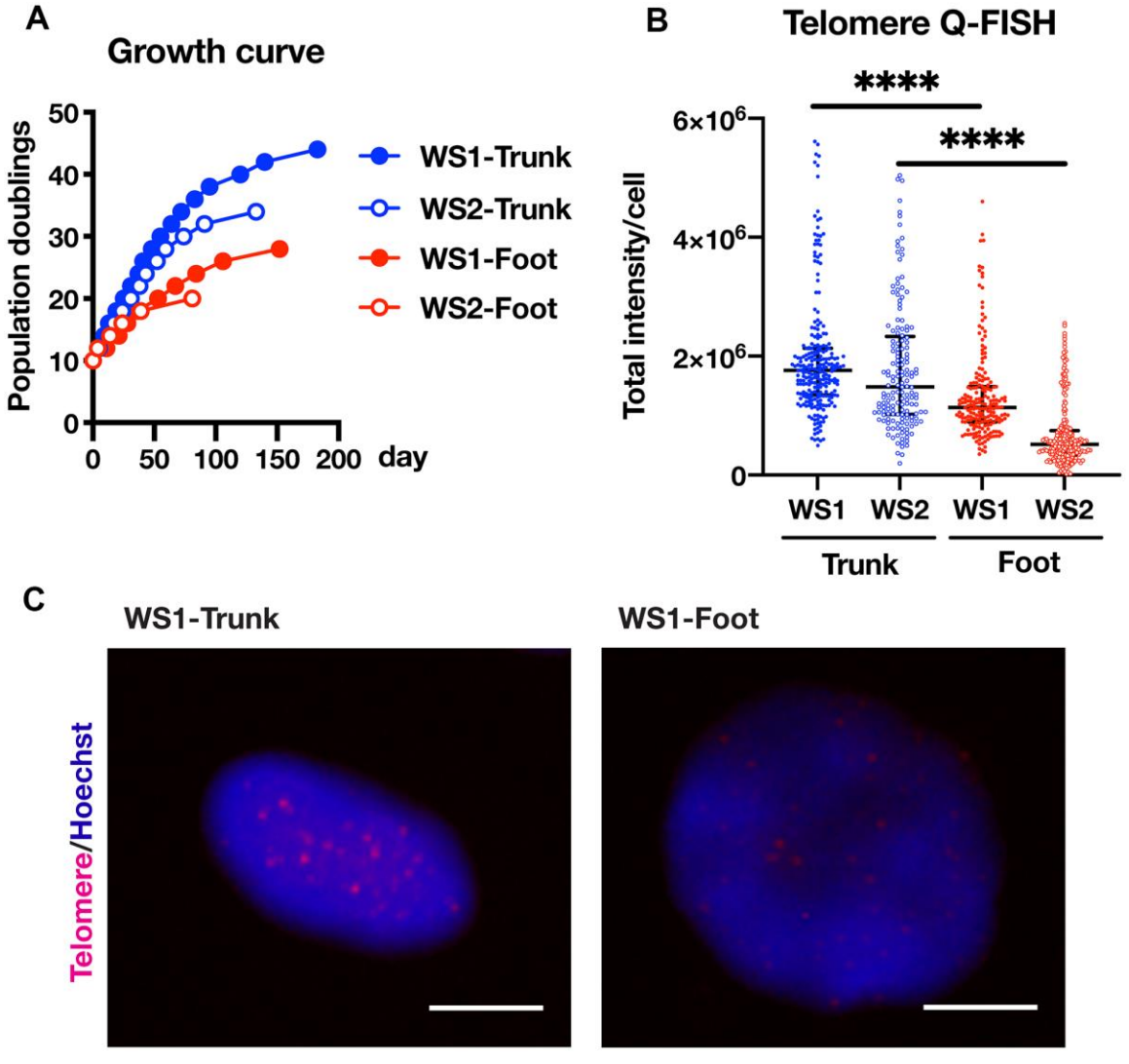

Figure 1. Foot fibroblasts exhibited reduced proliferative capacity compared to that from the trunk in a telomere length-dependent manner. (**A**) Growth curves of the fibroblasts from the trunk and foot in two WS patients. (**B**) Telomere length quantification through Q-FISH. Data are median values ± interquartile range of each cell line. More than 150 cells for each cell line were analyzed. For statistical analysis, Mann Whitney test was performed (****p<0.0001). (**C**) Representative image of telomere Q-FISH of WS1. Bar = 10 μm.

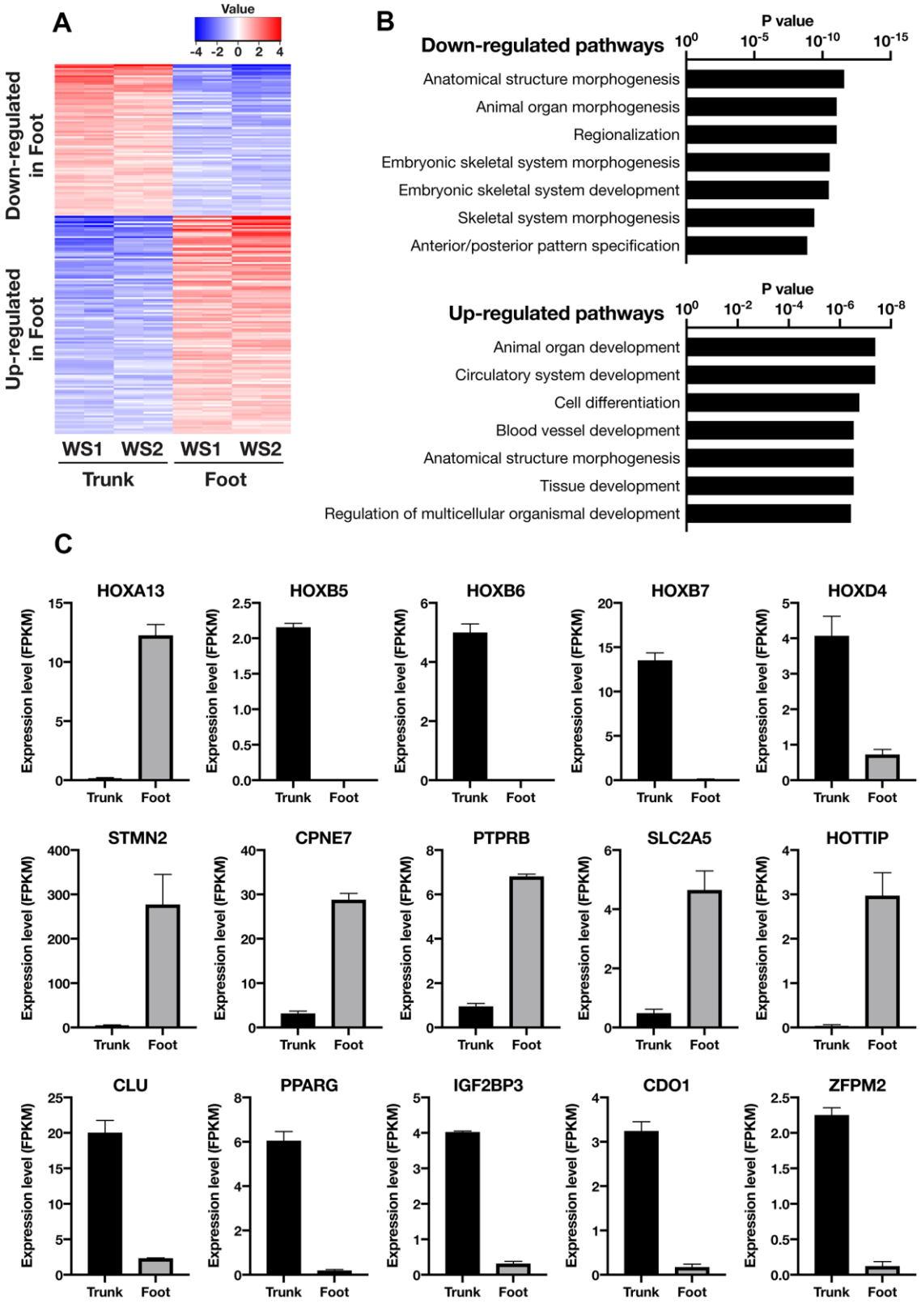

Figure 2. Transcriptome analysis showed distinct gene expression profiles between the trunk and foot fibroblasts. (**A**) Heatmap of differentially expressed genes between the trunk and foot. Cutoff: |log2(Foot/Trunk)| > 1 and FDR < 0.05. (**B**) List of the top seven Gene Ontology (GO: biological process) terms and corresponding p values related to Figure 2A. (**C**) Differentially expressed genes specifically involved in embryonic development and mesenchymal cell differentiation. Data are means ± SEM of two patients (technically n=2 in each sample).

showed foot fibroblasts with significantly fewer oil droplets than the trunk (Figure 3A, 3B and Supplementary Figure 3). In gene expression analysis by qRT-PCR, adipocyte marker genes, PPARG, Fatty Acid Binding Protein 4 (FABP4), CCAAT Enhancer Binding Protein Alpha (CEBPA), and Leptin (LEP) were significantly decreased in the foot group compared with the trunk (Figure 3C) [35]. These results indicate that the trunk fibroblasts of WS maintain adipogenic capacity but the foot fibroblasts do not.

Foot fibroblasts in WS exhibited an attenuated capacity for chondrogenesis

Next, we performed chondrogenic differentiation to confirm a disparity in chondrogenesis between the trunk and foot fibroblasts. After the induction of chondrogenesis using the pellet method, the spheroid diameter was significantly smaller in the foot fibroblasts from WS1 than in the trunk group (Figure 4A, 4B). On the other hand, WS2 foot fibroblasts failed to maintain spheroid morphology (Supplementary Figure 4). The chondrogenesis differentiation marker, SRY-Box Transcription Factor 9 (SOX9), was significantly decreased in the foot group, and this tendency was also observed for Aggrecan (ACAN) (Figure 4C) [36]. These results suggest that WS foot fibroblasts tend to have a reduced capacity for chondrogenic differentiation compared with the trunk.

Foot and trunk fibroblasts in WS were equally capable of osteogenesis

Next, the osteogenic differentiation ability was compared. After culturing in the osteogenesis medium, no clear difference was observed in the Alizarin red-

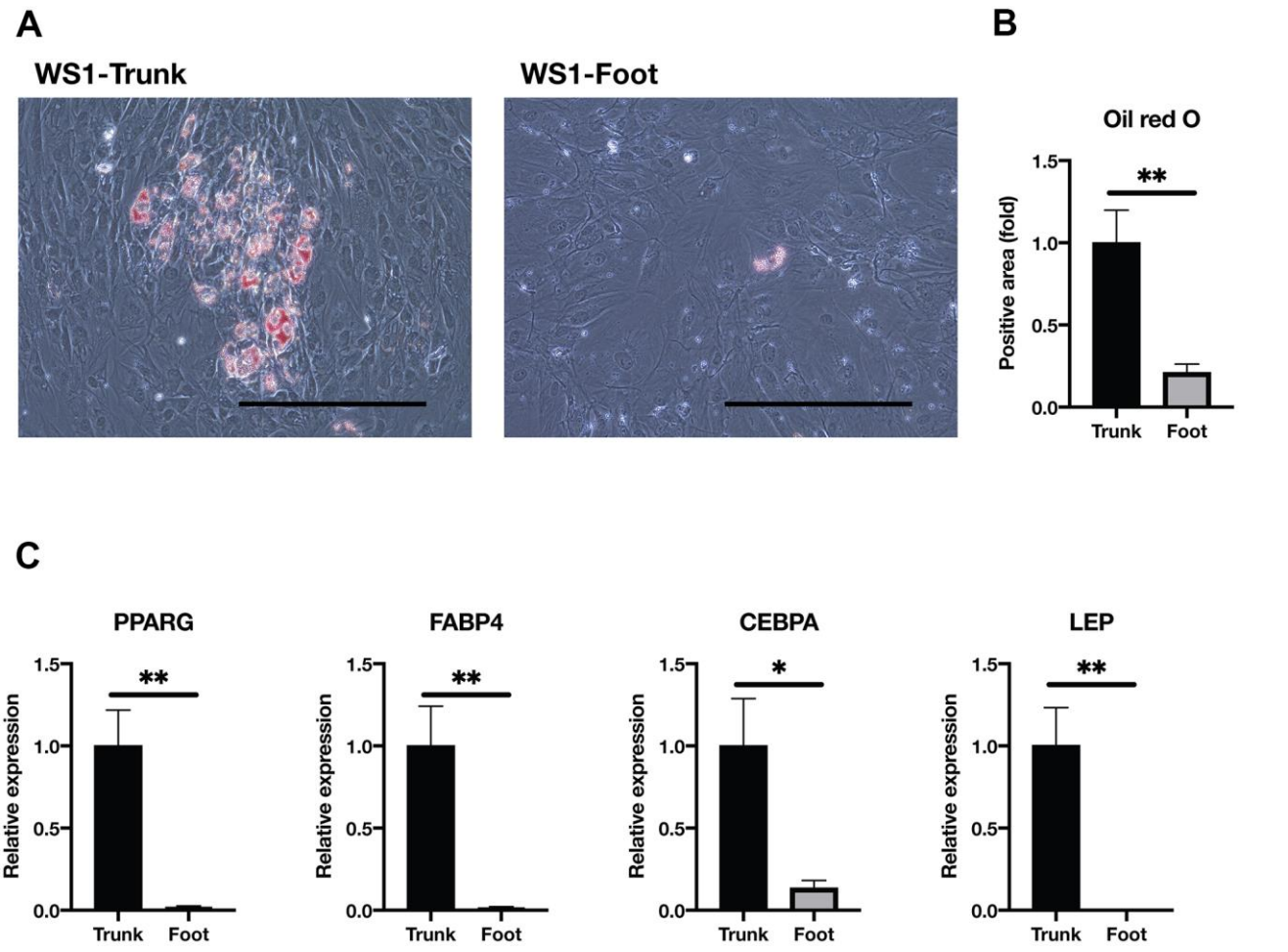

Figure 3. Adipogenesis was impaired in the foot fibroblasts. (**A**) Representative images of Oil red O staining after two weeks induction of adipogenesis in the trunk and foot fibroblasts of WS1. Bar = 300 μm. (**B**) Quantification of relative Oil red O staining area. Data are means ± SEM of two patients from four microscopic views. For statistical analysis, student t-test was performed (**p<0.01). (**C**) Relative gene expression analyzed by qRT-PCR. Data are means ± SEM of two patients with three technical replicates. For statistical analysis, student t-test was performed (*p<0.05; **p<0.01).

stained area between the trunk and foot groups (Figure 5A, 5B and Supplementary Figure 5). The expression of Alkaline Phosphatase, Biomineralization Associated (ALPL), a marker of osteogenesis, was significantly elevated in the foot group (Figure 5C). On the other hand, RUNX Family Transcription Factor 2 (RUNX2) expression was significantly elevated in the trunk group, and there were no significant differences in other differentiation markers (Secreted Phosphoprotein 1, SPP1; Collagen Type I Alpha 1 Chain, COL1A1) (Figure 5C) [37]. These results suggest that foot fibroblasts in WS maintain the equivalent level of osteogenic differentiation capacity to the trunk.

DISCUSSION

This is the first report comparing the phenotypes of dermal fibroblasts taken from different parts of the body of the same WS patient. The WS foot fibroblasts showed a reduced proliferative capacity with shorter telomeres, in comparison to the trunk fibroblasts. Transcriptome analysis showed increased gene

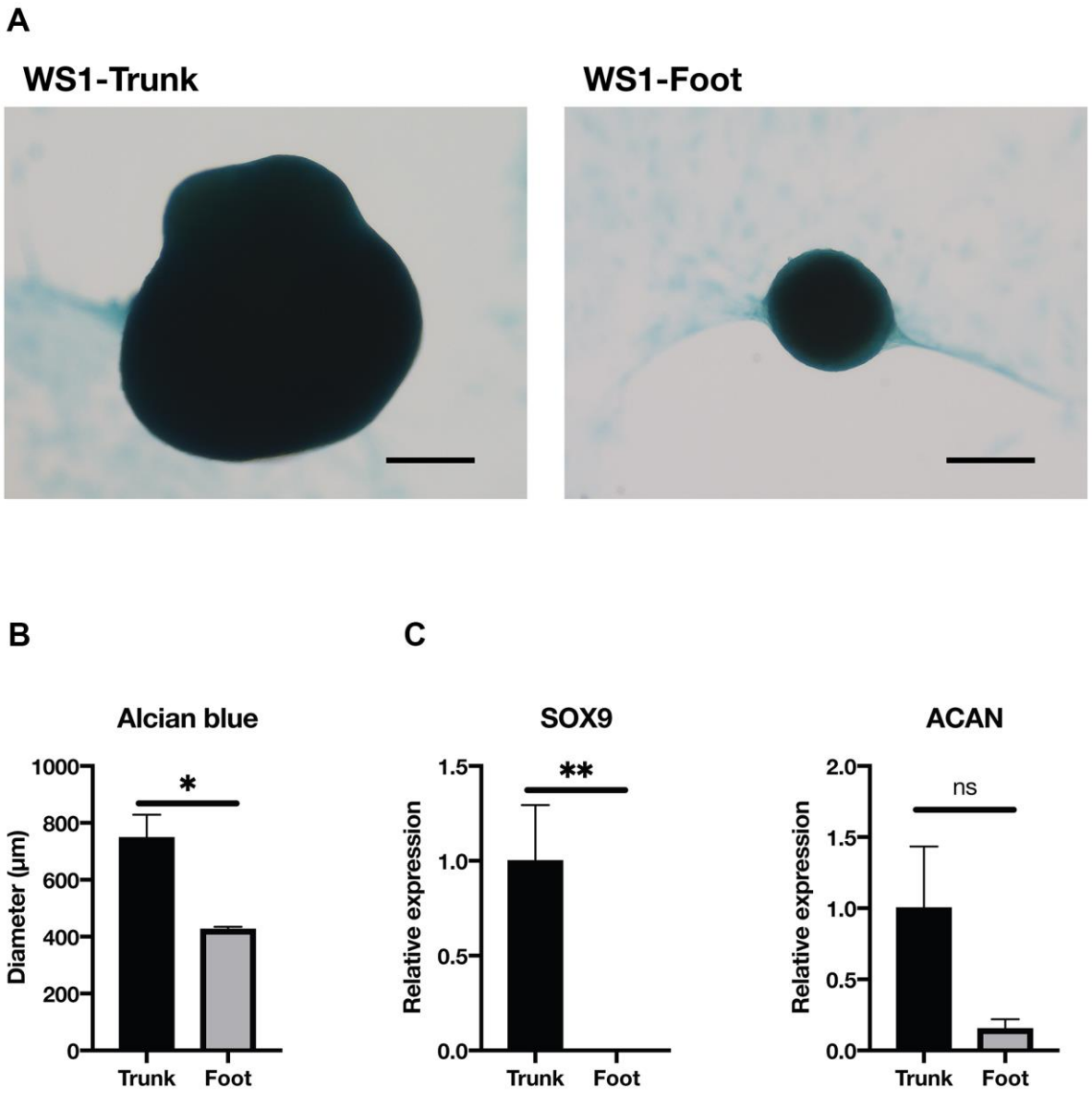

Figure 4. Chondrogenesis tended to be reduced in the foot fibroblasts. (**A**) Representative images of Alcian blue staining after two weeks induction of chondrogenesis in the trunk and foot fibroblasts of WS1. Bar = 300 μm. (**B**) Quantification of the diameter of chondrogenic spheroids. WS1-trunk, WS2-trunk, and WS1-foot were included. Data are means ± SEM. For statistical analysis, student t-test was performed (*p<0.05). (**C**) Relative gene expression analyzed by qRT-PCR. Data are means ± SEM of two patients with three technical replicates. For statistical analysis, student t-test was performed (ns, not significant; *p<0.05; **p<0.01).

expression related to osteogenic differentiation in the foot group and that of adipogenic and chondrogenic differentiation in the trunk group. Indeed, *in vitro* induction of adipogenesis and chondrogenesis of the foot fibroblasts showed significantly reduced differentiation capacity compared with the trunk. However, there was no difference in osteogenic capacity between the trunk and foot fibroblasts.

Previously, Rinn et al. conducted transcriptome analyses among normal human fibroblasts taken from different sites in the body [17, 18]. Among the DEGs between the extremities and trunk, the expression distribution of HOX genes is consistent with cell migration during human development [38]. Rinn et al. identified that HOXA13 was explicitly up-regulated in foot-derived fibroblasts, while the HOXB gene cluster was trunk-specific [17, 18]; these data are consistent with our results.

