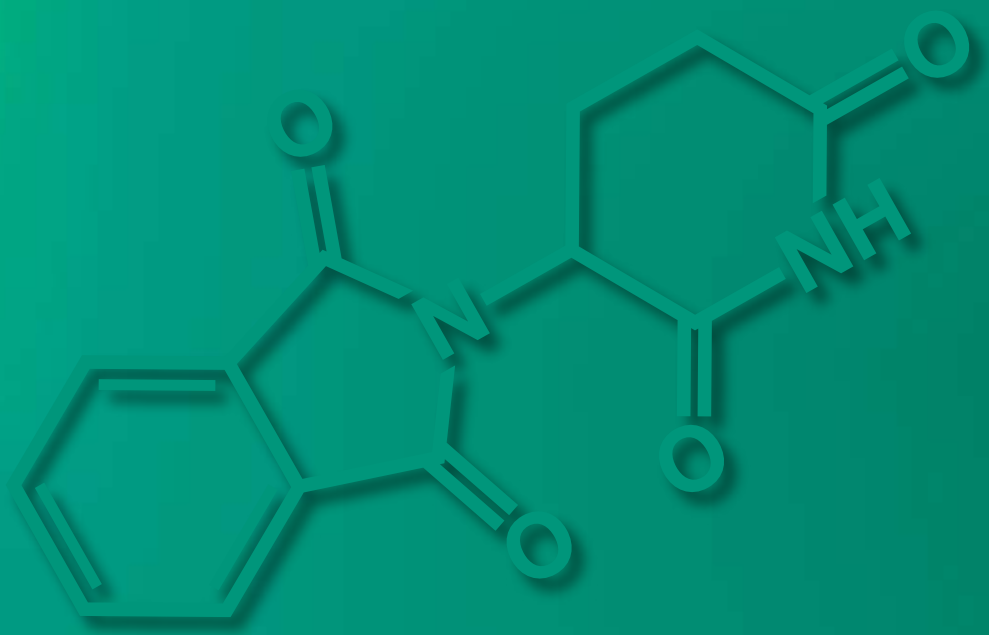

Guide for the Management of Thalidomide Embryopathy 2020

Edited by
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2020 Guide for the Management of Thalidomide Embryopathy

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

Keiko Ebi

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

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

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

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

I Introduction

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

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

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

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

March 1, 2021

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II History and Overview of Thalidomide Embryopathy (TE)

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

1 The Advent and Efficacy Profile of Thalidomide

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

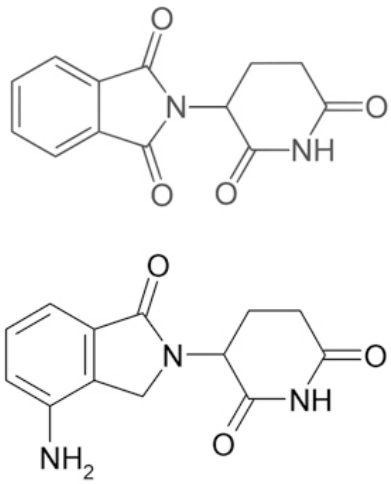


Figure 1 Chemical formula of thalidomide
The upper formula shows thalidomide, a shortened form of α-phthal-imido-glutarimide.
The lower formula shows lenalidomide, a compound now used in the treatment of multiple myeloma