However, most of the genes we extracted through the DEG analysis in this study did not show site-specific changes in the previous reports [17, 18]. PPARG, which we found to be up-regulated in the trunk fibroblasts of the WS patients, is a master regulator of adipogenesis, and its overexpression promotes adipose differentiation [39]. In this study, the WS trunk-derived fibroblasts showed higher PPARG expression than the foot-derived ones, and there was a clear difference in the *in vitro* adipose differentiation ability. These apparent

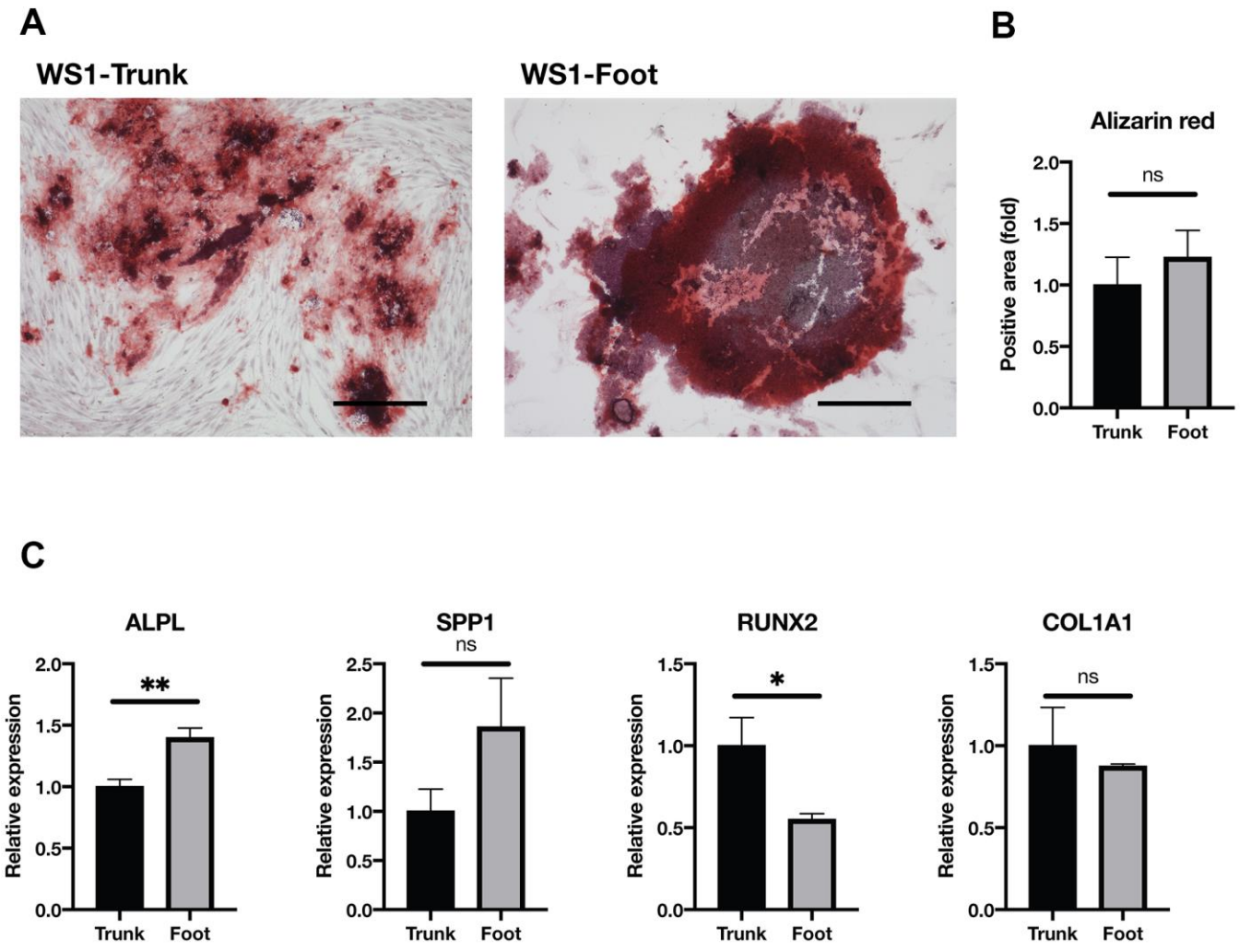

Figure 5. Osteogenesis was maintained in both groups. (**A**) Representative images of Alizarin red staining two weeks after induction of osteogenesis in the trunk and foot fibroblasts of WS1. Bar = 300 μm. (**B**) Quantification of relative stained area with Alizarin red. Data are means ± SEM of two patients with four microscopic views. For statistical analysis, student t-test was performed (ns, not significant). (**C**) Relative gene expression analyzed by qRT-PCR. Data are means ± SEM of two patients with three technical replicates. For statistical analysis, student t-test was performed (ns, not significant; *p<0.05; **p<0.01).

discrepancies are reminiscent of WS phenotypes, namely the trunk with relatively abundant subcutaneous fat and the extremities with lipoatrophy [15, 16]. In addition, although the anatomic origin of the fibroblast is unclear, WRN-depleted fibroblasts exhibit upregulation of PPARG [40]. Taken together with our findings, these results suggest that the regulation of PPARG gene expression in WRN-depleted cells might be context-dependent and that they can be down-regulated in the fibroblasts in the disease site. Further research is needed to understand the mechanism of downregulation of PPARG in WS foot fibroblasts compared to the WS trunk-derived fibroblasts. In addition, STMN2, a marker of osteogenesis, which is up-regulated during the osteogenic induction of mesenchymal stem cells [19], is the gene with the most distinct regulation in this study: the expression was overwhelmingly increased in the foot fibroblasts compared with the trunk.

Honjo et al. reported that painful subcutaneous calcification precedes skin ulcers in WS patients [13]. Patients with WS frequently suffer painful clavus and callus on the feet, which leads to the development of intractable skin ulcers [1, 12]. Ectopic soft tissue calcification also occurs in the limbs of WS patients [41]. Considering our findings that WS foot fibroblasts have a diminished ability to differentiate into adipocytes and chondrocytes while their osteogenic differentiation capacity remains fully preserved, the ossification of fibroblasts in the dermal and subcutaneous layers of the skin may result in these symptoms. In addition, reversible direct conversion of subcutaneous adipocytes into fibroblasts, *in vivo*, has been reported [42–44]. Therefore, our results suggest the possibility that subcutaneous lipoatrophy in WS extremities might attribute to the inability of adipogenic differentiation in fibroblasts in the disease site.

In this study, we revealed the distinct gene expression profiles and phenotypes in WS dermal fibroblasts derived from the foot and trunk. This study highlights the relationship between fibroblast phenotypes and WS-specific symptoms, refractory skin ulcers and subcutaneous lipoatrophy in extremities. These results could lead to a further understanding of the disease's mechanism and development of a new therapeutic strategy in the future.

MATERIALS AND METHODS

Establishment of fibroblasts and cell culture

WS dermal fibroblasts were established from two WS patients (WS1 and WS2, Supplementary Table 4). Both were hospitalized for treatment of their foot skin ulcers, and the skin graft was taken from the trunk (groin). The healthy skin neighboring the ulcer and the skin partly taken from the graft were explanted into a dish as previously described [45]. Cell culture was performed with DMEM (043-30085, Wako, Osaka, Japan), supplemented with 10% FBS (10270106, Gibco, Waltham, MA, U.S.A), and antibiotic-antimycotic (15240062, Gibco) in humidified 5% CO_2 air. The medium was changed every two days. When reaching sub-confluency, cells were passaged at a 1:4 split ratio until growth arrest and population doublings were calculated.

Telomere quantitative fluorescence *in situ* hybridization (Q-FISH)

Fibroblasts at PD10 were treated with the colcemid kit (Chromocenter, Tottori, Japan) and fixed in Carnoy's solution following the manufacturer's protocol. The fixed cells on coverslips were treated with ribonuclease (312-01931, Nippon Gene, Tokyo, Japan) and 0.005 % pepsin (V1959, Promega, WI, U.S.), hybridized with peptide nucleic acid oligonucleotide probes (F1002, Panagene, Daejeon, South Korea), and immuno-stained with Hoechst 33342 (H342, Dojindo, Kumamoto, Japan), according to the manufacturer's protocols. Images were recorded using a BZ-X700 microscope (Keyence, Osaka, Japan). Quantification was performed using the Telometer (https://demarzolab.pathology.jhmi.edu/telometer/), as previously described [46, 47].

Quantitative polymerase chain reaction (qPCR)

RNA was extracted and reverse-transcribed, as previously described [48]. TaqMan Gene Expression Assays for PPARG (Hs01115513_m1), FABP4 (Hs01086177_m1), CEBPA (Hs00269972_s1), LEP (Hs00174877_m1), SOX9 (Hs00165814_m1), ACAN (Hs00153936_m1), ALPL (Hs01029144_m1), SPP1 (Hs00959010_m1), RUNX2 (Hs01047973_m1), COL1A1 (Hs00164004_m1), and B2M (Hs00187842_m1) were purchased from Applied Biosystems (Waltham, MA, U.S.). Quantification was performed with the ⊿⊿Ct method using B2M as an internal control.

Tri-lineage differentiation

In vitro differentiation potentials of the fibroblasts into three mesenchymal lineages were evaluated by using adipogenesis, chondrogenesis, and osteogenesis differentiation kits (A1007001, A1007101, and A1007201, respectively; Gibco) according to manufacturer's protocols. Cells at PD 9 to 10 were used. After two weeks of differentiation, cells were sampled and stained. For each staining assay, Oil red O, Alcian

blue, and Alizarin red staining (Sigma-Aldrich, St. Louis, MO, U.S.A) were used, respectively. Quantification of the stains was performed using a BZ-X700 microscope (Keyence, Osaka, Japan).

Transcriptome analysis

mRNA was extracted from fibroblasts at PD 10 and the cDNA library was synthesized using the NEBNext Ultra RNA Library Prep Kit (E7370S, New England BioLabs, Beverly, MA, U.S.A). Sequencing was carried out (technically n=2 in each sample) by HiSeq1500 (Illumina, San Diego, CA, U.S.A) with 60bp single-reads. The reference genome mapping (UCSC/hg19) was performed using TopHat (version 2.0.13; with default parameters) with annotation data from iGenomes (Illumina). Cuffdiff (Cufflinks version 2.2.1; with default parameters) was used to quantify the gene expression levels. FPKM data were analyzed by iDEP (http://bioinformatics.sdstate.edu/idep/) as described by the authors [49].

Study approval

All experiments were approved by the institutional review boards at the Chiba University Graduate School of Medicine (Chiba, Japan). Written informed consent was obtained from study participants before the commencement of this research.

Abbreviations

DEG: differentially expressed gene; FDR: false discovery rate; FPKM: fragments per kilobase million; PD: population doublings; Q-FISH: quantitative fluorescence *in situ* hybridization; qRT-PCR: quantitative reverse transcription polymerase chain reaction; SEM: standard error of the mean; WS: Werner syndrome.

AUTHOR CONTRIBUTIONS

H.Kato, Y.M., and K.Y. designed the study, analyzed the data, and wrote the manuscript; H.Kato carried out the experiments and made the figures; N.T., M.O., and A.I. conducted transcriptome analysis; Y.O., M.K., and K.E. discussed the data; H.Kaneko, D.K., and A.T.W. carried out the experiments; H.O., Y.K., and N.M. conducted sampling from patients; all authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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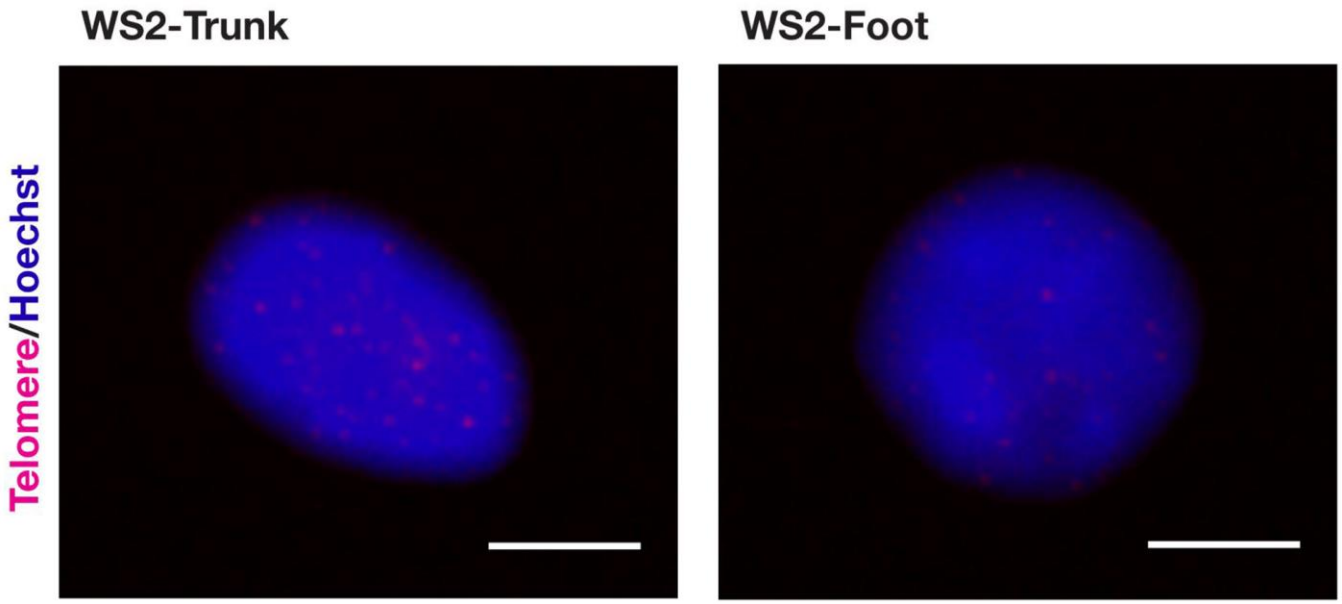
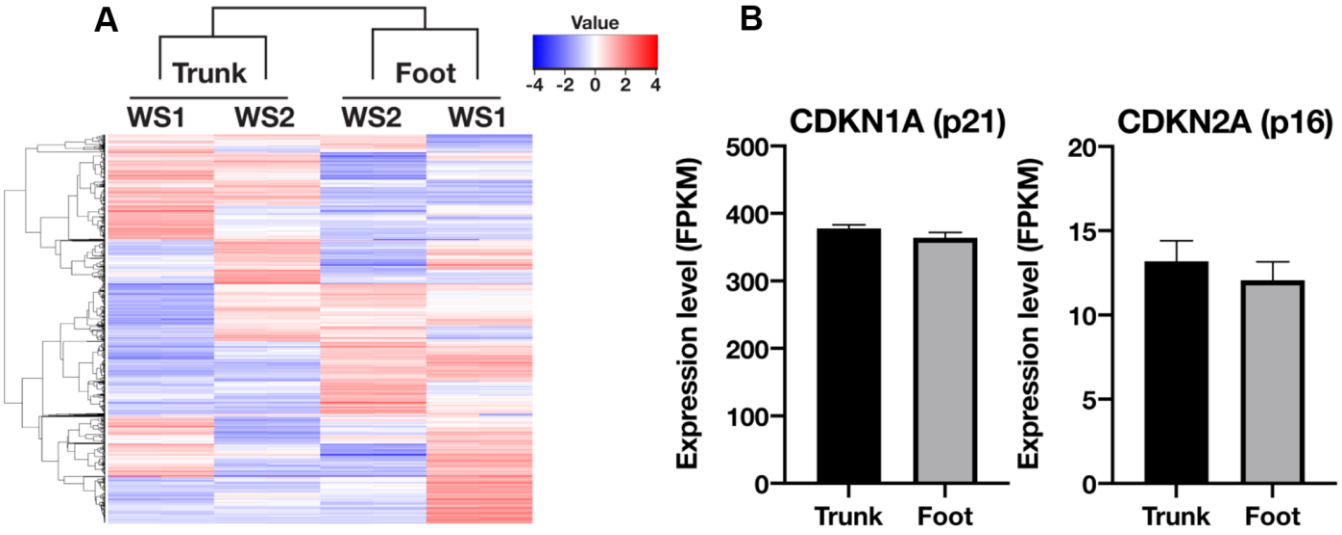
SUPPLEMENTARY MATERIALS

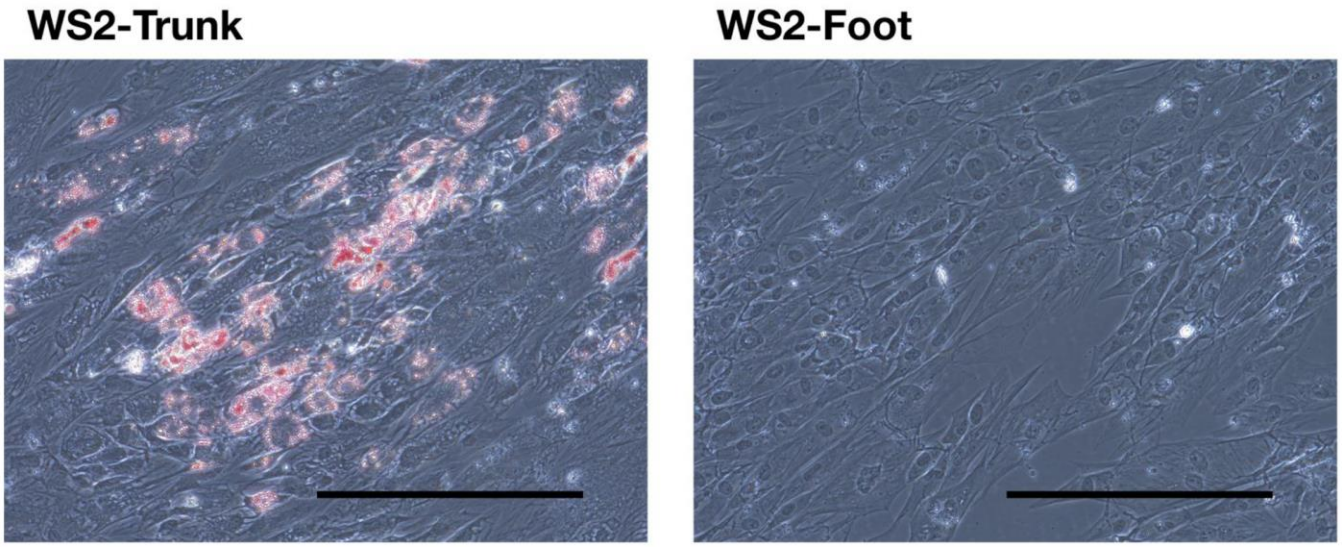
Supplementary Figures



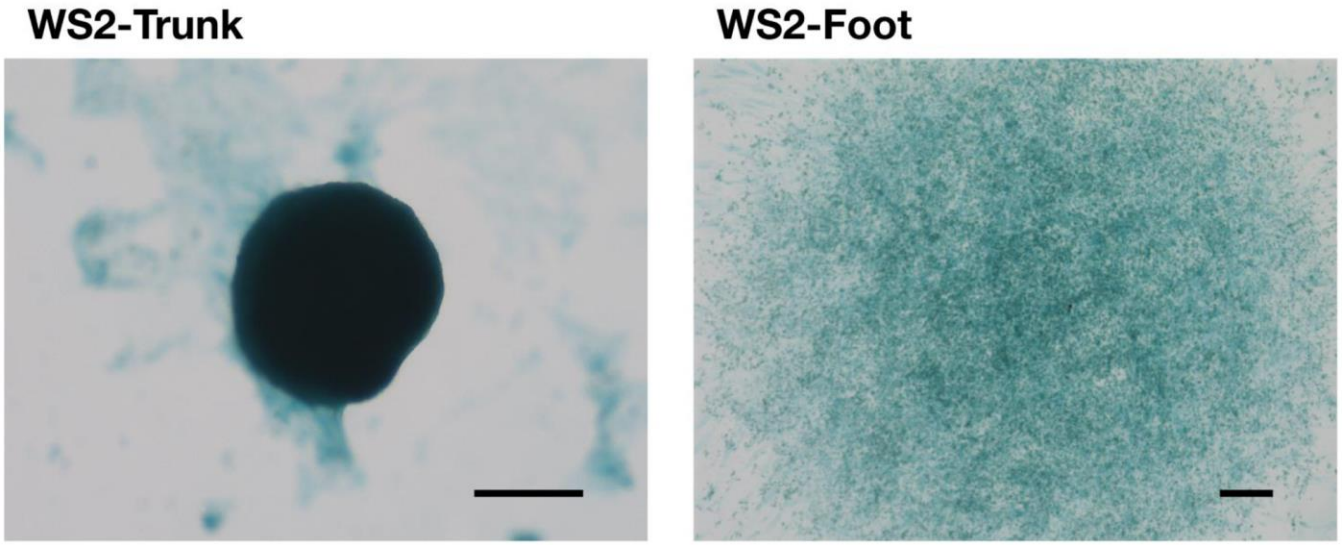
Supplementary Figure 1. Representative image of telomere Q-FISH of WS2. Bar = 10 μm.



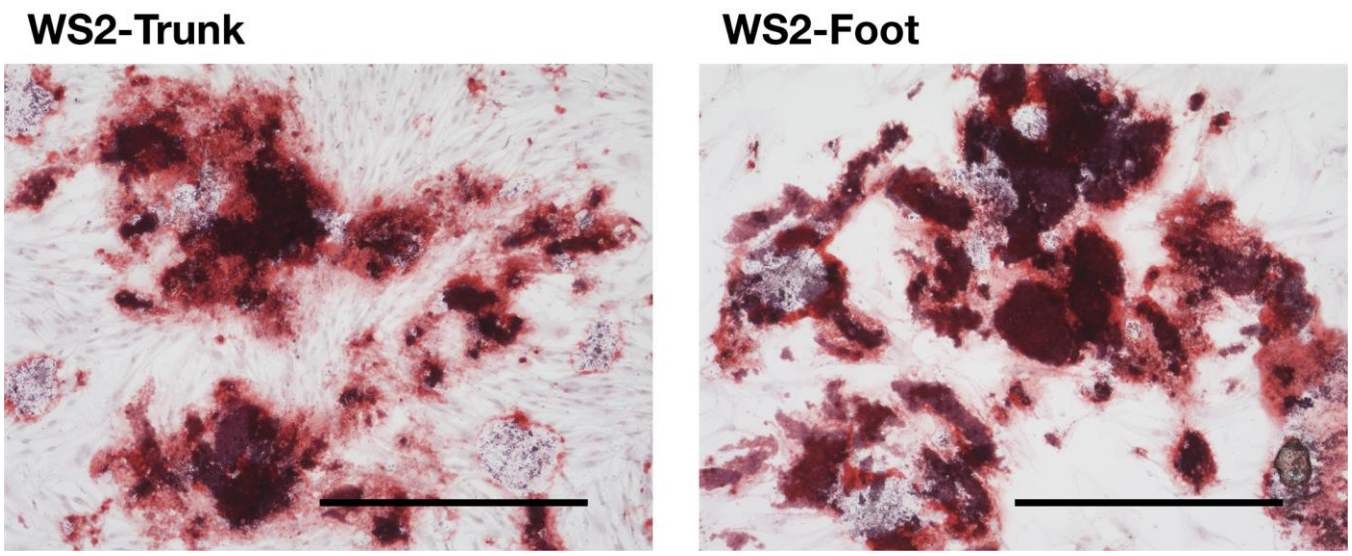
Supplementary Figure 2. Results of transcriptome analysis of the trunk and foot fibroblasts. (**A**) Heatmap of the hierarchical clustering analysis. (**B**) FPKM results of CDKN1A (p21) and CDKN2A (p16). Data are means ± SEM of two patients (technically n=2 in each sample).



Supplementary Figure 3. Representative images of Oil red O staining two weeks after induction of adipogenesis in the trunk and foot fibroblasts of WS2. Bar = 300 μm.



Supplementary Figure 4. Representative images of Alcian blue staining two weeks after induction of chondrogenesis in the trunk and foot fibroblasts of WS2. Bar = 300 μm.



Supplementary Figure 5. Representative images of Alizarin red staining two weeks after induction of osteogenesis in the trunk and foot fibroblasts of WS2. Bar = 300 μm.

Supplementary Tables

Please browse Full Text version to see the data of Supplementary Tables 1–4.

Supplementary Table 1. Raw data of hierarchical clustering analysis heatmap. Each value is represented as log2(FPKM+1).

Supplementary Table 2. Up-regulated genes in Foot fibroblasts. Each value is represented as log2(FPKM+1). Genes are listed in order from high to low of log2(Foot/Trunk). Cutoff: log2(Foot/Trunk) > 1 and FDR < 0.05.

Supplementary Table 3. Down-regulated genes in Foot fibroblasts. Each value is represented as log2(FPKM+1). Genes are listed in order from low to high of log2(Foot/Trunk). Cutoff: log2(Foot/Trunk) < -1 and FDR < 0.05.

Supplementary Table 4. Clinical characteristics of the patients.