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

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

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

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

2 Side Effects Begin to Appear

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

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

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

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

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

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

3 The Thalidomide Saga

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

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

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

4 Lenz's Warning Emerges from an Onerous Investigation

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

Figure 2 Dr. Jan Schulte-Hillen and his wife


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

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

Carl-Hermann Schulte-Hillen

* 28.3.1929 † 14.1.2017

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

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

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

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

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

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

5 Avoidable Cases of TE

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

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

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

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

6 New Cases Occur in Brazil

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

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

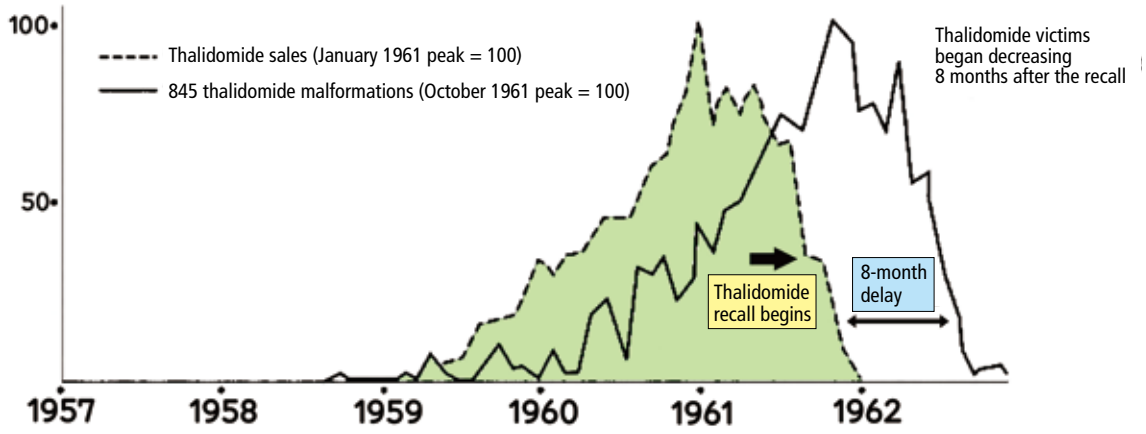


Figure 4 Thalidomide sales and the incidence of thalidomide malformations
Nilsson R, Sjöström H: Thalidomide and the Power of the Drug Companies, Penguin Books, UK Ltd., 1972.

7 The Use of Thalidomide Drug Products in Japan

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

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

8 One Hundred Years After the Birth of Dr. Lenz

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

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

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

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

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

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

Figure 5 Dr. Lenz in Alsdorf

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

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

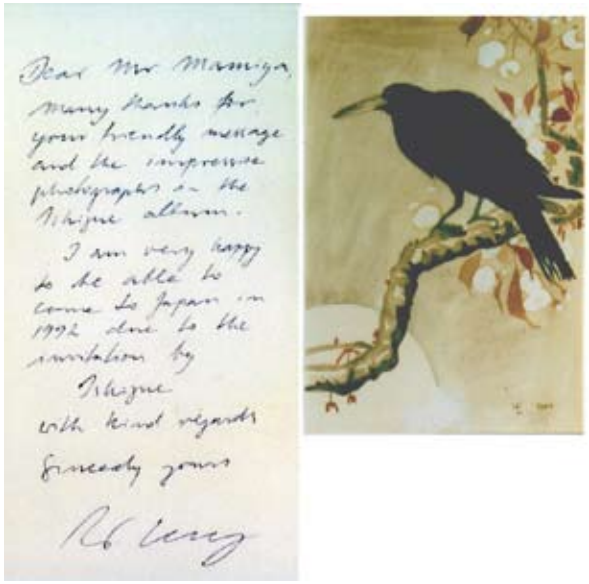
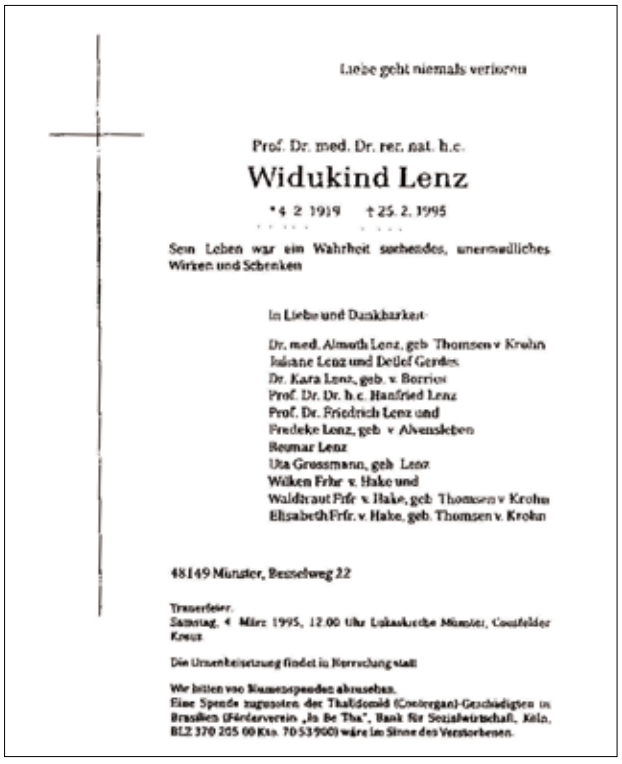


Figure 7 A postcard handwritten by Dr. Lenz


Liebe geht niemals verloren

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

Widukind Lenz

* 4. 2. 1919 † 25. 2. 1995

Sein Leben war ein Wahrheit suchendes, unermüdliches Wirken und Schenken

In Liebe und Dankbarkeit

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

48149 Münster, Besselweg 22

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

Die Urnenbeisetzung findet in Norderney statt

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

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

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URL

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

[Ryoji Kayamori]

III Mechanism of Thalidomide Embryopathy (TE)

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

1 About Drug Targets

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

2 Identifying Thalidomide's Target Molecule

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

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

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

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

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

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

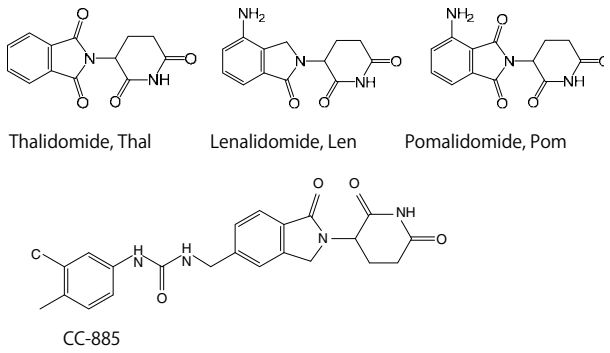

Figure 1 Molecular structures of thalidomide and thalidomide derivatives

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

(2) Proving that CRBN is a TE target

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

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

(1) Second-generation thalidomide derivatives

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

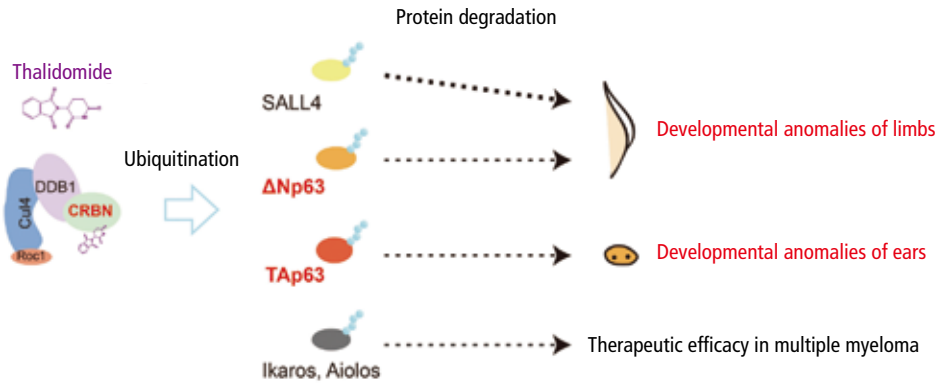

Figure 2 Molecular mechanism of thalidomide

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

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

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

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

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

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

(3) Optical isomers of thalidomide

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

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

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

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

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

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

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

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

4 Research Leads to New CRBN Modulators

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

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

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

5 Mechanism of TE

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

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

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

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

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

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

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

6 Conclusions

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

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[Takumi Ito, Yuki Yamaguchi, Hiroshi Handa]