Research Paper

Time gap between the onset and diagnosis in Werner syndrome: a nationwide survey and the 2020 registry in Japan

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ABSTRACT

Patients with Werner syndrome present with diverse signs of aging that begin in adolescence. A Japanese nationwide survey was conducted to establish a registry that could clarify the disease profile of patients with Werner syndrome. The questionnaires were sent to 7888 doctors. The survey identified 116 patients diagnosed with Werner syndrome based on the diagnosis criteria. Forty patients were enrolled in the registry. Data on clinical symptoms, treatment information, and laboratory examination from patients who provided informed consent were collected. The data at enrollment were analyzed. The patients' average age at enrollment was 50.1±7.5 years. The mean onset age was 26.1±9.5 years, but the mean age at diagnosis was 42.5±8.6 years. Average height and weight of the study patients were lower than those of Japanese individuals. Almost all patients experienced hair change and cataracts. More than 60% of patients presented with glycolipid abnormalities. Overall, 15% of patients had a history of foot amputation. Approximately 30% of the patients'

parents had a consanguineous marriage. The average grip strength, walking speed, and skeletal muscle mass index met the diagnostic criteria for sarcopenia. The registry revealed that there are opportunities for early diagnosis and intervention; therefore, sensitization about the disease is needed.

INTRODUCTION

Werner syndrome is a rare autosomal recessive, adult-onset progeroid syndromes resulting from genetic instability [1]. Although the exact number of patients diagnosed with Werner syndrome in Japan is unknown, it is estimated that there are approximately 2000 patients in Japan [2–5]. Patients with Werner syndrome display various signs of aging that appear from the second decade of life. Gray hair and hair loss appear around 20 years of age, bilateral cataracts and diabetes mellitus appear at 30 years of age, and myocardial infarctions and malignant tumors appear at 40 years. Patients with Werner syndrome die around the fifth decade of life [6]. A high percentage of patients also have intractable skin ulcers [7], which can lead to amputation of the lower limbs. Characteristics of patients with Werner syndrome include having a bird-like face and a high-pitched voice, which may offer difficulties with social integration. Sensitization of patients and medical practitioners on Werner syndrome is required to improve the quality of medical treatment, support the social reintegration, and improve the prognosis of patients with Werner syndrome.

Furthermore, manifestations of the disease can vary widely by individual with different grades of severity and age of onset. Coupled with an overall disease rarity, this heterogeneity makes diagnosis difficult and requires clearer guidelines.

Therefore, this study aimed to reveal the current disease profile of patients with Werner syndrome in Japan by conducting a nationwide survey and through the establishment of the Werner Syndrome Registry.

RESULTS

Werner syndrome nationwide survey in Japan

A nationwide survey of Werner syndrome was conducted with the goal of creating a Japanese Werner syndrome registry. In 2017, questionnaires were sent to 7888 doctors affiliated with hospitals that have more than 200 beds, and who work in divisions of internal medicine (endocrinology, collagen disease, and geriatrics), ophthalmology, dermatology, plastic surgery, or orthopedic specialties. Of the questionnaires sent out, 3154 (40%) responses were received. A total of 116 patients (57 men and 59 women) were being treated at the hospitals at the time of the survey (Supplementary Table 1). Fifty-one patients (29 men, 22 women) were suspected of having Werner syndrome. In addition, although they had not been attending the hospitals during the survey, there were 153 patients, including 80 men and 71 women (the sexes of two patients were unknown), who had visited the hospital in the past 10 years.

The breakdown based on the departments that responded to the survey is shown in Table 1. The percentage of reported patients per researched clinical departments is also presented. Ninety-seven patients were reported from the departments of internal medicine, which included metabolism and geriatric medicine. However, the departments of plastic surgery and dermatology reported the highest proportion of patients (7.7% and 7.9%). Patient overwraps could not be excluded completely. Two clinical departments answered in 32 facilities. Three clinical departments answered in 6 facilities.

The distribution of the patients is shown in Figure 1. Werner syndrome was distributed nationally (Figure 1A). A combination of diagnosed cases, suspected cases, and past confirmed cases was also evenly distributed throughout Japan (Figure 1B). Since there are differences in population in each region, the patient population per million people was calculated for diagnosed cases (Figure 1C), and for the combination of diagnosed cases, suspected cases, and past confirmed cases (Figure 1D). There were no statistically significant differences in the distributions of the patients with Werner syndrome (P=0.471). Details are shown in Supplementary Table 2 and Supplementary Figure 1.

Werner syndrome registry cross-sectional analysis

Thirty-two facilities participated in the registry. Of the 116 diagnosed patients in the nationwide survey, 40 (34.5%) were enrolled in the registry. Table 2 shows the major signs of Werner syndrome, which include graying hair, hair loss, cataracts, skin atrophic changes, and soft-tissue calcification. Almost all patients exhibited some of the major signs. Approximately 90% of patients had a characteristic bird-like face and high-pitched voice. Over half of the patients had diabetes, impaired glucose tolerance (67.5%), dyslipidemia (65.0%), and fatty liver (52.5%). A small percentage of patients had a history of atherosclerosis, such as cerebral infarction (0%), angina pectoris or myocardial infarction (2.5%), or arteriosclerosis obliterans (ASO) (15.0%) (Table 2).

Table 1. Number of patients with Werner syndrome by attendance to different clinical department.

	Reported patients (n)	Researched clinical departments (n)	Reported patients / researched clinical departments (%)
Internal medicine	97	2804	3.5
Dermatology	91	1147	7.9
Plastic surgery	57	744	7.7
Orthopedics	40	1319	3.0
Ophthalmology	28	1165	2.4
Cardiac surgery	7	713	1.0
Total	320	7892	4.1

Reported patients includes 116 diagnosed patients who were attending the hospital for treatment during the survey, 51 patients suspected of having Werner syndrome, and 153 patients visited the hospital in the past 10 years although not having attended the hospitals during the survey. The numerator is "reported patients" and the denominator is "researched clinical departments". Patient overwraps could not be excluded completely. Two clinical departments answered in 32 facilities. Three clinical departments answered in 6 facilities.

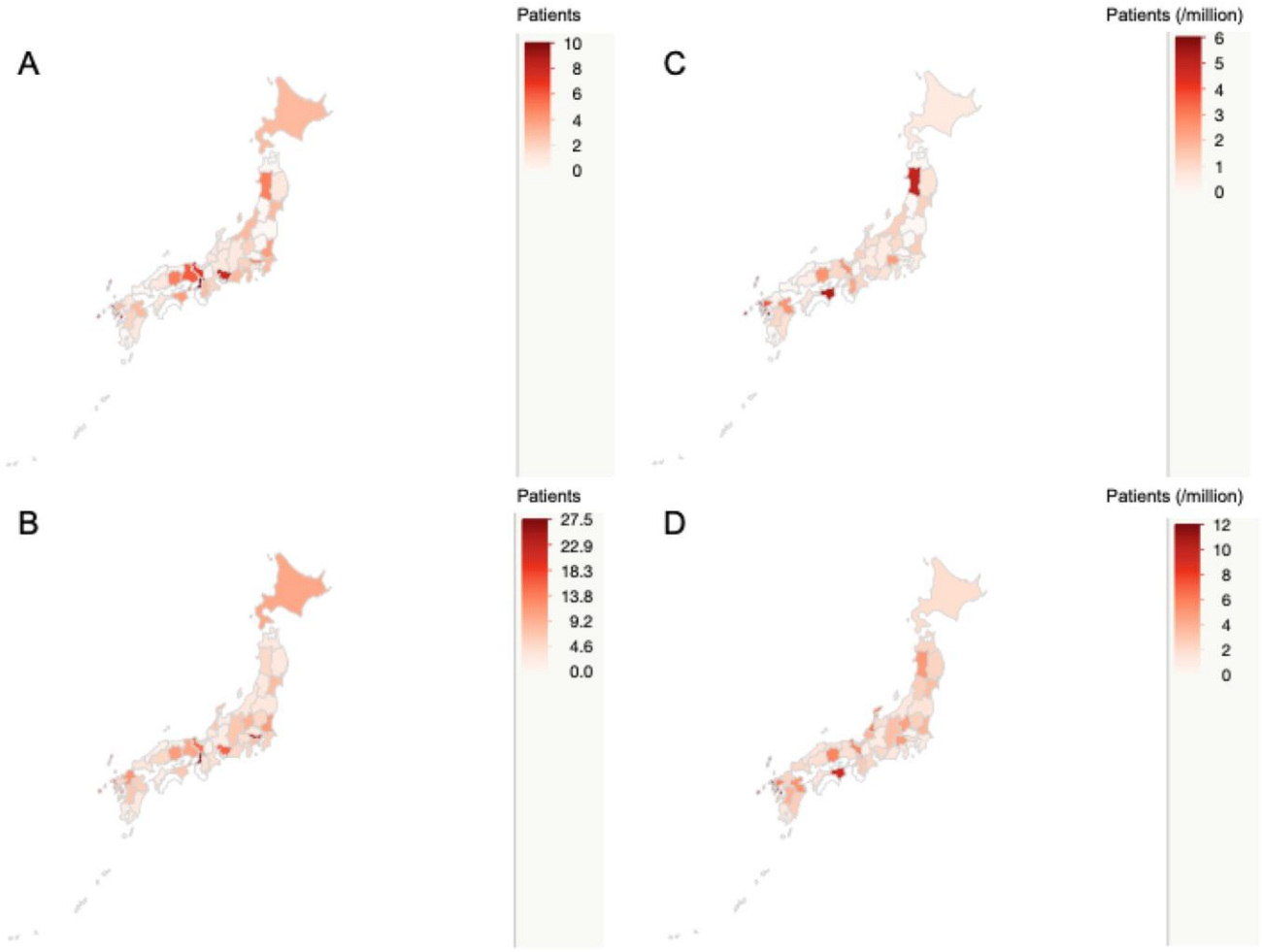

Figure 1. Nationwide distribution of patients with Werner syndrome in Japan. The map shows the nationwide distribution of patients with Werner syndrome. The concentration of red indicates the number of patients. The upper left map (**A**) shows the nationwide distribution of diagnosed cases. The lower left map (**B**) shows the nationwide distribution of total patients including diagnosed cases, suspected cases, and past confirmed cases. The upper right map (**C**) shows the diagnosed cases per million population. The lower right map (**D**) shows total patients including diagnosed cases, suspected cases, and past confirmed cases per million population.

Table 2. Frequency of major signs, clinical symptoms, and medications administered to patients with Werner syndrome.

	%	n	N
Major signs			
Graying of hair, hair loss	97.5	39	40
Cataracts	100	40	40
Skin changes	97.5	39	40
Intractable skin ulcers	67.5	27	40
Soft-tissue calcification	87.5	35	40
Bird-like face	90	36	40
High-pitched voice	87.5	35	40
Clinical symptoms			
Diabetes, IGT	67.5	27	40
Dyslipidemia	65	26	40
Hypertension	42.5	17	40
Fatty liver	52.5	21	40
Cerebral bleeding	0	0	40
Cerebral infarction	0	0	40
AP or MI	2.5	1	40
ASO	15	6	40
Amputation	15	6	40
Malignant tumor	20	8	40
Medications			
Diabetes, IGT			
DPP-4 inhibitor	37.0	10	27
Biguanide	33.3	9	27
Thiazolidine	48.1	13	27
alpha GI	7.4	2	27
Sulfonylurea	11.1	3	27
SGLT2 inhibitor	3.7	1	27
Glinide	0	0	27
GLP-1 analog	3.7	1	27
Insulin	14.8	4	27
Dyslipidemia			
Statin	65.4	17	26
Fibrate	3.8	1	26
Ezetimibe	0	0	26
EPA	11.5	3	26
Resin	0.0	0	26
Nicotinic acid	19.2	5	26
Probucol	0	0	26
Hypertension, among others			
Ca blocker	47.1	8	17
ARB	35.3	6	17
ACE inhibitor	0.0	0	17
Alpha1 blocker	0.0	0	17
Beta blocker	11.8	2	17
Diuretics	0.0	0	17
Antiplatelet	5.0	2	40
Anticoagulant	12.5	5	40

The percentages of medications administered to treat abnormal glucose metabolism, dyslipidemia, and hypertension are shown for the total number of patients with each disorder. N, number of patients; n, number of patients with symptoms or treatment drugs, IGT, Impaired glucose tolerance; AP, Angina pectoris; MI, Myocardial infarction; ASO, Arteriosclerosis obliterans; DPP-4, Dipeptidyl peptidase-4; alpha GI, alpha glucosidase inhibitor; SGLT2, Sodium-glucose cotransporter-2; GLP-1, Glucagon-like peptide-1; EPA, Eicosapentaenoic acid; Ca, Calcium; ARB, Angiotensin-II receptor blocker; ACE, Angiotensin-converting enzyme inhibitor.

Limb amputation was observed in 15.0% of patients. Malignant tumor was observed in 20.0% of patients (Table 2) and comprised lung cancer, lung adenocarcinoma, undifferentiated pleomorphic sarcoma, fibrosarcoma, osteosarcoma, colorectal cancer, follicular thyroid cancer, and melanoma.

Table 2 provides details of the medications administered to treat abnormal glucose metabolism, dyslipidemia, and hypertension. More than 30% of patients with diabetes were treated with a dipeptidyl peptidase-4 (DPP-4) inhibitor, biguanide, or thiazolidine. Two-thirds of patients with dyslipidemia were treated with a statin. Calcium antagonists and angiotensin-II receptor blockers were often used for patients with hypertension.

The change in major signs and clinical symptoms over time is shown in Table 3. There were no differences in patients' demographic characteristics between 2009 and 2017; sex (male 46.6% vs. 55.0%, P=0.388). Although the data in 2009 had age groups and not the actual age, the mean age group in 2009 was 50s, while the mean age in 2017 was 50.1 years. Compared with that in 2009, the percentage of patients with intractable skin ulcers had decreased (87.5% vs. 67.5%, P<0.01) and that of soft-tissue calcification had increased (76.7% vs. 87.5%, P=0.048). The percentage of angina pectoris or myocardial infarction had significantly decreased (14.8% vs. 2.5%, P=0.049). The percentage of malignant tumor had significantly decreased (42.4% vs. 20.0%, P=0.010).

Table 4 shows the change in medications administered between 2009 and 2020. DPP-4 inhibitor, sodium-glucose cotransporter-2 (SGLT2) inhibitor, and glucagon-like peptide-1 (GLP-1) analog were not used in 2009. While not statistically significant, the use of alpha glucosidase inhibitor and sulfonylurea usage had decreased in 2020 compared with 2009. Statin and anti-hypertensive medication use was similar in 2020, while the use of fibrate had significantly decreased (19.2% vs. 3.8%, P=0.017).

Table 5 shows the results of blood tests. The mean red blood cell counts and hemoglobin levels in men were lower than the normal range. On average, patients had more than two times higher levels of gamma-glutamyl transpeptidase than the upper normal limit. Aspartate aminotransferase, alanine aminotransferase (ALT), lactate dehydrogenase, and triglyceride (TG) in men and ALT in women were slightly higher than normal range. Average glycated hemoglobin (HbA1c) level was less than 6.5%. Average fasting plasma glucose (FPG) level was less than 126 mg/dL. Average postprandial plasma glucose (PPG) level was less than 200 mg/dL. Low-density lipoprotein cholesterol (LDL-C) level was below 120 mg/dL. Although FPG, PPG, and HbA1c were higher than normal range, these values were lower than the treatment target values of diabetes and hyper LDL-cholesterolemia, which indicated that the levels of HbA1c, plasma glucose, and LDL-C levels were well controlled.

The patients' average age at enrollment was 50.1 ± 7.5 years. The average age at Werner syndrome onset was 26.1 ± 9.5 years; however, the age of diagnosis was 42.5 ± 8.6 years (Table 6).

The patients' average height, body weight, and body mass index (BMI) (159.7 cm, 49.0 kg, BMI 19.2 kg/m^2 in men, 147.2 cm, 38.1 kg, BMI 17.6 kg/m^2 in women) (Table 6) were lower than those of the average Japanese individual in the fifth decade of life as reported by the Japanese Ministry of Health, Labour, and Welfare's 2018 National Health and Nutrition Survey Report (169.2 cm, 68.1 kg, BMI 23.5 kg/m^2 in men, 156.6 cm, 55.0 kg, BMI 22.2 kg/m^2 in women). In Werner syndrome, patients present with central obesity; the average abdominal circumference was 80.4 ± 12.2 cm in men and 73.0 ± 10.8 cm in women. The average abdominal circumference was large, although the respective BMI were low (Table 6). Namely, the patients with Werner syndrome have lipodystrophy.

The average of the total limb skeletal mass index (SMI), identified using dual-energy X-ray absorptiometry (DEXA), was 4.5 ± 0.9 kg/m^2 for men and 4.1 ± 0.6 kg/m^2 for women. Although one patient had four toes amputated, the other patients had not undergone amputation. Grip strengths were (right) 20.8 ± 8.6 kg and (left) 19.5 ± 7.3 kg for men, and (right) 12.3 ± 6.3 kg and (left) 11.4 ± 5.3 kg for women. Walking speed was 0.8 ± 0.6 m/sec on average (Table 6).

DISCUSSION

Our mission is to improve the prognosis and support social reintegration for patients with Werner syndrome, by improving the quality of medical treatment. To address the clinical questions regarding Werner syndrome and to collect high quality evidence, we conducted this nationwide survey and established the Werner Syndrome Registry (case registration system). The Werner syndrome nationwide survey identified 116 confirmed cases of Werner syndrome in Japan; a total of 32 facilities participated in the Werner Syndrome Registry and 40 patients were enrolled in the registry.

As the maps show, there were no statistically significant differences in the distributions of the patients with Werner syndrome throughout Japan in 2017. However, compared to the patient population per million people

Table 3. Major signs and clinical symptom changes showing a positive percentage over time.

	In 2009 (%)	In 2020 (%)	*P* value
Sex (male)	46.6	55.0	0.388
Graying of hair, hair loss	98.1	97.5	1.000
Cataracts	92.5	100	0.124
Skin changes	97.4	97.5	1.000
Intractable skin ulcers	87.5	67.5	<0.01
Soft-tissue calcification	76.7	87.5	0.048
Bird-like face	96.1	90.0	0.220
High-pitched voice	88.0	87.5	1.000
Diabetes, impaired glucose tolerance	71.43	67.5	0.700
Dyslipidemia	68.5	65.0	0.701
Hypertension	34.6	42.5	0.250
Fatty liver	44.2	52.5	0.330
Cerebral bleeding	1.5	0	1.000
Cerebral infarction	3.7	0	0.591
Angina pectoris or myocardial infarction	14.8	2.5	0.049
Arteriosclerosis obliterans	24.4	15.0	0.277
Malignant tumor	42.4	20.0	0.010
Consanguineous marriage	39.0	29.7	0.424

The data in this registry in 2020 was compared with the data of survey in 2009. Fisher's exact test was used for the statistical comparison.

Table 4. Medications administered changes over time.

	In 2009 (%)	In 2020 (%)	*P* value
Diabetes, IGT			
DPP-4 inhibitor	0	37.0	<0.01
Biguanide	19.1	33.3	0.261
Thiazolidine	40.4	48.1	0.630
alpha GI	25.5	7.4	0.067
Sulfonylurea	29.8	11.1	0.086
SGLT2 inhibitor	0	3.7	0.375
Glinide	4.3	0	0.527
GLP-1 analog	0	3.7	1.000
Insulin	27.7	14.8	0.381
Dyslipidemia			
Statin	65.4	65.4	0.610
Fibrate	19.2	3.8	0.017
Ezetimibe	1.9	0	1.000
EPA	5.8	11.5	0.557
Resin	1.9	0	1.000
Nicotinic acid	1.9	19.2	0.153
Probucol	5.8	0	0.503
Hypertension, among others			
Ca blocker	42.1	47.1	1.000
ARB	47.4	35.3	0.510
ACE inhibitor	5.3	0.0	1.000
Alpha1 blocker	0.0	0.0	1.000

Beta blocker	5.3	11.8	1.000
Diuretics	10.5	0.0	0.487
Antiplatelet	NA	5.0	NA
Anticoagulant	NA	12.5	NA

The data in this registry in 2020 was compared with the data of survey in 2009. Fisher's exact test was used for the statistical comparison.

The percentages of medications administered to treat abnormal glucose metabolism, dyslipidemia, and hypertension are shown for the total number of patients with each disorder. DPP-4, Dipeptidyl peptidase-4; alpha GI, alpha glucosidase inhibitor; SGLT2, Sodium-glucose cotransporter-2; GLP-1, Glucagon-like peptide-1; EPA, Eicosapentaenoic acid; Ca, Calcium; ARB, Angiotensin-II receptor blocker; ACE, Angiotensin-converting enzyme inhibitor, NA; not available.

Table 5. Blood test findings.

	Total				Men				Women				Normal range
	Mean		SD	n	Mean		SD	n	Mean		SD	n	
WBC (/μL)	7502	±	2400	39	7663	±	2845	22	7293	±	1724	17	3300 – 8600
RBC (/μL)	424	±	64	39	423*	±	76	22	426	±	46	17	Men 435 – 555, Women 386 – 492
Hgb (g/dL)	12.6	±	2.0	39	13.0*	±	2.3	22	12.2	±	1.7	17	Men 13.7 – 16.8, Women 11.6 – 14.8
Plt (x 10^3/μL)	28.9	±	7.9	39	27.1	±	6.6	22	31.2	±	8.9	17	15.8 – 34.8
AST (U/L)	29	±	13	40	34*	±	16	22	24	±	6	18	13 –30
ALT (U/L)	39	±	29	340	43*	±	30	22	34*	±	27	18	Men 10 – 42, Women 7 – 23
γ-GTP (U/L)	100*	±	116	38	87*	±	104	22	116*	±	131	16	Men 13 – 64, Women 9 – 32
LDH (U/L)	230*	±	181	37	255*	±	230	22	193	±	44	15	124 – 222
ALP (U/L)	313	±	176	34	311	±	141	21	317	±	229	13	106 – 322
ChE (U/L)	363	±	102	30	364	±	121	17	363	±	74	13	Men 240 – 486, Women 201 – 421
T-Bil (mg/dL)	0.5	±	0.2	34	0.5	±	0.3	20	0.5	±	0.2	14	0.4 – 1.5
TC (mg/dL)	194	±	34	33	198	±	35	21	187	±	34	12	125 – 219
TG (mg/dL)	158*	±	91	38	166*	±	87	21	148	±	98	17	35 – 149
LDL-C (mg/dL)	115	±	32	36	114	±	36	19	117	±	28	17	less than 140
HDL-C (mg/dL)	57	±	17	35	58	±	22	18	55	±	11	17	40 and more
TP (g/dL)	7.8	±	0.6	36	7.9	±	0.5	21	7.7	±	0.7	15	6.6 – 8.1
Alb (g/dL)	4.2	±	0.8	37	4.2	±	0.9	20	4.2	±	0.6	17	4.1 – 5.1
UA (mg/dL)	5.4	±	1.3	36	5.7	±	1.2	20	4.9	±	1.3	16	7.0 and less
BUN (mg/dL)	16	±	8	37	17	±	9	22	15	±	7	15	8 – 20
Cre (mg/dL)	0.8	±	1.0	39	1.0	±	1.2	22	0.5	±	0.2	17	Men 0.65 – 1.07, Women 0.46 – 0.79
Na (mEq/L)	139	±	3	37	139	±	3	21	139	±	4	16	138 – 145
K (mEq/L)	4.2	±	0.4	37	4.3	±	0.5	21	4.2	±	0.3	16	3.6 – 4.8
Cl (mEq/L)	104	±	4	36	105	±	3	20	103	±	4.5	16	101 – 108
Ca (mg/dL)	9.3	±	0.5	28	9.2	±	0.6	15	9.4	±	0.4	13	8.8 – 10.1
FPG (mg/dL)	114*	±	28	14	116*	±	35	6	112*	±	23	8	73 – 109
PPG (mg/dL)	144*	±	57	21	150*	±	49	12	136	±	69	9	less than 140
HbA1c (%)	6.4*	±	1.3	35	6.1*	±	0.8	18	6.8*	±	1.7	17	4.9 – 6.0

*shows abnormal values. WBC; white blood cell, RBC; red blood cell, Hgb; hemoglobin, Plt; platelet, AST; aspartate aminotransferase, ALT; alanine aminotransferase, γ-GTP; gamma-glutamyl transpeptidase, LDH; lactate dehydrogenase, ALP; alkaline phosphatase, ChE; cholinesterase, T-Bil; total bilirubin, TC; total cholesterol, TG; triglyceride, LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol, TP; total protein, Alb; albumin, UA; uric acid, BUN; blood urea nitrogen, Cre; creatinine, Na; natrium, K; potassium, Cl; chlorine, Ca; calcium, FPG; fasting plasma glucose, PPG; postprandial plasma glucose, HbA1c; glycated hemoglobin, SD; standard deviation.