IV Diagnostic Procedures for Thalidomide Embryopathy (TE)

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

1 Introduction

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

2 New Claimers Around the World

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

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

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

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

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

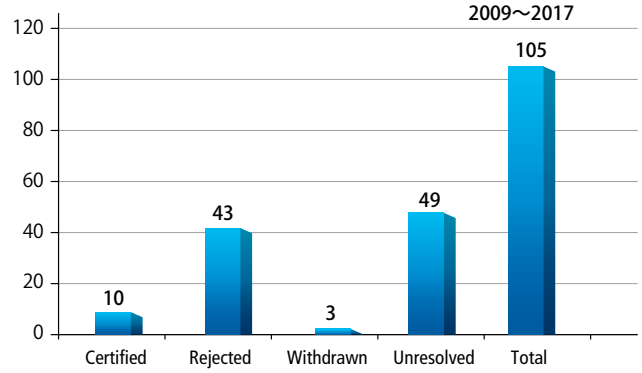

Figure 1 New claimers in Germany

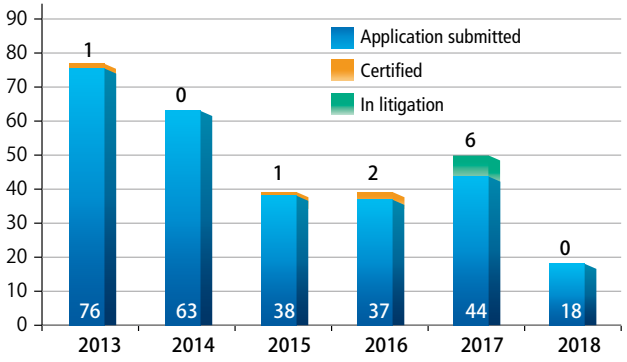

Figure 2 New claimers in the UK

3 Requirements for a Diagnosis of TE

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

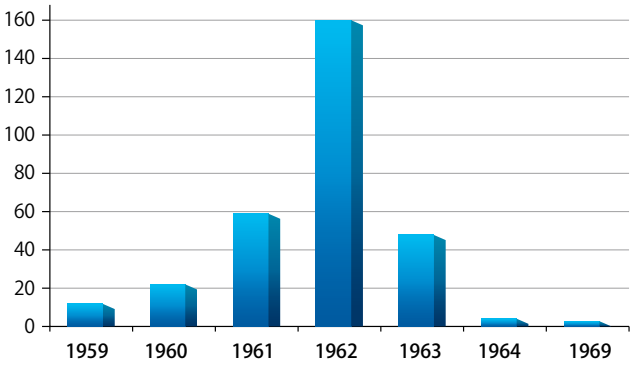

Figure 3 Numbers of babies born with thalidomide embryopathy in Japan