Table 6. Patient background, physical findings, body composition, and physical function.

	Total				Men				Women			
	Mean		SD	n	Mean		SD	n	Mean		SD	n
Patients' backgrounds												
Age (years)	50.1	±	7.5	40	49.4	±	7.6	22	50.9	±	7.5	18
Onset age (years)	26.1	±	9.5	30	28.2	±	8.5	16	23.7	±	10.2	14
Diagnosed age (years)	42.5	±	8.6	39	42.0	±	6.4	21	43.2	±	10.8	18
Physical findings												
Height (cm)	154.0	±	10.7	40	159.7	±	8.6	22	147.2	±	9.0	18
Body weight (kg)	44.1	±	9.5	40	49.0	±	9.3	22	38.1	±	5.4	18
BMI (kg/m^2)	18.5	±	3.1	40	19.2	±	3.5	22	17.6	±	2.5	18
Waist circumference (cm)	77.3	±	12.0	24	80.4	±	12.2	14	73.0	±	10.8	10
Visceral fat area (cm^2)	102.3	±	61.4	10	112.4	±	81.5	4	95.6	±	51.7	6
SMI (kg/m^2)	4.3	±	0.8	9	4.5	±	0.9	5	4.1	±	0.6	4
Physical function												
Mean grip strength (right) (kg)	17.1	±	8.7	23	20.8	±	8.6	13	12.3	±	6.3	10
Mean grip strength (left) (kg)	16.0	±	7.6	23	19.5	±	7.3	13	11.4	±	5.3	10
Mean walking speed (m/sec)	0.8	±	0.6	13	0.9	±	0.6	6	0.8	±	0.6	7

BMI; body mass index, SMI; skeletal muscle mass index, SD; standard deviation.

for each region in 2009 (Nagasaki 7.6 patients, Tokushima 6.3 patients, Nagano 5.5 patients, Miyazaki 5.3 patients) [7], there were some changes in 2017 (Nagasaki 5.9 patients, Tokushima 5.4 patients, Akita 5.0 patients, Saga 3.6 patients), which suggests that there were regional temporal changes in the incidence of Werner syndrome.

Previously, widespread consanguineous marriages resulted in localized and uneven distribution of Werner syndrome [8]. The absence of significant regional biases in patients' distribution across the country may be a result of the low percentage of consanguineous marriages and increased movement of the populations due to advances in transportation.

The time gap between the age of onset and the age of diagnosis was similar to that reported in the 2006 international Werner syndrome registry [9]. In the international Werner syndrome registry, the mean age of cataracts was 31 years and age of diagnosis or referral was 43 years.

These results suggest that it is necessary to consider measures for early diagnosis and early intervention. Werner syndrome onset is usually recognized by bilateral cataracts or gray hair and hair loss, which are usually the first symptoms [7]. The patients normally undergo cataract surgery around third decade of life. However, many of patients and ophthalmologists may not have adequate information to diagnose Werner syndrome. Around the fourth decade of life, the patients tend to have intractable ulcers and visit the dermatologist or plastic surgeon. As the national survey showed, many patients with Werner syndrome were reported by dermatologists or plastic surgeons, and not by ophthalmologists.

In order to promote early diagnosis of Werner syndrome, it is necessary to create awareness regarding Werner syndrome among ophthalmologists. As part of the solution, we plan to advertise in journals and conferences whose readership includes ophthalmologists.

It has previously been reported that the average life span of patients with Werner syndrome is around 50 years. However, in our analysis, the average age at enrollment was 50.1 ± 7.5 years, which suggests that the life expectancy of patients with Werner syndrome may be longer than that reported two decades ago [8]. Notably, few patients had a history of atherosclerosis, such as cerebral infarction, angina pectoris, myocardial infarction, or ASO in the registry. Compared with the previous survey conducted in 2009 [7], the percentages of patients with a history of cerebral bleeding, cerebral infarction, angina pectoris, myocardial infarction, and ASO decreased in 2020. This may have been due to improved control of diabetes with better treatment modalities. The high percentage of pioglitazone use, which increases insulin sensitivity, is a characteristic diabetes treatment for patients with Werner syndrome [10]. In the current decade, DPP-4 inhibitors are often used to treat the common form of type 2 diabetes in Japan [11]. The effectiveness of the DPP-4 inhibitor, sitagliptin, for a pioglitazone non-responder patient with Werner syndrome has been reported [12]. Reportedly,

GLP-1 analog improves vascular function and reduces abdominal fat accumulation in patients with Werner syndrome [13]. In a large-scale clinical study for type 2 diabetes, the cardiovascular preventive effects of GLP-1 analog and SGLT2 inhibitor have been reported [14–18].

Although the usage of fibrate decreased, there is little evidence that fibrate prevents angina pectoris and myocardial infarction. Therefore, the decreased use of fibrate did not affect the outcome. The frequency of use of statins, calcium antagonists, and angiotensin-II receptor blockers may be similar to that of patients being treated for dyslipidemia or hypertension. Regarding risk factors, comprehensive treatment with these medications might have ameliorated the arteriosclerotic outcomes in the patients with Werner syndrome.

Although the percentage of patients with intractable skin ulcers decreased compared to that reported a decade ago, two thirds of patients with Werner syndrome still had intractable ulcers. The nationwide survey revealed that a high percentage of patients with Werner syndrome were reported by plastic surgeons or dermatology specialties. We speculate that patients with Werner syndrome visited the hospital for the treatment of ulcers or to receive more specialized treatments.

The percentage of patients with soft-tissue calcification increased. Soft-tissue calcification was changed from "other symptoms" to "major symptoms" in the 2012 diagnostic criteria. Therefore, soft-tissue calcification may have been checked more frequently than in 2009.

The registry contributed to the recruitment of patients with Werner syndrome for a clinical trial. Based on the Werner Registry, patients were introduced to a physician-initiated clinical study of limb ulcers treated with the functional peptide, SR-0379. Treatment with this peptide resulted in reduced size of skin ulcers compared with a placebo after 28 days [19, 20]. The reduction rate of ulcer size in patients with Werner syndrome treated with 0.1% SR-0379 was 22.90%. The DESIGN-R score index, which is calculated based on six components (exudate, size, infection/inflammation, granulation tissue, necrotic tissue, and pocket size) and used as a tool to score pressure ulcer severity, decreased by 4.0 points in patients with Werner syndrome [20]. In near future, this functional peptide may be able to use as the treatment for the patients with Werner syndrome and intractable skin ulcers. As results, it may lead to reduce limb amputation.

The physique of patients with Werner syndrome is smaller than that of the average Japanese in the fifth decade of life. Moreover, the SMI of the patients was far below the threshold of 7.0 kg/m^2 for men and 5.4 kg/m^2 for women, which is one of the diagnostic criteria for sarcopenia in Asia according to the Asian Working Group for Sarcopenia [21]. Handgrip strength, another diagnostic criteria for Asian sarcopenia, was well below the thresholds of <28 kg and <18 kg for men and women, respectively [21]. Another indicator of sarcopenia, walking speed, was <1.0 m/sec on average, and most patients performed below the threshold. Therefore, in this registry, most patients aged over 40 years had sarcopenia. At least half of patients also had visceral fat accumulation; therefore, they have exhibited lipodystrophy and sarcopenic obesity. Reportedly, the observed prevalence of sarcopenia in patients with type 2 diabetes aged 65 years and older has been reported to be 18.7% in Japanese outpatient clinics [22]. Therefore, the prevalence of sarcopenia and sarcopenic obesity in patients with Werner syndrome is higher than that in patients with type 2 diabetes aged ≥65 years. Patients with sarcopenic obesity are generally less active and are at a higher risk of falls, fractures, and death [23–26].

Almost all patients showed a decrease in grip strength; however, two patients did not show a decrease in grip strength. One of these patients belonged to the Self-Defense Forces in his twenties. His muscle training exercises and well-balanced diet may have affected his grip strength result. Therefore, muscle training and nutrition improvement may be useful for preventing sarcopenia. Sarcopenia appears early in most patients with Werner syndrome; therefore, sarcopenia in the patients Werner syndrome may be prevented by early intervention with strength training and with treatments that include amino acids such as leucine, whey protein, calcium, and vitamin D [27, 28].

Fortunately, the percentage of patients with malignant tumors has decreased compared with the percentage in 2009. However, morbidity of malignant tumors is still high in patients with Werner syndrome. Reportedly, the age at cancer diagnosis in patients with Werner syndrome had advanced by 20 years compared with that in the general Japanese population [29]. Therefore, periodical cancer screening is required. Reportedly, Werner syndrome patients with diabetes had a significantly higher cancer prevalence than Werner syndrome patients without diabetes [30]. Therefore, especially for Werner syndrome patients with diabetes, periodic cancer screening is important.

There was a report that dementia and/or schizophrenia appears around 40 years of age [8]; however, there were no patients with dementia and/or schizophrenia identified in this registry.

We plan to maintain the registry active and conduct a longitudinal analysis. We also intend to use the data

obtained by the registry follow-up as evidence for the revision of Werner syndrome clinical practice guidelines. We are also developing tools that can be used for early diagnosis based on the characteristics of the voice and face. We are planning clinical trials to examine treatment with new medicines, such as nicotinamide riboside.

Some limitations of the study should be noted. Since Werner syndrome is a rare disease, the number of patients was small. Of the patients diagnosed with Werner syndrome in the nationwide survey, 34.5% were included in this registry; therefore, this is one of the largest databases of patients with Werner syndrome. We continue to enroll more patients in this registry to make it more complete. The questionnaires of the registry require to be improved in the following aspects: The effects of drug prescriptions were not evaluated and further studies should address effective treatments in this patient population. Osteoporosis was not included in the survey items and should be added to the survey items in future. The false positive/negative rates also require to be evaluated.

In conclusion, the results of the Werner Syndrome Registry revealed the current disease profile of patients with Werner syndrome in Japan. The data suggest that although the prognosis of patients with Werner syndrome has not worsened, there are opportunities for early diagnosis and intervention, which may result in improved quality of medical treatment of patients with Werner syndrome. Sensitization about this condition is needed.

MATERIALS AND METHODS

The nationwide survey

A nationwide primary survey was conducted to identify patients who were diagnosed with Werner syndrome, in a collaboration with the National Health Labor Science Research Policy Research Project. Primary information of Werner syndrome patients was also gathered and updated, based on the results of the previous nationwide survey that was conducted in 2009 [7]. For the nationwide survey, questionnaires were sent to 7888 physicians in Japan in 2017. The physicians were asked whether they had patients with Werner syndrome based on the diagnostic criteria [7]. The difference in patients' distribution for each region was analyzed using Wilcoxon rank sum test. JMP pro 13 (SAS Institute, Cary, NC) was used in the analysis.

Establishment, management, data collection and analysis of the Werner Syndrome Registry

The Werner Syndrome Registry was established to investigate the disease, recruit participants for clinical trials, and to provide information to enrolled patients and physicians. A data sheet for the registration system (Supplementary File) was prepared, based on the previous survey [7], and was referenced to domestic and international intractable disease registration systems. For the Werner Syndrome Registration system, DATATRACK ONE (NTT DATA, Tokyo, Japan) has been used, supported by the Chiba University Clinical Research Center. A registry infrastructure has been completed.

The facilities that reported definitive Werner syndrome cases in the nationwide survey participated in the registry and performed case registration of confirmed diagnosed patients. We obtained informed consent to access the survey of case information, in which the data of clinical symptoms/natural history (course from onset to treatment start), mutation pattern of the causative gene, and treatment information were collected. Blood samples were collected from the patients who provided consent, which served as a repository; complete blood count, liver function, renal function, electrolytes, lipid profile, and glucose metabolism were measured. As patients' background, age at enrolment, onset age, and age at diagnosis were investigated. As physical findings, height, body weight, and BMI, waist circumference, visceral fat area measured by computed tomography, and SMI measured by DEXA were investigated. As physical function, mean grip strength and mean walking speed were investigated. The patients' data were collected annually to enable cross-sectional and longitudinal analysis.

Data at enrollment for each patient of the registry was analyzed with JMP pro 13 (SAS Institute, Cary, NC), and served as the pilot data. The data were extracted on July 6, 2020. Regarding major signs, the clinical symptoms, and treatments, the data in this registry were compared with the data in 2009. Fisher's exact test was used for the comparison.

The study complied with the ethical rules for human experimentation as specified by in the Declaration of Helsinki. The study received approval from the Ethics Board of Chiba University on 27th July 2016, approval number 278. The study was registered at UMIN Clinical Trial Registry (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034058) on 3rd November 2017 (ID: UMIN000029812).

The key inclusion criteria for the registry were as follows: 1) patients with confirmed Werner syndrome based on the diagnostic criteria [7] and 2) patients who provided written informed consent prior to their participation in the study.

AUTHOR CONTRIBUTIONS

MK, YM, TI, KK, MK, MT and KY managed the project. MK, YM, YM, MS, HK, HK, DK, JK, AS, SM, HN, YY, ST, AT, KS, YS, KH, TY, DS and KY recruited the patients and carried out examinations. MK, YM and SM analyzed data. MK drafted the manuscript. MK, YM, MS, HK, TI and DK edited and revised the manuscript. KY acted as the "clinical investigator." All authors contributed significantly, read, and approved the final manuscript.

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CONFLICTS OF INTEREST

No conflicts of interest are declared for all authors.

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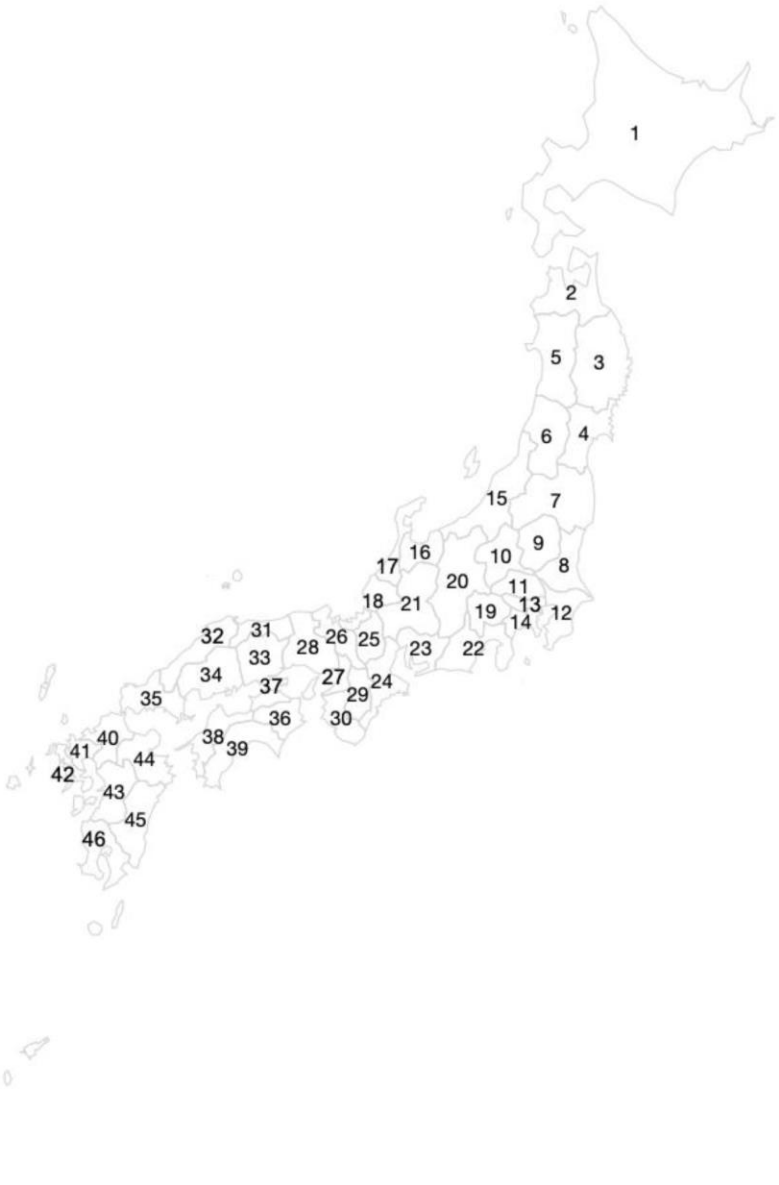
SUPPLEMENTARY MATERIALS

Supplementary Figure



Supplementary Figure 1. Number of patients with Werner syndrome in each region in Japan. Number on map indicates in Supplementary Table 2.

Supplementary Tables

Supplementary Table 1. Breakdown of patients with Werner syndrome and suspected cases.

	Total	Male	Female
Patients with Werner syndrome at the hospitals at the time of the survey	116	57	59
Patients suspected of having Werner syndrome	51	29	22
Patients with Werner syndrome visited the hospital in the past 10 years	153 (The sexes of two patients were unknown)	80	71
Total	320	166	152

Reported patients includes 116 diagnosed patients who were attending the hospital for treatment during the survey, 51 patients suspected of having Werner syndrome, and 153 patients visited the hospital in the past 10 years although not having attended the hospitals during the survey. In total, 320 patients with Werner syndrome or suspected cases were reported.

Supplementary Table 2. Number of patients with Werner syndrome in each region in Japan.

Region	Number on map	Diagnosed cases	Suspected cases	Past confirmed cases	Combination	Diagnosed cases / million	Combination / million	Population (million)
Nagasaki	42	8	0	8	16	5.9	11.8	1.35
Tokushima	36	4	1	2	7	5.4	9.4	0.74
Akita	5	5	0	0	5	5.0	5.0	1.00
Saga	41	3	0	2	5	3.6	6.1	0.82
Kyoto	26	7	1	7	15	2.7	5.8	2.60
Okayama	33	5	2	4	11	2.6	5.8	1.91
Oita	44	3	1	2	6	2.6	5.2	1.15
Yamanashi	19	2	1	1	4	2.4	4.9	0.82
Nara	29	3	0	1	4	2.2	3.0	1.35
Ibaraki	8	4	2	5	11	1.4	3.8	2.89
Niigata	15	3	0	0	3	1.3	1.3	2.27
Miyagi	4	3	3	2	8	1.3	3.4	2.32
Fukui	18	1	1	1	3	1.3	3.9	0.78
Osaka	27	10	3	14	27	1.1	3.1	8.82
Kumamoto	43	2	3	2	7	1.1	4.0	1.77
Mie	24	2	1	1	4	1.1	2.2	1.80
Hyogo	28	6	0	4	10	1.1	1.8	5.50
Aichi	23	8	5	3	16	1.1	2.1	7.53
Gunma	10	2	1	6	9	1.0	4.6	1.96
Toyama	16	1	1	0	2	0.9	1.9	1.06
Miyazaki	45	1	0	2	3	0.9	2.8	1.09
Ishikawa	17	1	1	5	7	0.9	6.1	1.15
Shizuoka	22	3	1	1	5	0.8	1.4	3.68
Iwate	3	1	1	1	3	0.8	2.4	1.26
Ehime	38	1	0	1	2	0.7	1.5	1.36
Hokkaido	1	3	1	6	10	0.6	1.9	5.32
Gifu	21	1	0	1	2	0.5	1.0	2.01
Nagano	20	1	2	4	7	0.5	3.4	2.08
Chiba	12	3	1	2	6	0.5	1.0	6.25
Tokyo	13	5	6	11	22	0.4	1.6	13.72

Hiroshima	34	1	0	4	5	0.4	1.8	2.83
Fukuoka	40	1	3	8	12	0.2	2.3	5.11
Kanagawa	14	1	1	6	8	0.1	0.9	9.16
Okinawa	47	0	1	0	1	0	0.7	1.44
Saitama	11	0	1	2	3	0	0.4	7.31
Yamagata	6	0	1	2	3	0	2.7	1.10
Yamaguchi	35	0	2	1	3	0	2.2	1.38
Shiga	25	0	0	1	1	0	0.7	1.41
Kagoshima	46	0	0	2	2	0	1.2	1.63
Aomori	2	0	1	2	3	0	2.3	1.28
Tottori	31	0	0	1	1	0	1.8	0.57
Shimane	32	0	0	1	1	0	1.5	0.69
Tochigi	9	0	2	3	5	0	2.6	1.96
Fukushima	7	0	0	3	3	0	1.6	1.88

Number on map indicates in Supplementary Figure 1.

Supplementary File

Please browse Full Text version to see the data of Supplementary File 1.

Supplementary File 1. Werner Syndrome Registry sheet.

ウェルナー症候群ハンドブック

ウェルナー症候群の皆さんと家族、医療者のためのガイド

第1版

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7 目の病気 …… P7
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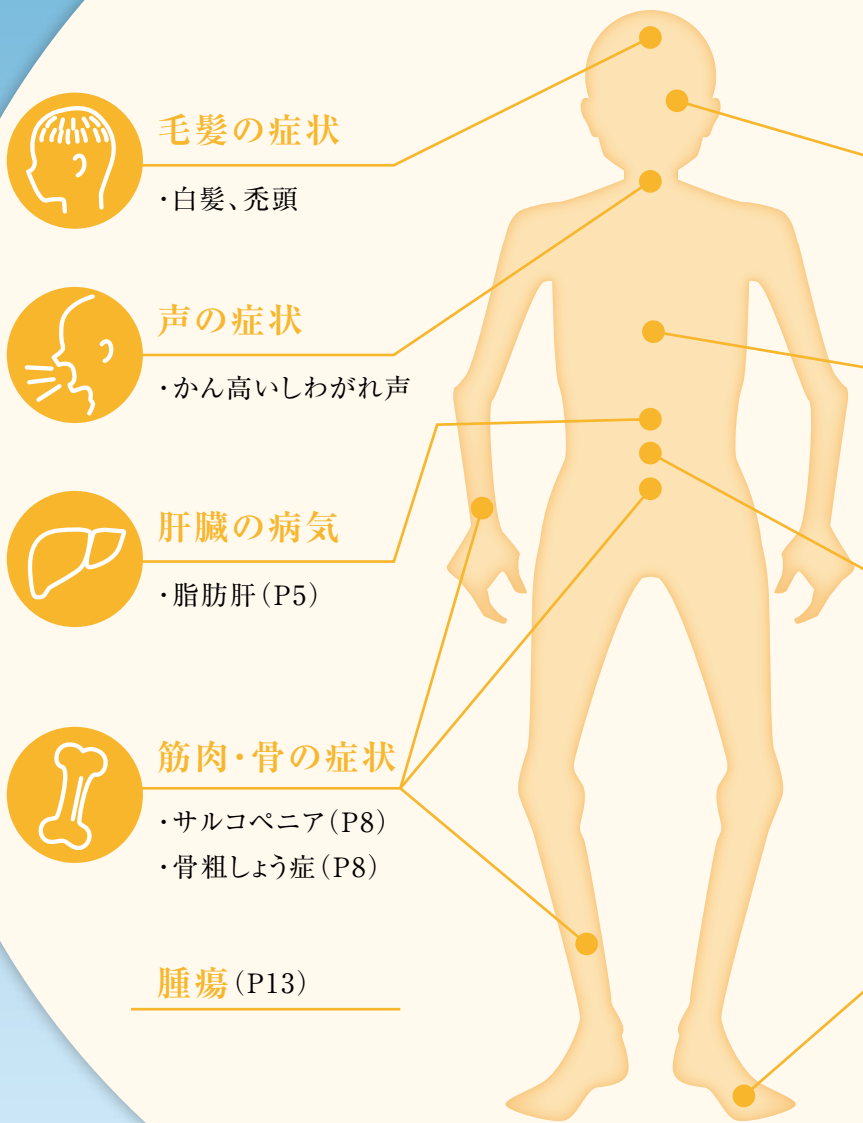
9 足の潰瘍(治りにくいキズ) … P10
10 腫瘍 …… P13

ウェルナー症候群の臨床症状



毛髪の症状
・白髪、禿頭

声の症状
・かん高いしわがれ声

肝臓の病気
・脂肪肝(P5)

筋肉・骨の症状
・サルコペニア(P8)
・骨粗しょう症(P8)

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目の病気
・白内障(P7)

心臓の病気
・動脈硬化
狭心症、心筋梗塞

代謝の異常
・内臓脂肪蓄積
・糖尿病(P3)
・脂質異常症(P4)

足の症状
・皮膚潰瘍(P6、P10)
・末梢動脈疾患

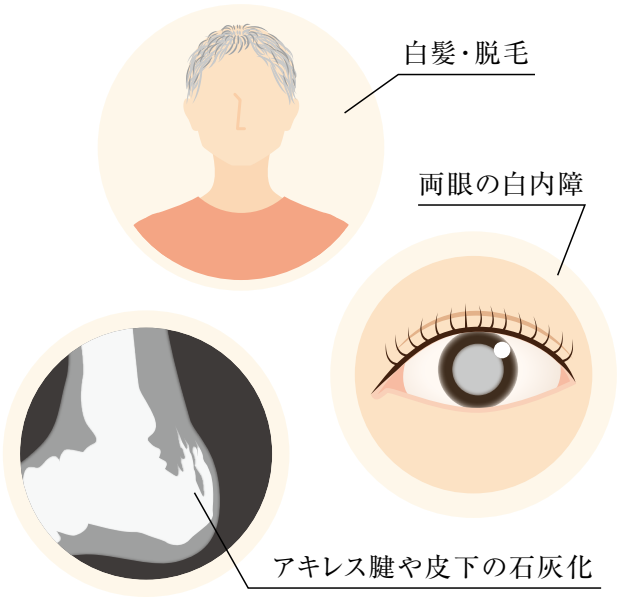
1 ウェルナー症候群とは?

ウェルナー症候群とは、思春期を過ぎる頃より急速に老化が進んでいくようにみえることから、「早く老いる」病気=早老症のひとつとされています。実年齢より「老けて見える」ようになります。

症状として、20歳代以降に白髪・脱毛や、両眼の白内障、かん高くかすれた声があらわれます。また腕や脚の筋肉がやせたり、皮膚が硬くなってタコができたり、また足や肘などにキズができて治りにくくなることがあります(難治性皮膚潰瘍)。身長は低いことが多く、レントゲンでアキレス腱や皮下の石灰化(カルシウム成分の蓄積)が見つかることがあります。

また糖尿病や脂質異常症(コレステロールや中性脂肪の異常)も多く、動脈硬化や癌になりやすいので、注意深い経過観察が必要です。潰瘍から感染を繰り返すと骨の中の骨髄まで細菌が入ってしまうことがあるので、皮膚のケアがとても重要です。

主な症状



日本のウェルナー症候群の患者数は約2,000人と推定されており、世界中で報告されている患者さんの約6割が日本人であり、我が国に多いと考えられています。以前は、血縁が濃くなる近親婚の多い地域で報告されてきましたが、最近では近親婚によらない患者さんも増加しています。日頃の食べ物や運動などの生活習慣は、発病とは関係ないと考えられています。

ウェルナー症候群はWRNと呼ばれる遺伝子の異常が原因と考えられており、2つのWRN遺伝子の両方に異常がある時だけ発病します。患者さんの両親はそれぞれひとつだけ原因遺伝子を持ち、ご自身は発病していないことがほとんどです。患者さんの兄弟姉妹では確率的に約4人に1人が発病しますが、患者さんのお子さんや、さらにそのお子さんが同じように発病する確率は計算上200 ～ 400人に1人以下であり、可能性は非常に少ないです。

ウェルナー症候群にはまだ根本的に治す方法がありませんが、一方、癌や白内障、糖尿病や脂質異常症などは、手術や薬などが有効であり、早期発見と治療が重要で、これによって予後を改善することができることがわかっています。

かつては、癌や、心筋梗塞などの動脈硬化の病気によって、多くの患者さんが40歳代半ばで亡くなると言われていました。しかし、最近の研究では平均寿命が10年以上延び、今では60歳以上の患者さんも多くなってきています(最高年齢77歳)。

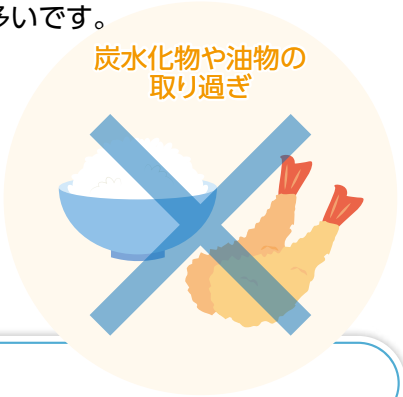
② 生活で気をつけること

内臓脂肪型肥満、糖尿病、脂質異常症の予防・治療

お腹に脂肪がたまりやすく（内臓性肥満）、これにより主に糖尿病や脂質異常症になりやすいため、炭水化物や油物を取り過ぎないようにしましょう。また可能な範囲で運動も行いましょう。糖尿病の治療は、一般の2型糖尿病に準じての治療が推奨されますが、インスリンという血糖値を低下させるホルモンの効きが悪くなることが主な原因なので、インスリンの効きを良くする薬を用いることが多いです。

脂質異常症の治療も、一般的な脂質異常症の治療に準じ、スタチンと呼ばれるLDL-コレステロール低下薬を使われることが多いです。

高血圧症の治療も、塩分を摂りすぎないようにし、必要に応じて、一般的な降圧薬を用います。これらの危険因子を良好にコントロールすることで、動脈硬化の進展を抑え、心筋梗塞の予防につながります。

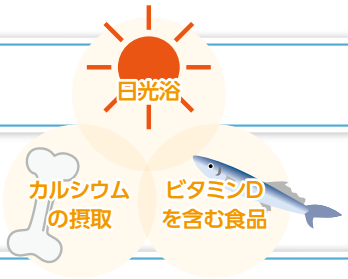


サルコペニア（筋肉が痩せ細ること）の予防

大豆製品、魚や肉などのタンパク質の摂取を心がけましょう。ロイシンと呼ばれるアミノ酸サプリが一般のサルコペニア予防に効果的とされており、ウェルナー症候群患者さんでも有効である可能性があります。

骨粗しょう症の予防

ビタミンDを含む食品、カルシウムの摂取、日光浴を行いましょう。



皮膚のキズ（難治性潰瘍）の予防・治療

足のキズは治りにくく、日常生活に大きな支障をきたすので、足にあった靴を履き、靴ずれを起こさないことが重要です。薄く固くなった皮膚は骨に圧迫されてキズができ、深い潰瘍を生じやすいため、当たって痛い箇所やキズになりかけたところは特殊な靴（装具）を作って保護する方法もあります。日頃からアキレス腱やかかと、足、肘など潰瘍になりやすい部位を保護し観察しましょう。できてしまった場合には、洗浄や消毒・保護・保湿などの対症療法が中心になりますが、自分のからだの他の場所から皮膚を移植する手術が有効な場合もあります。

癌の早期発見

通常よりも癌を発症することが多いため、早期発見・早期治療が大切です。このため、癌検診などを定期的に受けることをお勧めします。

3 糖尿病

糖尿病とは?

糖尿病とは、インスリンというホルモンが少なくなったり、うまく働かなくなったりして血糖値（血液中のブドウ糖濃度）が高くなる病気です。

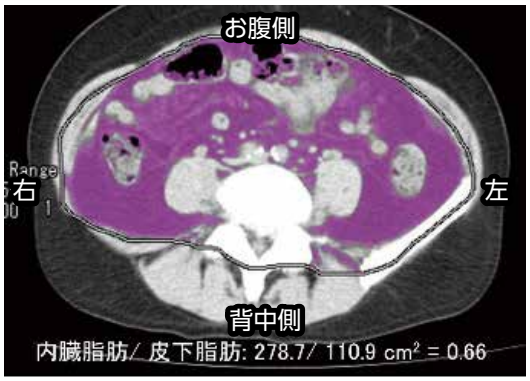
「最近、口が乾く」、「以前よりもおしっこの回数や量が増えた」、「疲れやすい」などの症状が出ることもありますが、症状があまりないこともあります。

糖尿病が怖いのは、病気を放っておくことにより、さまざまな病気があらわれることです。「目が見えなくなる」、「おしっこがうまく作れなくなって体の中に老廃物がたまる（尿毒症）」、「足が腐ってしまう」などの病気に加え、心臓病や脳卒中、さらには癌や認知症を増やしてしまいます。

主な症状

糖尿病とウェルナー症候群

わが国で行われた調査によると、男性、女性に関わらずウェルナー症候群患者の約6割の方に糖尿病を合併することがわかっています。お腹の回りに脂肪がたまる、いわゆるメタボ型の体形になり、インスリンがうまく働かなくなることが原因の一つと考えられています。



内臓脂肪CT（紫色の部分が内臓脂肪）

糖尿病の治療

間食やジュースは控えめにしてください。腹7～8分目を心がけると良いでしょう。可能な範囲での運動（ペットボトルを使った体操など）は有効と考えられます。メトホルミンやピオグリタゾンというお薬に効果があることが知られており、最近ではインクレチン関連薬という薬の効果も示されています。

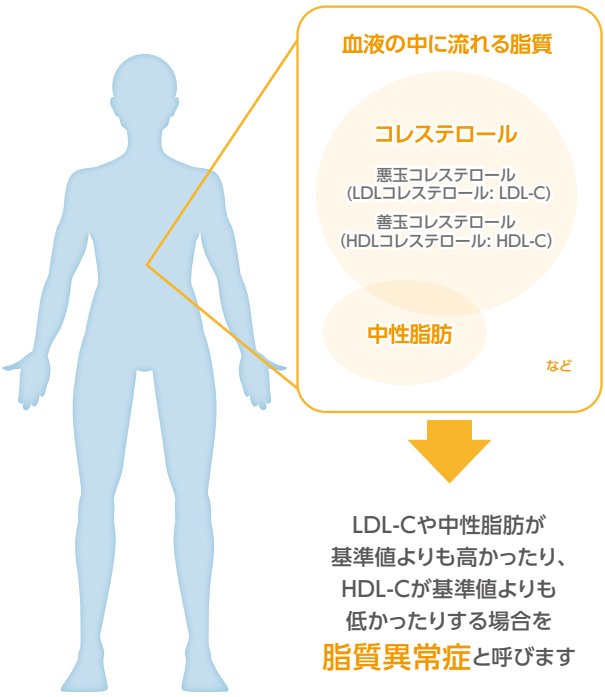
メトホルミン
ピオグリタゾン
インクレチン

4 脂質異常症

脂質異常症と動脈硬化

わたしたちの血液の中にはコレステロールや中性脂肪といったあぶら(脂質)が流れています。

さらにコレステロールは悪玉コレステロール(LDLコレステロール: LDL-C)と善玉コレステロール(HDLコレステロール: HDL-C)に分けられますが、LDL-Cや中性脂肪が基準値よりも高かったり、HDL-Cが基準値よりも低かったりする場合を脂質異常症と呼び、この状態は動脈硬化を起こしやすく、狭心症や心筋梗塞といった心臓の病気や脳卒中の危険因子になります。

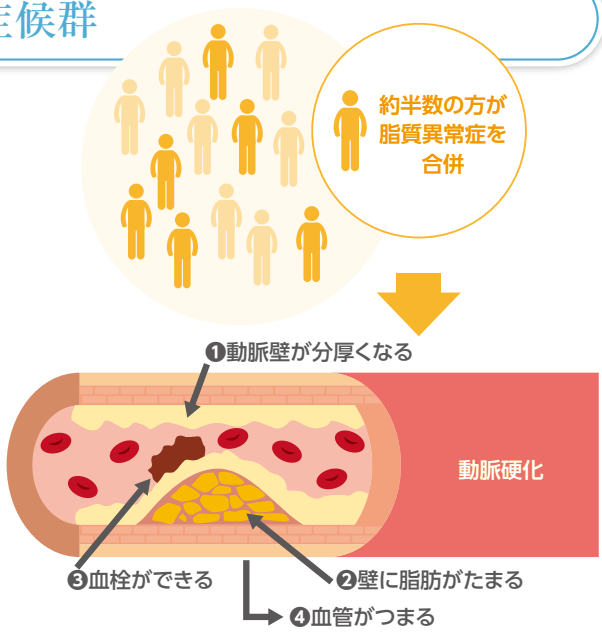


脂質異常症、動脈硬化とウェルナー症候群

日本で行われた調査によると、ウェルナー症候群患者の約半数の方に脂質異常症を合併することがわかっています (高LDL-C血症は約7割、高中性脂肪血症は約8割、低HDL-C血症は約3割)。

糖尿病と同じようにメタボ型の体形になり、インスリンがうまく働かなくなることが脂質異常症をきたす原因の一つと考えられています。

動脈硬化に関してはウェルナー症候群の方は一般の方に比べて狭心症や心筋梗塞が多い一方、脳卒中の発症はむしろ少ないとの報告があります。



脂質異常症の治療

動脈硬化症の予防には、生活習慣の改善、動物性の脂質を控えめにすることや、スタチン薬など、標準的な治療が用いられています。

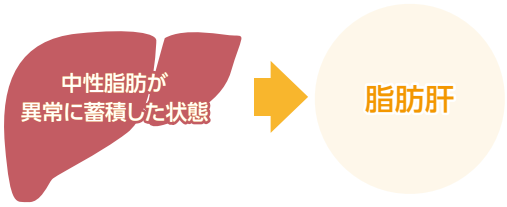
5 脂肪肝

脂肪肝について

肝臓の中に脂質の一種である中性脂肪が異常に蓄積した状態を脂肪肝といいます。

飲酒によるアルコール性脂肪肝がよく知られていますが、最近ではお酒をあまり飲んでもいないのに肝臓に脂肪がたまる非アルコール性脂肪肝が注目されています。

どちらも肝硬変や肝癌といった病気へ進行してしまうことがあります。



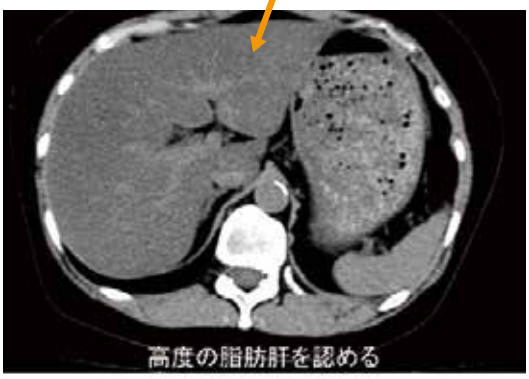
脂肪肝とウェルナー症候群

ウェルナー症候群患者の約3割の方に脂肪肝を合併することがわかっています。

一般的には非アルコール性脂肪肝の場合は太った方に多いのに対して、ウェルナー症候群の方は標準体重を大きく下回っても脂肪肝を合併することが特徴とされます。

脂肪肝を合併したウェルナー症候群の方に肝硬変や肝癌が多いという報告はまだありません。

暗く写っている所が脂肪の蓄積を示す
(普通は白っぽい明るい色)



腹部CT

脂質異常症の治療

脂肪肝に対する特効薬はまだありません。

アスタキサンチンというサプリメントがウェルナー症候群の方の脂肪肝を改善したという1例報告があります。

6 感染症

皮膚潰瘍の感染症について

ウェルナー症候群では皮膚の異常を起こしやすいことから、足底にうおの目（鶏眼）ができやすく、そこから皮膚の表面が炎症を起こして崩れてしまい、内部までキズがおよんでしまう潰瘍ができることがしばしばあります。このような状態は糖尿病でも起こりやすいことが知られています。ウェルナー症候群では糖尿病も合併しやすいことから、足底潰瘍をより起こしやすい状況にあると言えでしょう。また足底のみならず膝や肘にも潰瘍ができやすいことが知られています。

ここで一番大切なのはフットケアです。まずはうおの目を作らないこと、できた場合にはすぐに診察を受けてください。もし皮膚がえぐれて「潰瘍ができたかな」と思ったらすぐに主治医の診察を受けてください。その状態であれば、まだ感染を起こしていません。

周囲が赤く腫れてきたり、熱感を持つ感じがしたり、痛みがあるようですと、感染を起こしている可能性があります。このような場合には治療が必要になる可能性が高いです。

赤く腫れ上がる部位（発赤）が潰瘍の周り2cm以内の場合には、えぐれている深さにもよりますが抗菌薬の飲み薬で治療できる可能性が高いです。この場合には目安として2週間、長くても4週間の治療が必要となります。しかしながら発赤部位が2cm以上、もしくは深くまで感染している場合には感染している組織を削り取り、点滴で抗菌薬による治療を受ける必要が高くなります。このような場合には入院が必要となることが多いです。このような場合には目安として2〜4週間の治療が必要となります。点滴による治療が終わったあとに飲み薬に切り替えることもあります。

潰瘍が深くまで進むと、皮膚や皮下組織だけではなく関節や骨の感染症を起こすことがあります。こうした状態を関節炎や骨髄炎といいます。このような場合には入院して点滴で抗菌薬による治療を受ける必要があります。抗菌薬だけでは感染がよくならないときには外科的な切除が必要となることが多いです。一般的に関節や骨まで感染がおよんでいると少なくとも4週間以上と治療期間は長くなります。

また感染を繰り返している場合には、抗菌薬が効きにくい細菌（耐性菌）による感染症を起こす場合があります。この場合、飲み薬では治療できないことがありますので軽症でも点滴による治療が必要となります。

その他の感染症で気をつけたいこと

肺炎やインフルエンザなど、ワクチンで予防できる感染症はたくさんあります。主治医と相談して予防接種を受けることをおすすめします。

7 眼の病気

ウェルナー症候群は「早老症」ともいわれますが、文字通り年齢より早く老化がはじまります。目も例外ではなく老化がはじまります。最もよく見られる老化による眼症状は**白内障**です。早ければ20歳以降に発症しますが、平均では30歳で白内障が発症します。

一般の人では50歳頃から10%弱の人に白内障が発症し、70歳で80%以上で白内障が見られます。これに対しウェルナー症候群では100%で白内障が発症します。そのため、白内障を契機にウェルナー症候群の診断に至る場合もあるくらいです。

白内障は水晶体が混濁して視力低下をきたす病気で、症状は視力低下やまぶしさ、かすみなど様々です。初期症状としては単純な視力低下ではなく夜ヘッドライトがまぶしく感じる様になったりします。

また白内障進行に伴い近視化が進むこともあります。診断自体は眼科で一般的に用いられる細隙灯検査で容易にわかりますので開業医でも診断可能ですが、若年発症の白内障の原因は様々であるため、それだけでウェルナー症候群を疑う眼科医は多くはありません。

ただ、年齢に比べて水晶体の中央（核）の混濁・硬化が特徴であるため、若年で両眼の核白内障を認めたときはウェルナー症候群を疑うというのが基本的な考え方になります。

白内障は小切開（2−3mmの切開創）の水晶体再建術で重篤な合併症無く治療可能です。

基本は**超音波乳化吸引術**といって超音波で濁りを破砕して吸引し、残った袋（水晶体嚢）の中に人工レンズを挿入して終わります。ウェルナー症候群の場合、核が硬くなっている症例が多いため、手術の難易度が高くなりやすい傾向はあります。それでも昔の術式と比較すれば切開創は小さくなっているので創閉鎖不全のような重篤な合併症は起きなくなっています。

1つだけ特徴的な術後合併症として**嚢胞様黄斑浮腫**（のうほうようおうはんふしゅ）（網膜の中の黄斑という最も重要な場所にむくみが生じ、ぼやけたり、ゆがんで見えるといった症状が出ます）が見られることがあります。普通の白内障患者の場合、術後点眼の進歩により点眼のみで改善するのですが、ウェルナー症候群の場合、難治性になり恒久的な視力低下をきたす場合がありますので注意が必要です。本来炎症によって発症するものですがウェルナー症候群の場合嚢胞様黄斑浮腫の発症原因が不明のため頻度は不明ですが多くはないようです。総じて白内障手術手技の進歩によりウェルナー症候群の白内障は安全に手術が施行できるようになってきています。