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

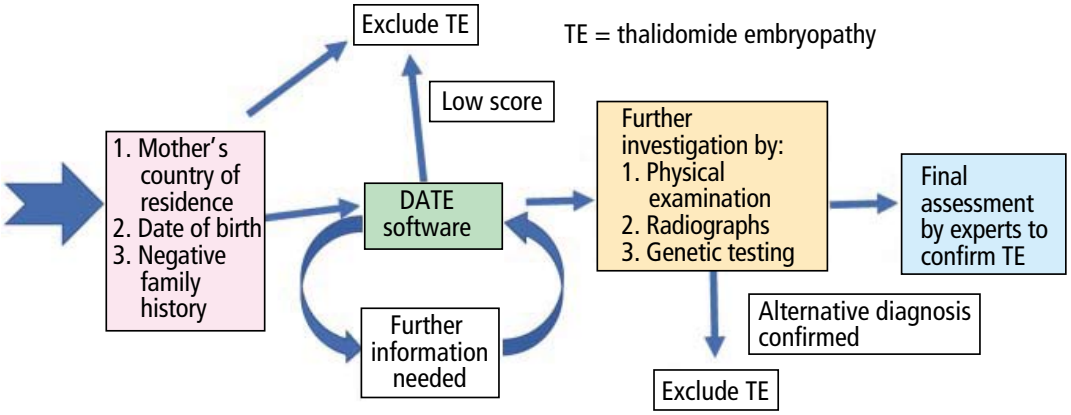

Figure 4 Overview of the Diagnostic Algorithm for Thalidomide Embryopathy (DATE) (adapted from Reference 3)
DATE Diagnostic algorithm for thalidomide embryopathy

4 Physical Manifestations of TE

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

(1) Preaxial longitudinal hypoplasia

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

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

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

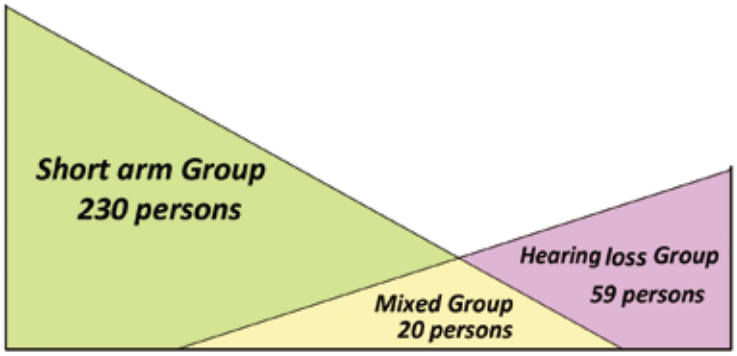

Figure 6 Physical manifestations of thalidomide embryopathy
Patients are classified into a short-arm or hearing-loss group.

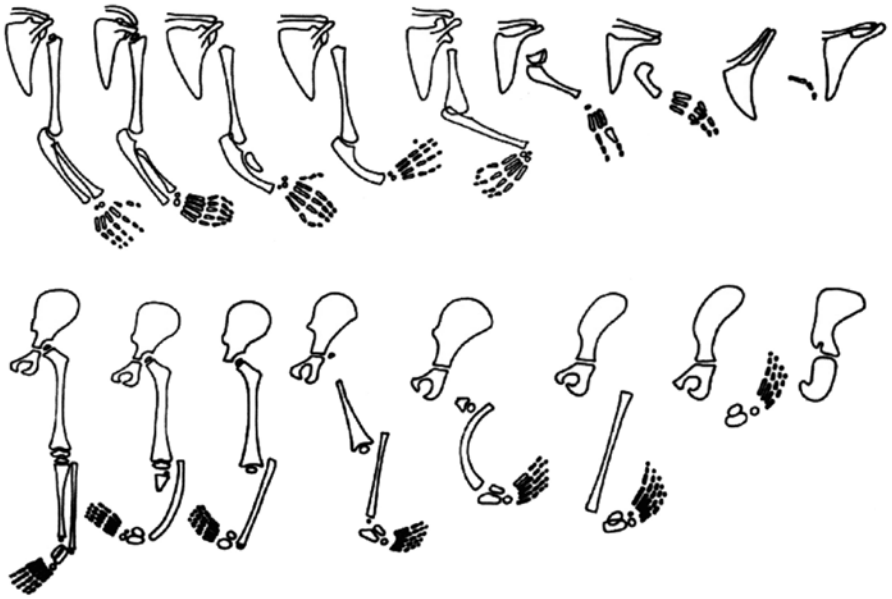

Figure 7 Pattern and severity classification of preaxial longitudinal hypoplasia in thalidomide embryopathy

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

(2) Symmetry and upper limb domination

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

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

(3) Severity classifications for upper-limb hypoplasia

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

(4) Lower-limb hypoplasia

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

Table 1 Severity classification criteria for upper-limb hypoplasia

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

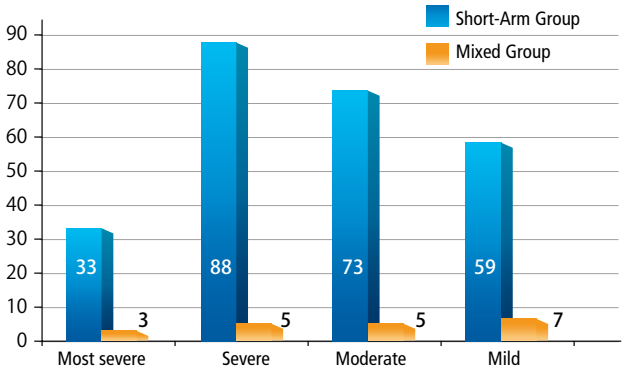

Figure 8 Severity classifications of upper-limb hypoplasia

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

(5) Auditory hypoplasia

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

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

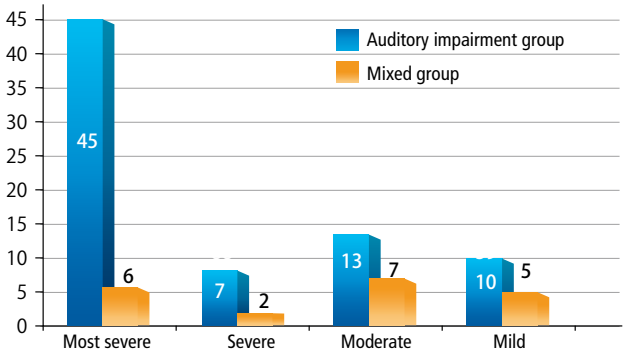

Figure 10 Classifications of deafness in auditory hypoplasia

5 Diagnosing TE

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

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

Table 2 Types and classifications of auditory defects

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

(Adapted from Reference 6)

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

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

6 New Claimers in Japan

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

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

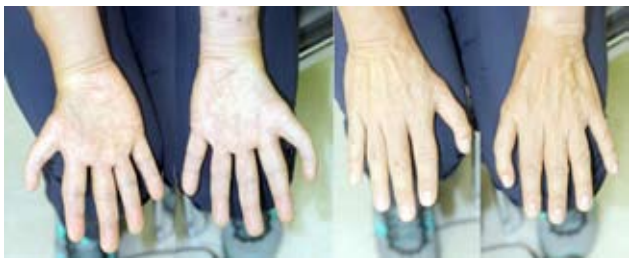

Figure 11 Triphalangeal thumbs of both hands
The thumbs are triphalangeal instead of having the normal two joints. Thenar hypoplasia is also present.
The affected digits are not actually thumbs. This constitutes polydactyly. Functionally, these digits lack the ability of thumbs to grip and pinch. The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

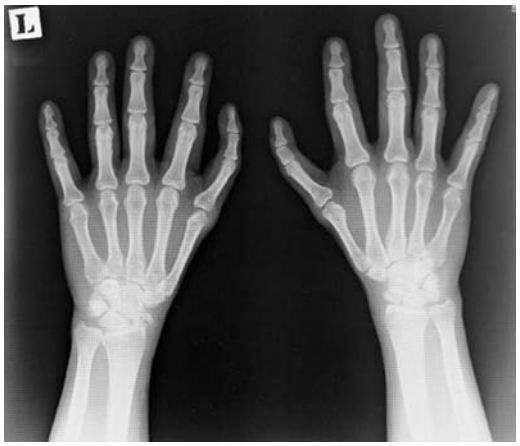

Figure 12 An X-ray of both hands
The thumbs are triphalangeal. Hypoplasia is seen in the trapezium, scaphoid, and styloid process of the radius.