8 サルコペニアと骨粗しょう症

サルコペニアとは

サルコペニアとは加齢により筋肉量が減り、筋力や歩行速度が低下している状態を指します。

サルコペニアは、将来的に介護を必要としたり、日常生活に何らかの支障をきたしたりする原因になります。つまり、サルコペニアは健康で長生きすることを妨げる要因となります。

ウェルナー症候群の患者さんは比較的若い時代（40歳未満）から手足の筋肉量が低下していることが報告されています。その原因はよくわかっていませんが、関節の拘縮（関節の動きが悪くなること）や足底に皮膚潰瘍が生じることが多いため、あまり体を動かすことが出来ないことも原因かもしれません。

主な症状

実際、中には習慣的なレジスタンス運動（筋肉に負荷をかける運動、いわゆる筋トレ）を行っているウェルナー症候群の患者さんでは骨格筋量の低下を認めない患者さんもいることから、適切な運動をすることにより、サルコペニアを予防できる可能性があります。

予　防

サルコペニアの予防には足底やアキレス腱にあまり負担がかからないような、レジスタンス運動と、食事からの十分なたんぱく質(筋肉の元)の摂取を心掛けてください。

たんぱく質は毎食少なくとも25g程度は摂っていただきたいと思います。ただし、慢性腎臓病などをお持ちの患者さんは、かかりつけ医の先生と是非ご相談ください。

骨粗しょう症とは

骨粗しょう症は加齢とともに骨の量（骨量）が減って骨がもろくなり、骨折しやすくなる病気です。

骨折により、日常生活に支障を来したり、寝たきりになったりすることもあり、これも健康寿命の延伸を阻害する危険な病気です。ウェルナー症候群の患者さんは若くして骨粗しょう症になりやすいことが報告されています。

患者さんの年齢にも寄りますが、日本における調査でも41%に、海外の報告では90%以上に骨粗しょう症を認めたとの報告もあります。ウェルナー症候群の患者さんの骨粗しょう症は椎骨（背骨）よりも下肢において重症となるケースが多くみられます。

主な症状

予防・治療

治療としては通常の骨粗しょう症の薬物療法が使用できます。

予防法としては、サルコペニアと同様にできるだけ運動をすることと、日光に適度にあびること（日光により皮膚でビタミンDを産生することが出来ます）も重要です。ビタミンDは食べ物からカルシウムの吸収を促し、骨粗しょう症の予防に重要です。サルコペニアと同様食事からの十分なたんぱく質の摂取も重要です。

サルコペニアも骨粗しょう症の予防も運動が重要ですが、ウェルナー症候群の患者さんの中には上で述べたように足底潰瘍ができやすく、また関節の拘縮がある方もおられるので、過度な運動は避け、できる範囲で負担の無い運動を取り入れることが重要です。

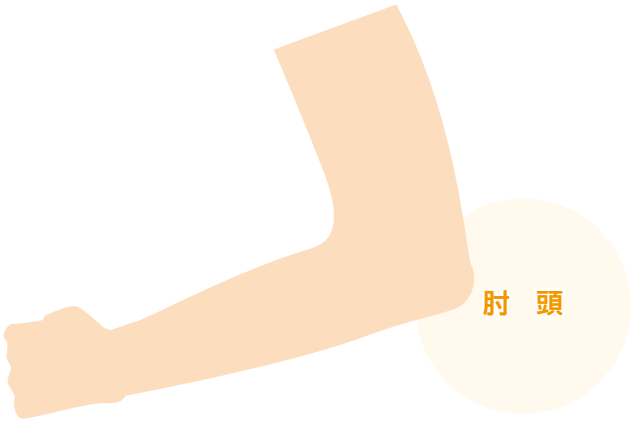
9 足の潰瘍（治りにくいキズ）

ウェルナー症候群では皮膚に治りにくいキズができやすいことが知られています。特にできやすい場所は、**肘、膝から下の足**です。

肘

肘の治りにくいキズは**肘の外側の出っ張ったところ（肘頭：ちゅうとう）**にできます。

皮膚が薄い部分でキズが肘関節の中とつながってしまうことがあるため注意が必要です。

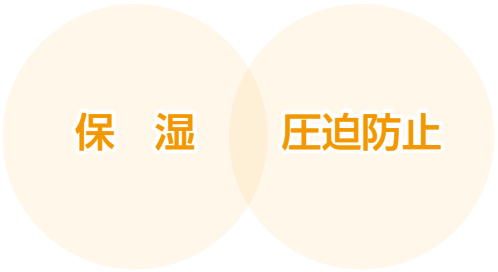


膝

特に治りにくいキズが出来やすい場所は、**アキレス腱のところ、くるぶし、かかと、足の裏、親指の内側、小指の外側**などです。皮膚が薄いため、キズが関節の中や骨の中につながってしまうことがります。

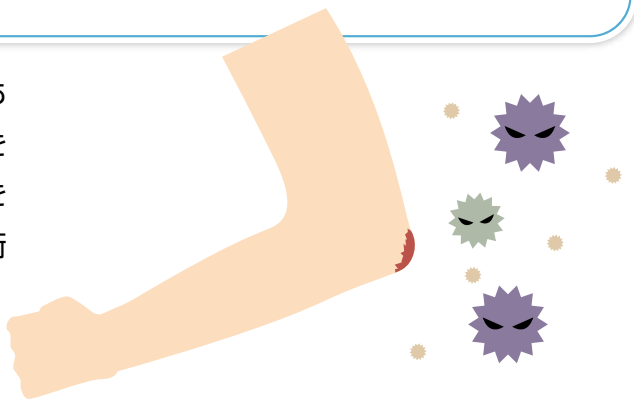
予　防

キズは一旦出来てしまうと治りにくいので予防が大切です。保湿と圧迫防止が大切です。圧迫のサインとしてタコができることがあります。タコを放置するとさらに皮膚が圧迫されてキズができるのでこまめに対処することが大切です。**タコができないようにするために足の形にあった靴を履きましょう。**



治　療

治りにくいキズのところにばい菌が溜まることがあります。ばい菌がそれ以上広がらないようにばい菌を外に出すことが必要です。また、ばい菌がついた組織を除去することも重要です。治りにくいキズに対して手術してふさぐこともあります。

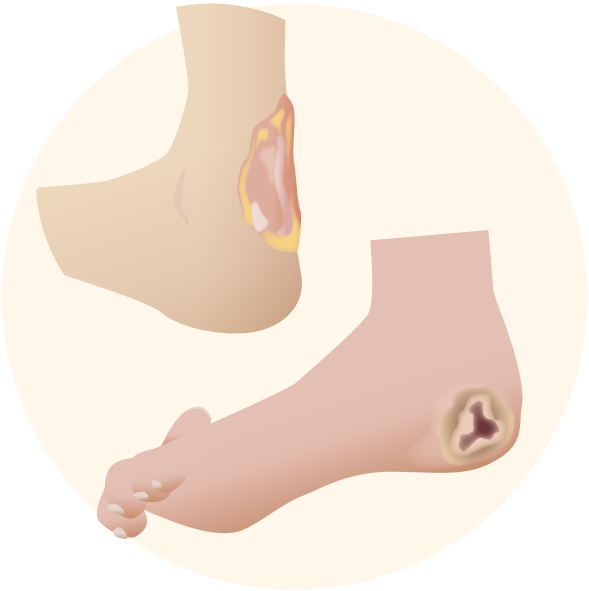


難治性潰瘍の予防・治療

ウェルナー症候群の患者さんは**皮膚にキズ（潰瘍）ができやすく、治りにくいという特徴**があります。特に**足の裏の荷重部位（体重がかかるところ）**にできやすいです。他にも、**アキレス腱部, 足関節, 肘関節**など圧のかかりやすい部位に多くみられます。

キズが治りにくい原因としては、皮膚が薄くなり硬くなっていることと脂肪が少なくなっていることが考えられます。クッションがなくなってしまい骨が直接当たってしまうような感じです。

また、血管が細くなり血流が悪くなってしまうことや、皮膚の中に石灰ができてしまうこと、関節の変形が起こることなども原因として考えられています。

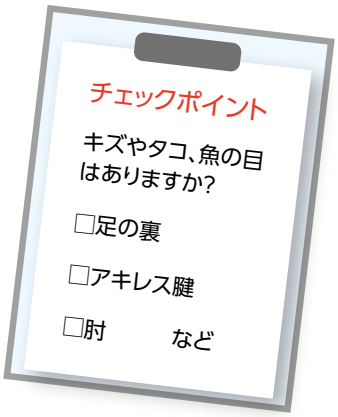


足の裏の体重がかかる部位には、いわゆる「タコ」（胼胝）や「魚の目」（鶏眼）ができやすく歩くときに当たって痛くなってしまいます。なるべく足の大きさにあった靴をはいて「靴擦れ」を防いだり、靴底に軟らかいソール（インソール）を入れたりして、一か所に体重がかからないようにする工夫が必要です。特殊な装具（靴）を作って、骨が出っ張ってキズになりやすい部位を保護する方法もありますので、専門の靴屋や装具販売店にご相談ください。

また、**常に足の裏やアキレス腱、肘などに、キズやタコ、魚の目ができていないかをチェック**してください。

タコや魚の目などの角質が厚くなっているところができはじめたら、早めに、角質を軟らかくする塗り薬や張り薬（尿素の入った角質軟化外用剤など色々あります）を塗る、もしくは貼ってください。角質を軟らかくする外用剤、貼付剤は薬局でも販売していますが、一度、皮膚科などの専門医にご相談ください。

塗り薬や張り薬を使ってもタコや魚の目がとれない場合は、はさみなどで切り取る方法がありますが、ご自身で行うとキズを作ってしまう可能性がありますので、皮膚科などの専門医で削り取ってください。



タコや魚の目を放っておくと、中央にキズができてしまい、なかなか治らなくなってしまいます。キズができてしまった場合には、細菌感染が起こらないように注意が必要です。毎日、石鹸などで良く洗浄して清潔に保ってください。きれいに洗い流したのちにキズを治す塗り薬を塗ってください。塗り薬はキズの具合に合わせた薬を使う必要があります。壊死した部分がある場合は、その部分を溶かすような薬が必要です。

また、赤い肉芽がでてきた場合は、さらに盛り上げてキズを小さくする薬が必要です。もし細菌感染を起こしてしまった場合は、消毒や感染を抑える塗り薬、抗菌剤の飲み薬が必要となります。細菌感染を起こしたり、キズが大きくなってしまうとなかなか治らなくなってしまいますので、キズができてしまったら、なるべく早く皮膚科専門医にご相談ください。

⑩ 腫瘍

悪性腫瘍とは

悪性腫瘍とは、ある細胞が体の中の秩序を無視して増え、周りの組織に広がったり、転移を起こしたりする腫瘍のことです。悪性腫瘍には上皮性腫瘍（癌）や非上皮性腫瘍（肉腫など）、白血病などの血液の腫瘍があります。癌と非上皮性腫瘍の発症する割合を比べると10:1程度と、一般的には癌が多く非上皮性腫瘍は稀です。

悪性腫瘍とウェルナー症候群

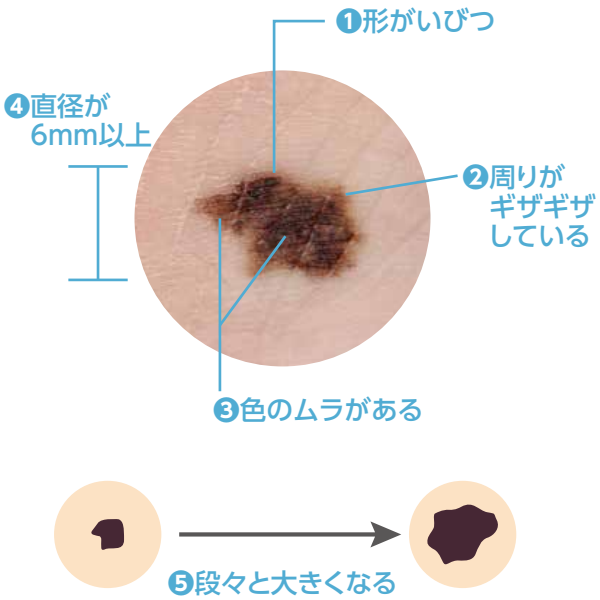
日本で行われた調査によると、ウェルナー症候群の方の約3割に悪性腫瘍が見つかり、比較的若い頃（40歳代）から発症する傾向があります。癌と非上皮性腫瘍の発症する割合は1:2程度と、通常稀な非上皮性腫瘍が多く、その中でも悪性黒色腫や悪性線維性組織球腫、髄膜腫瘍が多いと報告されています。癌では甲状腺癌が多くみられます。また1人に複数の悪性腫瘍が合併する多重癌（重複腫瘍）を発症することも少なくありません。最近、ウェルナー症候群の方の寿命が延長するにしたがって、癌が増えているとの報告もあります。

悪性腫瘍の検査と治療について

このように、ウェルナー症候群の方では悪性腫瘍に気をつける必要があります。できるだけ早く発見して、治療をするためにも定期的な人間ドックや癌検診を受けることが有用です。少なくとも3ヶ月に1回は採血・採尿検査を受け、半年から1年毎に胸部レントゲン写真、甲状腺エコー、腹部エコー、便潜血などの検査を受けることをお勧めします。またご自身で毎日全身を観察することも大切です。特に、皮膚に形がいびつな「ほくろ」ができた場合や皮膚の下にできた「こぶ」が大きくなってくる場合は主治医に相談してください。

悪性腫瘍は一般の方と同様に治療することができます。手足のキズの治りが悪いため、手術を心配される方もいらっしゃいますが、体の中心部（体幹部）の手術（例：肺癌）であればキズの治りも良く、一般の方と同様の手術が行われます。

悪性の「ほくろ」（悪性黒色腫）の特徴



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「早老症の医療水準やQOL向上を目指す集学的研究」

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協力：ウェルナー症候群患者家族の会

2021年3月

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疾患概要

（写真はプロジェリア研究財団のご厚意によるものです。ダウンロード、コピー、配布や修正を禁止します）

1. 「ハッチンソン・ギルフォード症候群」とはどのような病気ですか

1886 年に Jonathan Hutchinson と 1897 年に Hasting Gilford が報告したことから命名された疾患です。遺伝性早老症の中でも特に症状が重い疾患で、動脈硬化による 重篤 な脳や心臓の血管障害が 10 歳台で起こることが多く、平均寿命は 14.6 歳と報告されています。

2. この病気の患者さんはどのくらいいるのですか

きわめて稀な疾患で、国内で 10 例程度、全世界で 350～400 人の患者さんが報告されています。

3. この病気はどのような人に多いのですか

出生後から痩せ気味で皮下脂肪が少なく皮膚が厚く光沢があり、身長体重の伸びが著しく悪く、髪の毛も少なく四肢の関節が少し曲がった状態で十分伸びないのが特徴とされています。

4. この病気の原因はわかっているのですか

典型に分類される患者さんでは、LMNA 遺伝子内の点突然変異 c.1824C>T (p.Gly608Gly)によりプロジェリンと呼ばれる異常物質が産生されます。典型的な臨床表現型の患者さんの約 9 割がこの病的バリアントを保有しています。患者さんでは、加齢とともにプロジェリンが全身の細胞にたまってきて老化を引き起こすと考えられています。

5. この病気は遺伝するのですか

典型に分類されるほとんどの患者さんは LMNA 遺伝子の突然変異が原因のため通常は遺伝しません。LMNA 遺伝子を含めた核ラミナを構成する分子の遺伝子変異によるラミノパチーに分類される疾患の場合、タイプにより常染色体劣性や常染色体優性の遺伝形式をとります。

6. この病気ではどのような症状がおきますか

正常新生児として出生しますが、乳児期早期から皮膚が硬く光沢を帯びた感じに変化し、身長体重の伸びの著しい低下が現れてきます。乳幼児期から脱毛、前額突出、小顎等の早老様顔貌、皮膚の萎縮や硬化と関節拘縮（硬くて動きが悪くなること）が観察されるようになります。また、動脈硬化性疾患による重篤な脳血管障害や心血管疾患は加齢とともに顕在化し生命予後 を規定する重要な合併症です。悪性腫瘍は 10 歳前後から起こる合併症として重要です。

7. この病気にはどのような治療法がありますか

現時点では確立した治療法はありません。それぞれの症状に対する対症療法が主となりますが、近年Ｇタンパク質のファルネシル転移酵素阻害薬による治療が海外で試されており一定の効果が報告されています。そしてロナファルニブは、2020 年 11 月米国食品医薬品局（FDA）に医薬品として承認されました。国内の患者さんがこの治療薬を選択することができるように、ロナファルニブの国内承認の申請手続きを進めています。

8. この病気はどういう経過をたどるのですか

典型に分類される患者さんは 10 歳代でほぼ全例が亡くなってしまうと報告されています。一方で、非典型の患者さんでは 40 歳以上の長期生存例も報告されていますが、動脈硬化性の血管障害に加え，がんの発生（特に多重がん）に留意する必要があります。

9. この病気は日常生活でどのような注意が必要ですか

それぞれの症状に合わせた社会的サポートを受けて頂くことが大切です。また定期的な検査と予防療法が大切です。

10. この病気に関する資料・関連リンク

NPO 法人の Progeria Research Foundation が英語のホームページで詳細な情報・資料を公開しています（https://www.progeriaresearch.org/）。

トピックス

ファルネシル転移酵素阻害薬ロナファルニブは、2020 年 11 月米国食品医薬品局（FDA）に医薬品として承認されました。ハッチンソン・ギルフォード症候群に対して認可された世界で初めての医薬品です。

Leslie B. Gordon 氏らの報告によると、Eiger BioPharmaceuticals 社の薬剤 Zokinvy™（ロナファルニブ）の内服治療により、約 2 年間の観察期間で有意な死亡率の低下を認めました（3.7% vs 33.3%）（JAMA 2018）。

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ハッチンソン・ギルフォード症候群とは

１．疾患について

１．概要

遺伝性早老症の中で最も症状が重篤な疾患。生後半年から２年で水頭症様顔貌、禿頭、脱毛、小顎及び強皮症を呈しますが、精神運動機能や知能は正常です。脳梗塞、冠動脈疾患、心臓弁膜症、高血圧、耐糖能障害及び性腺機能障害を合併し平均寿命は 14.6 歳と報告されています。

難病研究班の全国調査で約 10 人の患者が確認されており、成人例も含まれます。国内で 20 歳を超えた生存例が報告されてます。頻度が高い合併症としては、脳血管障害、虚血性心疾患及び多重がんがあり、特に脳血管障害については繰り返し発症するという特徴があります。

２．原因

大多数の患者では、LMNA 遺伝子のエクソン 11 内の点突然変異（G608G, GGC>GGT）を認めます。 スプライシング異常が生じ、N 末の 50 アミノ酸が欠損した変異 Lamin A タンパク（progerin）が合成されます。変異タンパク progerin は、翻訳後のプロセッシング異常に伴い、タンパクのファルネシル化*注1が持続し、核膜や核内マトリックスに異常を生じると推定されています。

＊注１：ファルネシル化とは、タンパク質に行われる修飾の一種です（タンパク質修飾にはこの他に「リン酸化」、「アセチル化」、「ユビキチン化」などがあります）。ファルネシル化により、タンパク質の末端には疎水性のプレニル基が結合します。末端が疎水性になったタンパク質は、その疎水性の部分を細胞膜内に挿入するため、タンパク質は細胞膜（細胞の内側）につなぎ留められます。つまり、ファルネシル化されたタンパク質は、細胞の内側の細胞膜上に存在するようになります。

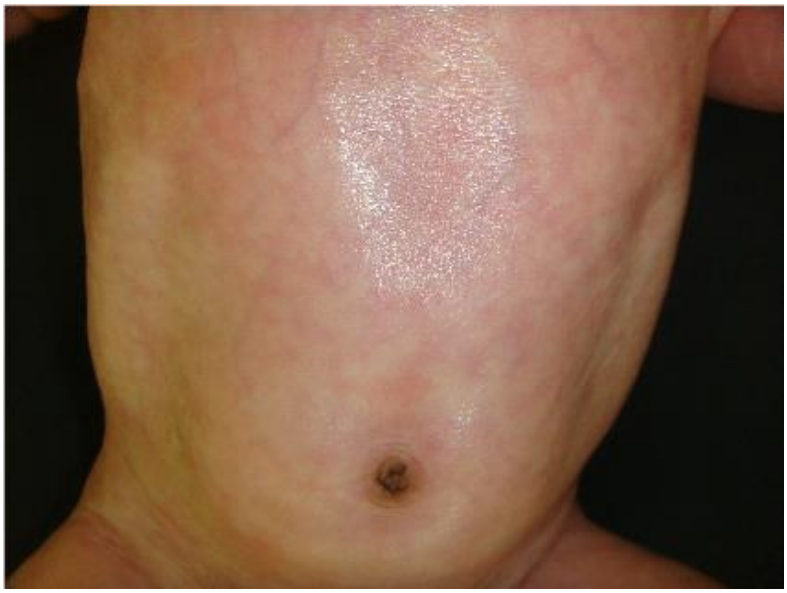
３．症状

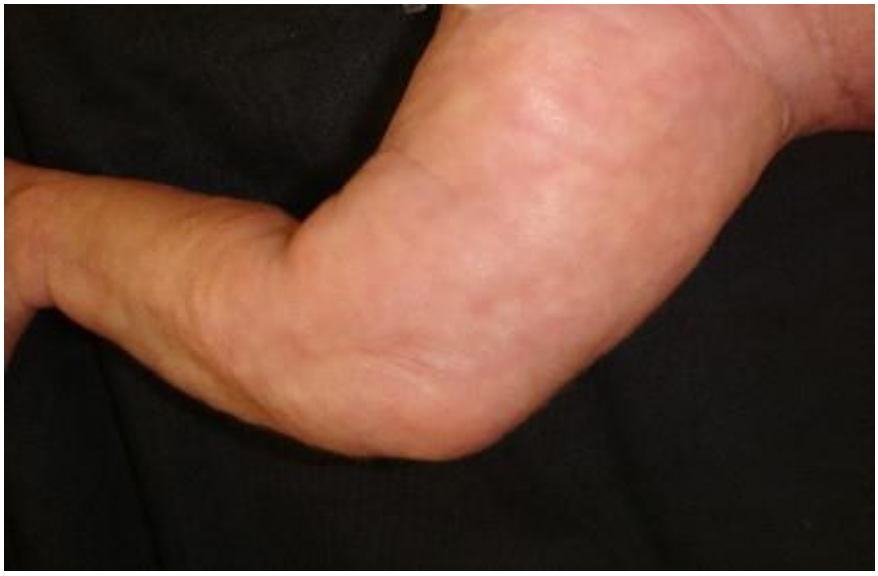
乳児期から全身の老化現象、成長障害及び特徴的顔貌を呈します。年齢を重ねるとともに、老化に伴う多彩な臨床徴候を呈します。