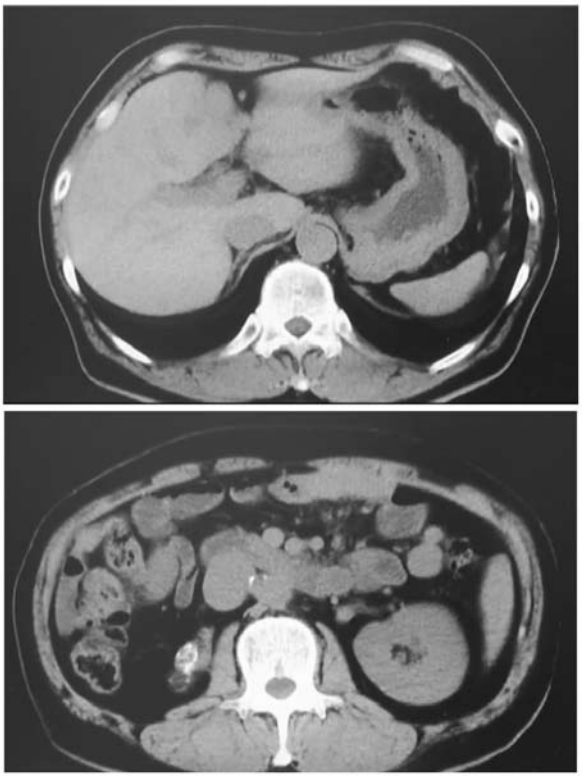

Figure 13 Axial abdominal cavity CT scans
The upper scan, a cross-section at the hepatobiliary level, shows gallbladder agenesis. The lower scan, at the renal level, shows severe atrophy of the right kidney. (Unless otherwise indicated, the right side from the perspective of the viewer is the left side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

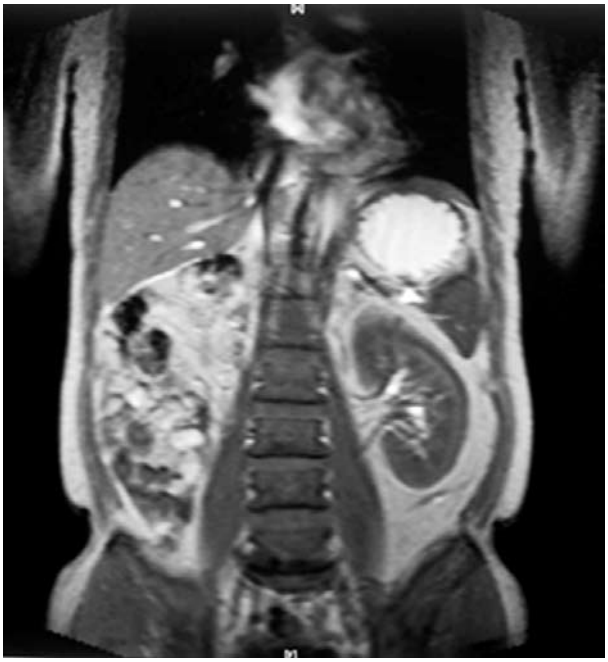

Figure 14 Coronal abdominal cavity MRI scan
The scan shows findings indicative of severe atrophy of the right kidney and multiple cysts and vascular malformation of the right posterior peritoneum.

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

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

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

Figure 15 Photographs of the forearms and hands

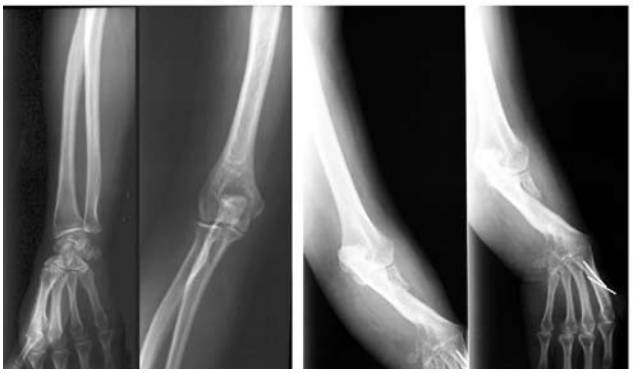

Figure 16 X-rays of the forearms and hands
The X-rays to the right show the patient's left forearm and hand. The X-rays to the left show the patient's right forearm and hand. There is agenesis of the left radius, hypoplasia of the ulna, and unseparated carpal bones as well as hypoplasia of the right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