乳幼児期から脱毛、前額突出、小顎等の早老様顔貌並びに皮膚の萎縮、硬化及び関節拘縮がほぼ全例に観察されます。 動脈硬化性疾患による重篤な脳血管障害及び心血管疾患は加齢とともに顕在化し、生命予後を規定する重要な合併症です。

10 歳以上、特に成人期に至る長期生存例に認められる合併症として悪性腫瘍があります。

皮膚所見:





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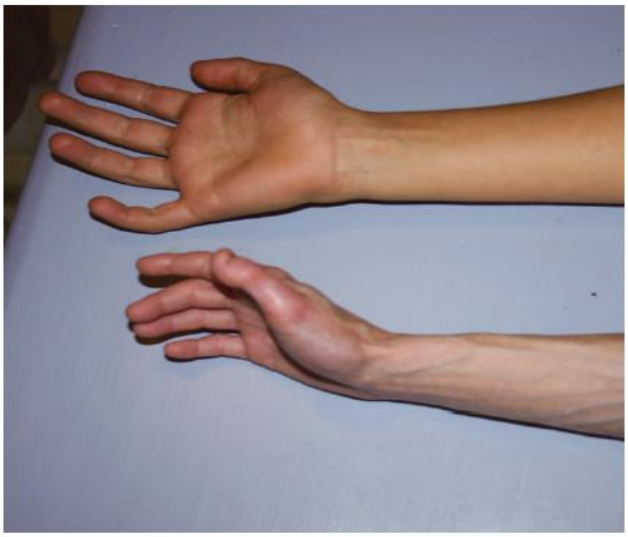
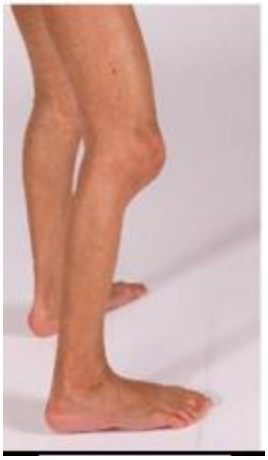
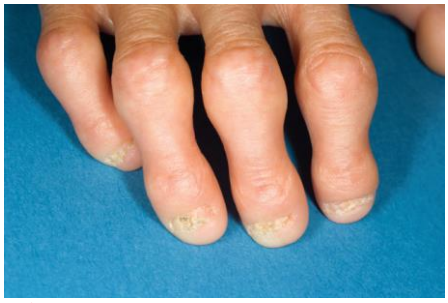
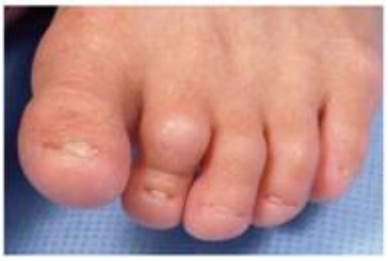

4. 治療法

現時点で国内では確立した治療法はありません。老化に伴う症状に対する対症療法のみです。

近年、Gタンパク質のファルネシル転移酵素（FT）阻害剤による治療が海外で試されており一定の効果が報告されています。ファルネシル転移酵素阻害薬ロナファルニブは、2020 年 11 月米国食品医薬品局（FDA）に医薬品として承認されました。

5. 予後

無治療では 10 歳代で患者の多くが死亡します。生命予後は極めて不良ですが、20 歳以上の生存例も報告されています。

Q and A

Q: この疾患を疑う必要があるのはどんな場合ですか？
A: 乳児期に体重と身長の伸びが極端に悪く、皮膚が 乾燥し関節が硬いなどの症状が現れてきます。

Q: ハッチンソン・ギルフォード症候群かもしれないと思ったら、どこに相談すればよいですか？
A: 公表されている診療ガイドラインなどに基づいて臨床診断を行うことは全国の医療施設で可能です。しかし稀な病気ですので、実際に診療経験がある医師・医療機関は国内で限られています。この疾患に関する最新の情報や遺伝子検査等の診断については、厚生労働省の早老症研究班の千葉大学（糖尿病・代謝・内分泌内科）、大分大学（小児科）、佐賀大学（小児科）、成育医療研究センター病院（遺伝診療科）などが対応しています。

Q: ハッチンソン・ギルフォード症候群の治療研究について情報を知りたいのですが。
A: 現時点で国内の研究施設が主体となった治療研究はありませんが、海外の施設の国際治験がいくつか進められています。詳細につきましては、Progeria Research Foundation に直接お問い合わせ頂くか、早老症研究班の佐賀大学(小児科学)までお問い合わせください。

診断基準と重症度分類

１．診断基準

＜診断基準＞

Definite 及び Probable を対象とする。

A. 大症状

1. 出生後の重度の成長障害（生後6か月以降の身長と体重が－3SD 以下）

２．白髪または脱毛、小顎、老化顔貌、突出した眼、の4症候中3症候以上

３．頭皮静脈の怒張、皮下脂肪の減少、強皮症様変化　の3症候中2症候以上

４．四肢関節拘縮と可動域制限

B. 小症状

１．胎児期には成長障害を認めない。

２．精神発達遅滞を認めない。

C. 遺伝学的検査

LMNA 遺伝子に G608G（コドン 608[GGC] > [GGT]）変異を認める。

＜診断のカテゴリー＞

Definite：Aのうち1つ以上＋Cを認めるもの

Probable：Aの4項目＋Bの2項目を認めるもの

２．重症度分類

＜重症度分類＞

以下の１）または２）のいずれかを満たすものを対象とする。

１）　心症状があり、薬物治療・手術によっても NYHA 分類で II 度以上に該当する場合

NYHA 分類

Ⅰ度	心疾患はあるが身体活動に制限はない。日常的な身体活動では疲労、動悸、呼吸困難、失神あるいは狭心痛（胸痛）を生じない。

II 度	軽度から中等度の身体活動の制限がある。安静時又は軽労作時には無症状。 日常労作のうち、比較的強い労作（例えば、階段上昇、坂道歩行など）で疲労、動悸、呼吸困難、失神あるいは狭心痛（胸痛）を生ずる。
III 度	高度の身体活動の制限がある。安静時には無症状。 日常労作のうち、軽労作（例えば、平地歩行など）で疲労、動悸、呼吸困難、失神あるいは狭心痛（胸痛）を生ずる。
IV 度	心疾患のためいかなる身体活動も制限される。 心不全症状や狭心痛（胸痛）が安静時にも存在する。 わずかな身体活動でこれらが増悪する。

NYHA：New York Heart Association

NYHA 分類については、以下の指標を参考に判断することとする。

NYHA 分類	身体活動能力 （Specific Activity Scale：SAS）	最大酸素摂取量 （peakVO2）
I	6 METs 以上	基準値の 80%以上
II	3.5～5.9 METs	基準値の 60～80%
III	2～3.4 METs	基準値の 40～60%
IV	1～1.9 METs 以下	施行不能あるいは 基準値の 40%未満

※NYHA 分類に厳密に対応する SAS はないが、
「室内歩行2METs、通常歩行 3.5METs、ラジオ体操・ストレッチ体操4METs、速歩5～6 METs、階段6～7METs」 をおおよその目安として分類した。

2）①modified Rankin Scale（mRS）、日本脳卒中学会による②食事・栄養、③呼吸のそれぞれの評価スケールを用いて、いずれかが3以上を対象とする。

①日本版 modified Rankin Scale （mRS）

日本版 modified Rankin Scale （mRS） 判定基準書		
modified Rankin Scale		参考にすべき点
0	全く症候がない	自覚症状及び他覚徴候がともにない状態である
1	症候はあっても明らかな障害はない： 日常の勤めや活動は行える	自覚症状及び他覚徴候はあるが、発症以前から行っていた仕事や活動に制限はない状態である
2	軽度の障害： 発症以前の活動が全て行えるわけではないが、自分の身の回りのことは介助なしに行える	発症以前から行っていた仕事や活動に制限はあるが、日常生活は自立している状態である
3	中等度の障害： 何らかの介助を必要とするが、歩行は介助なしに行える	買い物や公共交通機関を利用した外出などには介助を必要とするが、通常歩行、食事、身だしなみの維持、トイレなどには介助を必要としない状態である
4	中等度から重度の障害： 歩行や身体的要求には介助が必要である	通常歩行、食事、身だしなみの維持、トイレなどには介助を必要とするが、持続的な介護は必要としない状態である
5	重度の障害： 寝たきり、失禁状態、常に介護と見守りを必要とする	常に誰かの介助を必要とする状態である
6	死亡	

②日本脳卒中学会版　食事・栄養の評価スケール

食事・栄養（N）

0. 症候なし。
1. 時にむせる、食事動作がぎこちないなどの症候があるが、社会生活・日常生活に支障ない。
2. 食物形態の工夫や、食事時の道具の工夫を必要とする。
3. 食事・栄養摂取に何らかの介助を要する。
4. 補助的な非経口的栄養摂取（経管栄養、中心静脈栄養など）を必要とする。
5. 全面的に非経口的栄養摂取に依存している。

③日本脳卒中学会版　呼吸の評価スケール

呼吸（R）

0. 症候なし。
1. 肺活量の低下などの所見はあるが、社会生活・日常生活に支障ない。
2. 呼吸障害のために軽度の息切れなどの症状がある。
3. 呼吸症状が睡眠の妨げになる、あるいは着替えなどの日常生活動作で息切れが生じる。
4. 喀痰の吸引あるいは間欠的な換気補助装置使用が必要。
5. 気管切開あるいは継続的な換気補助装置使用が必要。

※診断基準及び重症度分類の適応における留意事項

1. 病名診断に用いる臨床症状、検査所見等に関して、診断基準上に特段の規定がない場合には、いずれの時期のものを用いても差し支えない（ただし、当該疾病の経過を示す臨床症状等であって、確認可能なものに限る。）。
2. 治療開始後における重症度分類については、適切な医学的管理の下で治療が行われている状態であって、直近6か月間で最も悪い状態を医師が判断することとする。
3. なお、症状の程度が上記の重症度分類等で一定以上に該当しない者であるが、高額な医療を継続することが必要なものについては、医療費助成の対象とする。

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ハンドブック

プロジェリア　ハンドブック

プロジェリアの子どもたちの家族と医療従事者のためのガイド

第2版

プロジェリア研究財団の使命は、ハッチンソン ギルフォード　プロジェリア症候群とそれに伴う心疾患を含む加齢関連の症状の原因、治療法、治癒への道を見つけることです。

さあ一緒に治癒を目指しましょう！

『プロジェリア ハンドブック：プロジェリアを持つ子どもたちの家族と医療従事者のためのガイド』第 2 版

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21.学校へ行くこと
22.プロジェリアと老化

プロジェリア研究財団（Progeria Research Foundation）の紹介

プロジェリア研究財団（PRF）はプロジェリアの子どもの両親であるレスリー・ゴードン医師、スコット・バーンズ医師、そしてプロジェリアの子どもたちの医師、患者、家族のための医療資源とプロジェリア研究のための資金の必要性を知った熱心な友人や家族により、1999 年に米国に設立されました。それ以来、PRF はプロジェリア遺伝子の歴史的発見と最初の治療法の発見を含むこの分野の進歩を促進する原動力となっています。
PRF はプロジェリアの子どもたちを支援するためのプログラムとプロジェリアの研究を行いたい研究者たちの包括的なネットワークを構築しました。PRF はプロジェリアとそれに伴う心臓病を含む加齢に関係した障害の治療法と治癒を見つけることに専念している唯一の世界的な非営利組織です。

正を禁止します)

＜4 ページ目＞

行政情報

公費負担医療制度

医療費の負担軽減と稀少疾患や難病に関する調査研究・医療の推進、患児・患者さんの自立支援を推進することを目的に、医療費の全部または一部を国や地方自治体が負担する制度で、医療費助成制度のひとつです。

●小児慢性特定疾病

ハッチンソン・ギルフォード症候群(21)

対象年令は 18 才未満です。

診断基準と「疾病の状態の程度」の基準を満たしていると受給が可能です。

複数の医療機関での入院・外来での医療費は合算されます。世帯の所得に応じた自己負担は必要です。指定医療機関での診察が対象です。

小児慢性特定疾　病情報センター

https://www.shouman.jp/disease/details/11_07_021/

重症患者認定基準

https://www.shouman.jp/assist/accreditation

●指定難病

ハッチンソン・ギルフォード症候群（指定難病３３３）

年令制限がありません。診断基準や重症度分類の要件があり、受給認定されれば、長期支援が受けられる可能性があります。

世帯の所得に応じた自己負担は必要です。指定医療機関での診察が対象です。

難病情報センター　https://www.nanbyou.or.jp/entry/6013

指定難病患者への医療費助成制度のご案内

https://www.nanbyou.or.jp/entry/5460

重症度分類(概要・診断基準等)

https://www.nanbyou.or.jp/entry/5466#333

●身体障害者手帳

身体障害者手帳は、身体の機能に一定以上の障害があると認められた方に交付される手帳です。視覚障害 ・ 聴覚又は平衡機能の障害 ・ 音声機能、言語機能又はそしゃく機能の障害 ・ 肢体不自由 ・ 心臓、じん臓又は呼吸器の機能の障害 ・ ぼうこう又は直腸の機能の障害 ・ 小腸の機能の障害 ・ ヒト免疫不全ウイルスによる免疫の機能の障害 ・ 肝臓の機能の障害がある方が対象です。障害の程度は、障害の種類別に重度の側から１級から６級の等級が定められています。認定には指定医療機関での診察が必要です。
具体的な手続方法等については、お住まいの市町村の担当窓口にお問い合わせください。
厚生労働省　身体障害者手帳
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hukushi_kaigo/shougaishahukushi/shougaishatechou/index.html
概要：
https://www.mhlw.go.jp/bunya/shougaihoken/shougaishatechou/dl/gaiyou.pdf

<5 ページ目>

症例登録

国内レジストリ：「準備中」

国際患者登録

プロジェリアは 2000 万人に 1 人発症すると言われています。プロジェリアは非常に珍しい病気のため、ほとんどの医師はプロジェリアの子どもに出会ったことがありません。さらに、そのような子どもを持つ家族が頼れるような地元の支援もほとんどないのです。PRF の国境を越えた患者登録のサービスは、家族やプロジェリアの子ども、医師や研究者にサービスや情報を提供し、プロジェリアの特性や過程についての理解を深めるために設立されました。プロジェリアの子どもを PRF に登録することで、このハンドブックや臨床試験の機会、最新の研究結果など、患者やその家族にとって有益で新しい情報に素早くアクセスできるようになります。
詳細については www.progeriaresearch.org/patient_registry.html をご覧ください。

出版物

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The clinical characteristics of Asian patients with classical-type Hutchinson-Gilford progeria syndrome. J Hum Genet. 62(12):1031-1035, 2017

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ハッチンソン・ギルフォード・プロジェリア症候群と老化
老年医学（上）―基礎・臨床研究の最新動向―
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重篤な遺伝性早老症：ハッチンソン・ギルフォード・プロジェリア症候群
内分泌症候群(第 3 版)
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核膜蛋白質ラミン A の異常が引き起こす早老症のメカニズム

医学のあゆみ　272(2) 162-167, 2020

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TEL: 03-3416-0181 / FAX: 03-3416-2222

ハッチンソン・ギルフォード症候群

「早老症の医療水準やＱＯＬ向上を目指す集学的研究」研究班

ホーム
診断基準
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リンク・出版物・問い合わせ先

- 難病情報センター
- 小児慢性特定疾病対策事業
- The Progeria Research Foundation
- 重症患者認定基準
- 重症度分類(概要・診断基準等)
- 厚生労働省　身体障害者手帳
- 身体障害者手帳制度の概要

疾患概要

（写真はプロジェリア研究財団のご厚意によるものです。ダウンロード、コピー、配布や修正を禁止します）

1. 「ハッチンソン・ギルフォード症候群」とはどのような病気ですか
1886年にJonathan Hutchinsonと1897年にHasting Gilfordが報告したことから命名された疾患です。遺伝性早老症の中でも特に症状が重い疾患で、動脈硬化による 重篤 な脳や心臓の血管障害が10歳台で起こることが多く、平均寿命は14.6歳と報告されています。

2. この病気の患者さんはどのくらいいるのですか
きわめて稀な疾患で、国内で10例程度、全世界で350～400人の患者さんが報告されています。

3. この病気はどのような人に多いのですか
出生後から痩せ気味で皮下脂肪が少なく皮膚が厚く光沢があり、身長体重の伸びが著しく悪く、髪の毛も少なく四肢の関節が少し曲がった状態で十分伸びないのが特徴とされています。

4. この病気の原因はわかっているのですか
典型に分類される患者さんでは、LMNA遺伝子内の点突然変異 c.1824C>T (p.Gly608Gly)により プロジェリンと呼ばれる異常物質が産生されます。典型的な臨床表現型の患者さんの約9割がこの病的バリアントを保有しています。患者さんでは、加齢とともにプロジェリンが全身の細胞にたまってきて老化を引き起こすと考えられています。

5. この病気は遺伝するのですか
典型に分類されるほとんどの患者さんはLMNA遺伝子の突然変異が原因のため通常は遺伝しません。LMNA遺伝子を含めた核ラミナを構成する分子の遺伝子変異によるラミノパチーに分類される疾患の場合、タイプにより常染色体劣性や常染色体優性の遺伝形式をとります。

6. この病気ではどのような症状がおきますか
正常新生児として出生しますが、乳児期早期から皮膚が硬く光沢を帯びた感じに変化し、身長体重の伸びの著しい低下が現れてきます。乳幼児期から脱毛、前額突出、小顎等の早老様顔貌、皮膚の萎縮や硬化と関節拘縮（硬くて動きが悪くなること）が観察されるようになります。また、動脈硬化性疾患による重篤な脳血管障害や心血管疾患は加齢とともに顕在化し 生命予後 を規定する重要な合併症です。悪性腫瘍は10歳前後から起こる合併症として重要です。

7. この病気にはどのような治療法がありますか
現時点では確立した治療法はありません。それぞれの症状に対する対症療法が主となりますが、近年Ｇタンパク質のファルネシル転移酵素阻害薬による治療が海外で試されており一定の効果が報告されています。そしてロナファルニブは、2020年11月米国食品医薬品局（FDA）に医薬品として承認されました。国内の患者さんがこの治療薬を選択することができるように、ロナファルニブの国内承認の申請手続きを進めています。

8. この病気はどういう経過をたどるのですか
典型に分類される患者さんは10歳代でほぼ全例が亡くなってしまうと報告されています。一方で、非典型の患者さんでは40歳以上の長期生存例も報告されていますが、動脈硬化性の血管障害に加え、がんの発生（特に多重がん）に留意する必要があります。

9. この病気は日常生活でどのような注意が必要ですか
それぞれの症状に合わせた社会的サポートを受けて頂くことが大切です。また定期的な検査と予防療法が大切です。

10. この病気に関する資料・関連リンク
NPO法人のProgeria Research Foundationが英語のホームページで詳細な情報・資料を公開しています (https://www.progeriaresearch.org/) 。

トピックス

ファルネシル転移酵素阻害薬ロナファルニブは、2020年11月米国食品医薬品局（FDA）に医薬品として承認されました。ハッチンソン・ギルフォード症候群に対して認可された世界で初めての医薬品です。

Leslie B. Gordon氏らの報告によると、Eiger BioPharmaceuticals 社の薬剤Zokinvy™（ロナファルニブ）の内服治療により、約2年間の観察期間で有意な死亡率の低下を認めました（3.7% vs 33.3%）（JAMA 2018）。

トピックス一覧へ

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ハッチンソン・ギルフォード症候群

「早老症の医療水準やＱＯＬ向上を目指す集学的研究」研究班

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- The Progeria Research Foundation
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- 重症度分類(概要・診断基準等)
- 厚生労働省　身体障害者手帳
- 身体障害者手帳制度の概要

ホーム > ハッチンソン・ギルフォード症候群とは

ハッチンソン・ギルフォード症候群とは

疾患について

概要

遺伝性早老症の中で最も症状が重篤な疾患。生後半年から２年で水頭症様頭貌、禿頭、脱毛、小顎及び強皮症を呈しますが、精神運動機能や知能は正常です。脳梗塞、冠動脈疾患、心臓弁膜症、高血圧、耐糖能障害及び性腺機能障害を合併し平均寿命は14.6歳と報告されています。

難病研究班の全国調査で約10人の患者が確認されており、成人例も含まれます。国内で20歳を超えた生存例が報告されてます。頻度が高い合併症としては、脳血管障害、虚血性心疾患及び多重がんがあり、特に脳血管障害については繰り返し発症するという特徴があります。

原因

大多数の患者では、LMNA遺伝子のエクソン11内の点突然変異（G608G, GGC>GGT）を認めます。スプライシング異常が生じ、N末の50アミノ酸が欠損した変異Lamin Aタンパク（progerin）が合成されます。変異タンパクprogerinは、翻訳後のプロセッシング異常に伴い、タンパクのファルネシル化＊注1が持続し、核膜や核内マトリックスに異常を生じると推定されています。

＊注1：ファルネシル化とは、タンパク質に行われる修飾の一種です（タンパク質修飾にはこの他に「リン酸化」、「アセチル化」、「ユビキチン化」などがあります）。ファルネシル化により、タンパク質の末端には疎水性のプレニル基が結合します。末端が疎水性になったタンパク質は、その疎水性の部分を細胞膜内に挿入するため、タンパク質は細胞膜（細胞の内側）につなぎ留められます。つまり、ファルネシル化されたタンパク質は、細胞の内側の細胞膜上に存在するようになります。

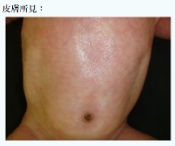
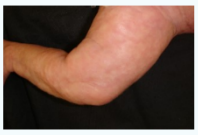
症状

乳児期から全身の老化現象、成長障害及び特徴的顔貌を呈します。年齢を重ねるとともに、老化に伴う多彩な臨床徴候を呈します。

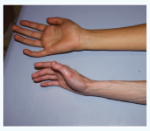
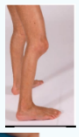
乳幼児期から脱毛、前額突出、小顎等の早老様顔貌並びに皮膚の萎縮、硬化及び関節拘縮が注目全例に観察されます。動脈硬化性疾患による重篤な脳血管障害及び心血管疾患は加齢とともに顕在化し、生命予後を規定する重要な合併症です。

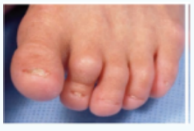
10歳以上、特に成人期に至る長期生存例に認められる合併症として悪性腫瘍があります。

皮膚所見：

関節拘縮：



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治療法

現時点で国内では確立した治療法はありません。老化に伴う症状に対する対症療法のみです。

近年、Gタンパク質のファルネシル転移酵素（FT）阻害剤による治療が海外で試されており一定の効果が報告されています。ファルネシル転移酵素阻害薬ロナファルニブは、2020年11月米国食品医薬品局（FDA）に医薬品として承認されました。

予後

無治療では10歳代で患者の多くが死亡します。生命予後は極めて不良ですが、20歳以上の生存例も報告されています。

Q and A

Q:　この疾患を疑う必要があるのはどんな場合ですか？

A:　乳児期に体重と身長の伸びが極端に悪く、皮膚が乾燥し関節が硬いなどの症状が現れてきます。

Q:　ハッチンソン・ギルフォード症候群かもしれないと思ったら、どこに相談すればよいですか？

A:　公表されている診療ガイドラインなどに基づいて臨床診断を行うことは全国の医療施設で可能です。しかし稀な病気ですので、実際に診療経験がある医師・医療機関は国内で限られています。この疾患に関する最新の情報や遺伝子検査等の診断については、厚生労働省の早老症研究班の千葉大学（膠原病・代謝・内分泌内科）、大分大学（小児科）、佐賀大学（小児科）、成育医療研究センター病院（遺伝診療科）などが対応しています。

Q:　ハッチンソン・ギルフォード症候群の治療研究について情報を知りたいのですが。

A:　現時点で国内の研究施設が主体となった治療研究はありませんが、海外の施設の国際治験がいくつか進められています。詳細につきましては、Progeria Research Foundationに直接お問い合わせ頂くか、早老症研究班の佐賀大学(小児科学)までお問い合わせください。

診断基準と重症度分類

診断基準

診断基準

Definite及びProbableを対象とする。

A. 主症状
1. 出生後の重度の成長障害（生後６か月以降の身長と体重が－3SD以下）
2. 白髪または脱毛、小顎、老化顔貌、突出した眼、の４症候中３症候以上
3. 頭皮静脈の怒張、皮下脂肪の減少、強皮症様変化　の３症候中２症候以上
4. 四肢関節拘縮と可動域制限

B. 小症状
1. 胎児期には成長障害を認めない。
2. 精神発達遅滞を認めない。

C. 遺伝学的検査
LMNA 遺伝子にG608G（コドン608[GGC]>[GGT]）変異を認める。

診断のカテゴリー

Definite：Aのうち１つ以上＋Cを認めるもの

Probable：Aの４項目＋Bの２項目を認めるもの

重症度分類

重症度分類

以下の１）または２）のいずれかを満たすものを対象とする。

１）　心症状があり、薬物治療・手術によってもNYHA分類でII度以上に該当する場合

NYHA分類

I度	心疾患はあるが身体活動に制限はない。 日常的な身体活動では疲労、動悸、呼吸困難、失神あるいは狭心痛（胸痛）を生じない。
II度	軽度から中等度の身体活動の制限がある。安静時又は軽労作時には無症状。 日常労作のうち、比較的強い労作（例えば、階段上昇、坂道歩行など）で疲労、動悸、呼吸困難、失神あるいは狭心痛（胸痛）を生ずる。
III度	高度の身体活動の制限がある。安静時には無症状。 日常労作のうち、軽労作（例えば、平地歩行など）で疲労、動悸、呼吸困難、失神あるいは狭心痛（胸痛）を生ずる。
IV度	心疾患のためいかなる身体活動も制限される。 心不全症状や狭心痛（胸痛）が安静時にも存在する。 わずかな身体活動でこれらが増悪する。

NYHA：New York Heart Association

NYHA分類については、以下の指標を参考に判断することとする。

NYHA分類	身体活動能力 （Specific Activity Scale：SAS）	最大酸素摂取量 （peakVO2）
I	6 METs以上	基準値の80％以上
II	3.5～5.9 METs	基準値の60～80％
III	2～3.4 METs	基準値の40～60％
IV	1～1.9 METs以下	施行不能あるいは 基準値の40％未満

※NYHA分類に厳密に対応するSASはないが、「室内歩行２METs、通常歩行3.5METs、ラジオ体操・ストレッチ体操４METs、速歩５～６METs、階段６～７METs」をおおよその目安として分類した。

２）①modified Rankin Scale（mRS）、日本脳卒中学会による②食事・栄養、③呼吸のそれぞれの評価スケールを用いて、いずれかが３以上を対象とする。

①日本版modified Rankin Scale（mRS）

日本版modified Rankin Scale（mRS）判定基準書		
modified Rankin Scale		参考にすべき点
0	全く症候がない	自覚症状及び他覚徴候がともにない状態である
1	症候はあっても明らかな障害はない： 日常の勤めや活動は行える	自覚症状及び他覚徴候はあるが、発症以前から行っていた仕事や活動に制限はない状態である
2	軽度の障害： 発症以前の活動が全て行えるわけではないが、自分の身の回りのことは介助なしに行える	発症以前から行っていた仕事や活動に制限はあるが、日常生活は自立している状態である
3	中等度の障害： 何らかの介助を必要とするが、歩行は介助なしに行える	買い物や公共交通機関を利用した外出などには介助を必要とするが、通常歩行、食事、身だしなみの維持、トイレなどには介助を必要としない状態である
4	中等度から重度の障害： 歩行や身体的要求には介助が必要である	通常歩行、食事、身だしなみの維持、トイレなどには介助を必要とするが、持続的な介護は必要としない状態である
5	重度の障害： 寝たきり、失禁状態、常に介護と見守りを必要とする	常に誰かの介助を必要とする状態である
6	死亡	

②日本脳卒中学会版　食事・栄養の評価スケール

食事・栄養（N）
0. 症候なし。
1. 時にむせる、食事動作がぎこちないなどの症候があるが、社会生活・日常生活に支障ない。
2. 食物形態の工夫や、食事時の道具の工夫を必要とする。
3. 食事・栄養摂取に何らかの介助を要する。
4. 補助的な非経口的栄養摂取（経管栄養、中心静脈栄養など）を必要とする。
5. 全面的に非経口的栄養摂取に依存している。

③日本脳卒中学会版　呼吸の評価スケール

呼吸（R）
0. 症候なし。
1. 肺活量の低下などの所見はあるが、社会生活・日常生活に支障ない。
2. 呼吸障害のために軽度の息切れなどの症状がある。
3. 呼吸症状が睡眠の妨げになる、あるいは着替えなどの日常生活動作で息切れが生じる。
4. 喀痰の吸引あるいは間欠的な換気補助装置使用が必要。
5. 気管切開あるいは継続的な換気補助装置使用が必要。

※診断基準及び重症度分類の適応における留意事項

1. 病名診断に用いる臨床症状、検査所見等に関して、診断基準上に特段の規定がない場合には、いずれの時期のものを用いても差し支えない（ただし、当該疾病の経過を示す臨床症状等であって、確認可能なものに限る。）。
2. 治療開始後における重症度分類については、適切な医学的管理の下で治療が行われている状態であって、直近６か月間で最も悪い状態を医師が判断することとする。
3. なお、症状の程度が上記の重症度分類等で一定以上に該当しない者であるが、高額な医療を継続することが必要なものについては、医療費助成の対象とする。

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ハンドブック

プロジェリア　ハンドブック

プロジェリアの子どもたちの家族と医療従事者のためのガイド

第2版

プロジェリア研究財団の使命は、ハッチンソン ギルフォード　プロジェリア症候群とそれに伴う心疾患を含む加齢関連の症状の原因、治療法、治癒への道を見つけることです。

さあ一緒に治癒を目指しましょう！

「プロジェリア ハンドブック：プロジェリアを持つ子どもたちの家族と医療従事者のためのガイド」第2版

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プロジェリア研究財団（Progeria Research Foundation）の紹介

プロジェリア研究財団（PRF）はプロジェリアの子どもの両親であるレスリー・ゴードン医師、スコット・バーンズ医師、そしてプロジェリアの子どもたちの医師、患者、家族のための医療資源とプロジェリア研究のための資金の必要性を知った熱心な友人や家族により、1999年に米国に設立されました。それ以来、PRFはプロジェリア遺伝子の歴史的発見と最初の治療法の発見を含むこの分野の進歩を促進する原動力となっています。

PRFはプロジェリアの子どもたちを支援するためのプログラムとプロジェリアの研究を行いたい研究者たちの包括的なネットワークを構築しました。PRFはプロジェリアとそれに伴う心臓病を含む加齢に関係した障害の治療法と治癒を見つけることに専念している唯一の世界的な非営利組織です。

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行政情報

公費負担医療制度

医療費の負担軽減と稀少疾患や難病に関する調査研究・医療の推進、患児・患者さんの自立支援を推進することを目的に、医療費の全部または一部を国や地方自治体が負担する制度で、医療費助成制度のひとつです。

小児慢性特定疾病

ハッチンソン・ギルフォード症候群(21)
対象年令は18才未満です。
診断基準と「疾病の状態の程度」の基準を満たしていると受給が可能です。
複数の医療機関での入院・外来での医療費は合算されます。世帯の所得に応じた自己負担は必要です。指定医療機関での診察が対象です。
小児慢性特定疾病情報センター
https://www.shouman.jp/disease/details/11_07_021/
重症患者認定基準
https://www.shouman.jp/assist/accreditation

指定難病

ハッチンソン・ギルフォード症候群（指定難病３３３）
年令制限がありません。診断基準や重症度分類の要件があり、受給認定されれば、長期支援が受けられる可能性があります。
世帯の所得に応じた自己負担は必要です。指定医療機関での診察が対象です。
難病情報センター
https://www.nanbyou.or.jp/entry/6013
指定難病患者への医療費助成制度のご案内
https://www.nanbyou.or.jp/entry/5460
重症度分類(概要・診断基準等)
https://www.nanbyou.or.jp/entry/5466#333

身体障害者手帳

身体障害者手帳は、身体の機能に一定以上の障害があると認められた方に交付される手帳です。
視覚障害・聴覚又は平衡機能の障害・音声機能、言語機能又はそしゃく機能の障害・肢体不自由・心臓、じん臓又は呼吸器の機能の障害・ぼうこう又は直腸の機能の障害・小腸の機能の障害・ヒト免疫不全ウイルスによる免疫の機能の障害・肝臓の機能の障害がある方が対象です。
障害の程度は、障害の種類別に重度の側から１級から６級の等級が定められています。認定には指定医療機関での診察が必要です。
具体的な手続方法等については、お住まいの市町村の担当窓口にお問い合わせください。
厚生労働省　身体障害者手帳
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hukushi_kaigo/shougaishahukushi/shougaishatechou/index.html
概要：
https://www.mhlw.go.jp/bunya/shougaihoken/shougaishatechou/dl/gaiyou.pdf：

症例登録

国内レジストリ：「準備中」

国際患者登録

プロジェリアは2000万人に1人発症すると言われています。プロジェリアは非常に珍しい病気のため、ほとんどの医師はプロジェリアの子どもに出会ったことがありません。さらに、そのような子どもを持つ家族が頼れるような地元の支援もほとんどないのです。PRFの国境を越えた患者登録のサービスは、家族やプロジェリアの子ども、医師や研究者にサービスや情報を提供し、プロジェリアの特性や過程についての理解を深めるために設立されました。プロジェリアの子どもをPRFに登録することで、このハンドブックや臨床試験の機会、最新の研究結果など、患者やその家族にとって有益で新しい情報に素早くアクセスできるようになります。
詳細については www.progeriaresearch.org/patient_registry.html をご覧ください。

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Sato-Kawano N, Takemoto M, Okabe E, Yokote K, Matsuo M, Kosaki R, Ihara K:
The clinical characteristics of Asian patients with classical-type Hutchinson-Gilford progeria syndrome. J Hum Genet. 62(12):1031-1035, 2017

井原健二：
ハッチンソン・ギルフォード・プロジェリア症候群と老化
老年医学（上）—基礎・臨床研究の最新動向—
日本臨床 76巻増刊号. pp186-188 （2018年6月）

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内分泌症候群(第3版)
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核膜蛋白質ラミンAの異常が引き起こす早老症のメカニズム
医学のあゆみ　272(2) 162-167, 2020

問い合わせ先

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ハッチンソン-ギルフォード プロジェリア症候群
(Hutchinson—Gilford Progeria syndrome)

GeneReviews著者: Leslie B Gordon, MD, PhD, W Ted Brown, MD, PhD, and Francis S Collins, MD, PhD
日本語訳者:小崎　里華(国立成育医療研究センター　遺伝診療科)

GeneReviews最終更新日: 2019.1.17　日本語訳最終更新日: 2021.1.13.

原文　Hutchinson—Gilford Progeria syndrome

要約

疾患の特徴

ハッチンソン-ギルフォード早老症候群（HGPS）は、通常、小児期に発症し、早老症状に似た臨床所見を特徴とする。HGPSの小児は通常、出生時は正常である。生後1年以内に重度の成長障害を呈する。特徴的な顔貌としては、顔に対して相対的大頭、狭い鼻隆起、狭い鼻尖、薄い上下口唇、小さな口、および下顎の後退、小顎症である。一般的な特徴には、皮下脂肪の減少、歯牙の萌出遅延と乳歯の喪失、腹部と大腿上部に小さな膨らみを生じる異常な皮膚、禿頭、爪の形成異常、股関節外反、および進行性の関節拘縮を含む。その後、低周波の伝音性難聴、歯義生および永久歯の一部欠損を呈する。精神運動発達は正常である。重度のアテローム性動脈硬化症の合併症としての心臓病（心筋梗塞、心不全）または脳血管疾患（脳卒中）によって、一般に6歳から20歳の間に死亡する。平均寿命は約14.5歳である。

診断・検査

古典的又は非古典的HGPSの遺伝子型の診断は、特徴的な臨床症状を有する発端者に異常ラミンAタンパク質であるプロジェリンを産生するヘテロ接合性の病的ヴァリアントを同定することによる。
古典的な遺伝子型HGPSは、ヘテロ接合性の*LMNA*の病的ヴァリアントc.1824C>Tを有する（HGPSの約90%）。非古典的遺伝子型HGPSは、HGPSの特徴的な臨床的症状をもち、*LMNA*のエクソン11またはイントロン11にあるプロジェリンを産生するヘテロ接合性の異なる病的ヴァリアントを有する（HGPSの約10%）。

臨床的マネジメント

定期的に少量の食事を頻回に摂取する食事療法が推奨される。歯義生を避けるため、永久歯萌出後に乳歯の抜歯を勧める。屋外での活動には、頭部を含む皮膚のすべての露出部分に日焼け止めの使用をすすめる。股関節脱臼には、理学療法と体幹装具が最も勧められる。股関節再建手術は可能だが、高リスク集団における手術の合併症を考慮する必要がある。体脂肪の減少により、下肢の疼痛を生じるかもしれない。靴パッドの使用により、この疼痛は軽減できる。日常的な理学療法と作業療法、積極的なストレッチおよび水中運動による強化エクササイズが推奨される。

脳卒中のリスクを最小限に抑えるために、身体活動を奨励しながら、最適な水分補給を維持する。心臓血管および神経血管の合併症に抗凝固療法は必要である。投薬量は年齢ではなく、体重または体表面積に基づく。ニトログリセリンは狭心症に有用で、うっ血性心不全の治療には、通常うっ血防止療法が行われる。全身麻酔と挿管は、細心の注意を払い、可能であれば、気管支ファイバー挿管が理想的である。ドライアイは、眼の潤滑剤で治療する。補聴器は、臨床的に必要な場合に使用する。通常、身体的に適応した年齢に応じた学校教育が推奨される。

二次合併症の予防：
心血管および脳卒中の合併症の予防には、低用量のアスピリン（2~3 mg / kg体重）が推奨される。硬化した末梢血管系は脱水症に対する耐性が低い可能性があり、経口で最適な水分補給を維持することを勧める。

サーベイランス：
半年ごとの心電図、年ごとの心エコー、頸動脈二重超音波検査、神経学的検査、頭頸部MRI / MRA、脂質プロファイル、歯科検査、無血管性壊死および進行性股関節外反を評価するための股関節X線、骨密度測定の二重X線吸収測定法/末梢皮膚CT、関節拘縮の理学療法評価、眼科検査、聴力検査、および日常生活の活動の評価。

避けるべきエージェント/状況：
脱水症; 背の高い/大きな仲間が集う大勢の集団による怪我のリスク、股関節脱臼のリスクを伴うトランポリンや乗馬。身体活動は自己で制限管理するべきである。

遺伝カウンセリング

ほぼすべてのHGPSは、新規の常染色体優性遺伝の病的のヴァリアントによる。発端者の同胞への再発リスクは小さいが（HGPSは通常、新規の病的ヴァリアントによって生じるため）、親の生殖細胞系列モザイクの可能性があるため、一般集団のリスクよりも高い。*LMNA*の病的のヴァリアントが家系内に同定されている場合、一般集団より高いリスクのため、妊娠中の出生前検査は可能である。

Gene reviewスコープ

ハッチンソン-ギルフォード プロジェリア症候群：含まれる遺伝子型
• ハッチンソン-ギルフォード プロジェリア症候群（HGPS）、古典的
• 非典型ハッチンソン-ギルフォード プロジェリア症候群

令和 3 年 3 月 24 日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学　長

氏　名　徳久　剛史　　印

次の職員の令和 2 年度厚生労働科学研究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　難治性疾患政策研究事業

2．研究課題名　早老症の医療水準やQOL向上を目指す集学的研究

3．研究者名　（所属部局・職名）　大学院医学研究院・教授

（氏名・フリガナ）　横手幸太郎・ヨコテコウタロウ

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	■	□	■	千葉大学	□
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）	■	□	■	千葉大学	□
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

国立保健医療科学院長　殿

機関名　国際医療福祉大学

所属研究機関長　職　名　学長

氏　名　大友　邦　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やＱＯＬ向上を目指す集学的研究

３．研究者名　（所属部局・職名）　医学部・主任教授

（氏名・フリガナ）　竹本　稔（タケモト　ミノル）

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）未審査の場合は、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 2月 24日

国立保健医療科学院長　殿

機関名　国立大学法人大阪大学
所属研究機関長　職　名　大学院医学系研究科長
氏　名　森井　英一　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やQOL向上を目指す集学的研究

３．研究者名　（所属部局・職名）大学院医学系研究科・寄附講座教授

（氏名・フリガナ）中神　啓徳（ナカガミ　ヒロノリ）

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	■　□	■	京都大学大学院医学系研究科・医学部及び医学部附属病院	□
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）	■　□	■	大阪大学医学部附属病院	□
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 24 日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学　長

氏　名　徳久　剛史　　印

次の職員の令和 2 年度厚生労働科学研究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　難治性疾患政策研究事業

2．研究課題名　早老症の医療水準やQOL向上を目指す集学的研究

3．研究者名　（所属部局・職名）　大学院医学研究院　形成外科・准教授

（氏名・フリガナ）　窪田吉孝・クボタヨシタカ

4．倫理審査の状況

	該当性の有無 有　無	左記で該当がある場合のみ記入（※1）		
		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24日

国立保健医療科学院長　殿

機関名　国立大学法人群馬大学

所属研究機関長 職　名　学　長

氏　名　平塚　浩士　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やＱＯＬ向上を目指す集学的研究

３．研究者名　（所属部局・職名）　群馬大学大学院医学系研究科皮膚科学　教授

（氏名・フリガナ）　茂木　精一郎　・　モテギ　セイイチロウ

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）	☑	□	☑	群馬大学医学部附属病院	□
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（2021年）３月２２日

国立保健医療科学院長　殿

機関名　　国立大学法人大分大学
所属研究機関長　職　名　　学長
氏　名　　北野　正剛　　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やＱＯＬ向上を目指す集学的研究

３．研究者名　（所属部局・職名）　医学部　小児科学講座・教授

（氏名・フリガナ）　井原　健二・イハラ　ケンジ

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）	☑	□	☑	大分大学医学部	□
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）未審査の場合は、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　16　日

国立保健医療科学院長　殿

機関名　国立大学法人東海国立大学機構
名古屋大学未来社会創造機構

所属研究機関長　職　名　機構長

氏　名　佐宗　章弘　　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やＱＯＬ向上を目指す集学的研究

３．研究者名　（所属部局・職名）　未来社会創造機構・教授

（氏名・フリガナ）　葛谷雅文・クズヤマサフミ

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）	■	□	■	名古屋大学	□
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）未審査の場合は、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　4月　23日

国立保健医療科学院長 殿

機関名　佐賀大学

所属研究機関長　職　名　学長

氏　名　兒玉　浩明　　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やQOL向上を目指す集学的研究

３．研究者名　（所属部局・職名）　医学部　教授

（氏名・フリガナ）　松尾　宗明　（ マツオ　ムネアキ ）

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）	□　■	□		□
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３日

国立保健医療科学院長　殿

機関名　公立大学法人奈良県立医科大学

所属研究機関長　職　名　理事長

氏　名　細井　裕司　　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やQOL向上を目指す集学的研究

３．研究者名　（所属部局・職名）　医学部・准教授

（氏名・フリガナ）　谷口　晃・タニグチ　アキラ

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）	■	□	■	奈良県立医科大学	□
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 ２ 月２６ 日

国立保健医療科学院長 殿

機関名　　国立大学法人千葉大学

所属研究機関長　職　名　　学　長

氏　名　徳　久　剛　史　　印

次の職員の令和２年度厚生労働科学研究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　　難治性疾患政策研究事業

２．研究課題名　　早老症の医療水準やQOL向上を目指す集学的研究

３．研究者名　（所属部局・職名）　　医学部附属病院　・　講師

（氏名・フリガナ）　　谷口　俊文　・　タニグチ　トシブミ

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）	■	□	■	千葉大学大学院医学研究院	□
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 24 日

国立保健医療科学院長　殿

機関名　国立大学法人千葉大学

所属研究機関長　職　名　学　長

氏　名　徳久　剛史　　印

次の職員の令和 2 年度厚生労働科学研究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　難治性疾患政策研究事業

2．研究課題名　早老症の医療水準やQOL向上を目指す集学的研究

3．研究者名　（所属部局・職名）　大学院医学研究院・特任教授

（氏名・フリガナ）　忍足俊幸・オシタリトシユキ

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）	□　■	□		□
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

国立保健医療科学院長　殿

機関名　地方独立行政法人
岐阜県総合医療センター

所属研究機関長　職　名　院長

氏　名　滝谷　博志　　印

次の職員の令和２年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準やＱＯＬ向上を目指す集学的研究

３．研究者名　（所属部局・職名）　小児療育内科・部長

（氏名・フリガナ）　金子　英雄・カネコ　ヒデオ

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）	☑　□	☑	岐阜県総合医療センター	□
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）未審査の場合は、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4月1日

国立保健医療科学院長 殿

機関名　国立成育医療研究センター

所属研究機関長　職　名　理事長

氏　名　五十嵐　隆

次の職員の平成 2 年度厚生労働科学研究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　難治性疾患政策研究事業

２．研究課題名　早老症の医療水準や QOL 向上を目指す集学的研究

３．研究者名　（所属部局・職名）　生体防御系内科部遺伝診療科・診療部長

（氏名・フリガナ）　小崎　里華・コサキ　リカ

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。