7 Differentiating TE from SALL4-related Disorders

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

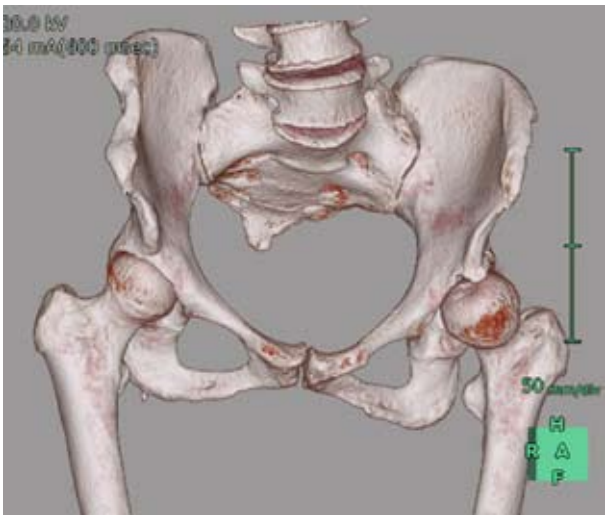

Figure 17 Hypoplasia of the left hip acetabulum in 3D CT

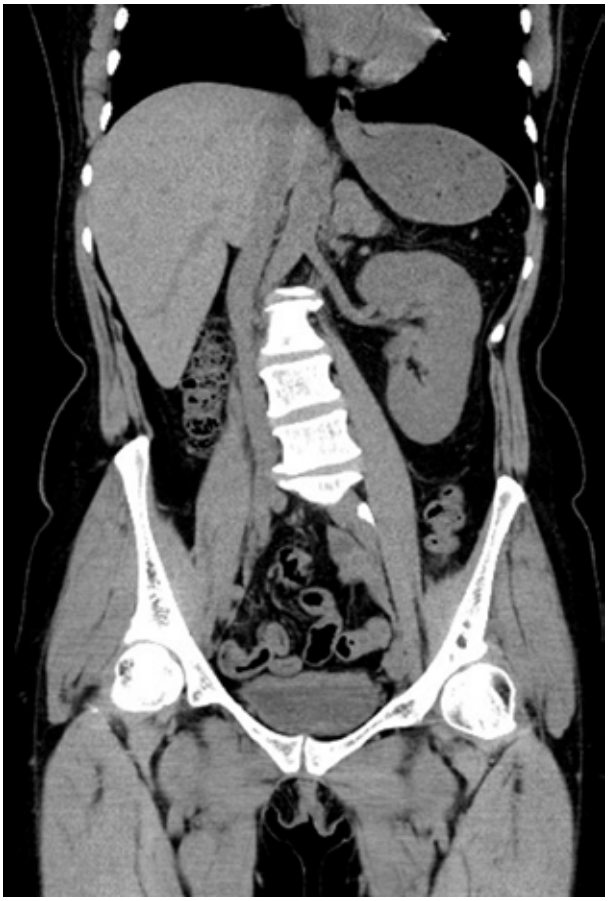

Figure 18 Severe atrophy of the right kidney seen in abdominal cavity CT
Marked scoliosis is also present.

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

8 Is Embryopathy Genetically Heritable?

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

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[Ryoji Kayamori]

Table 3 Clinical findings in SALL4-related diseases

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

Adopted from reference URL 4.

V Internal Medical Care

1 Managing Lifestyle Diseases

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

1 Lifestyle Diseases

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

(1) Definition and concept of lifestyle diseases

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

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

(2) Frequency of lifestyle diseases in patients with TE

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

Table 1 Frequency of lifestyle diseases in patients with thalidomide embryopathy

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

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

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

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

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

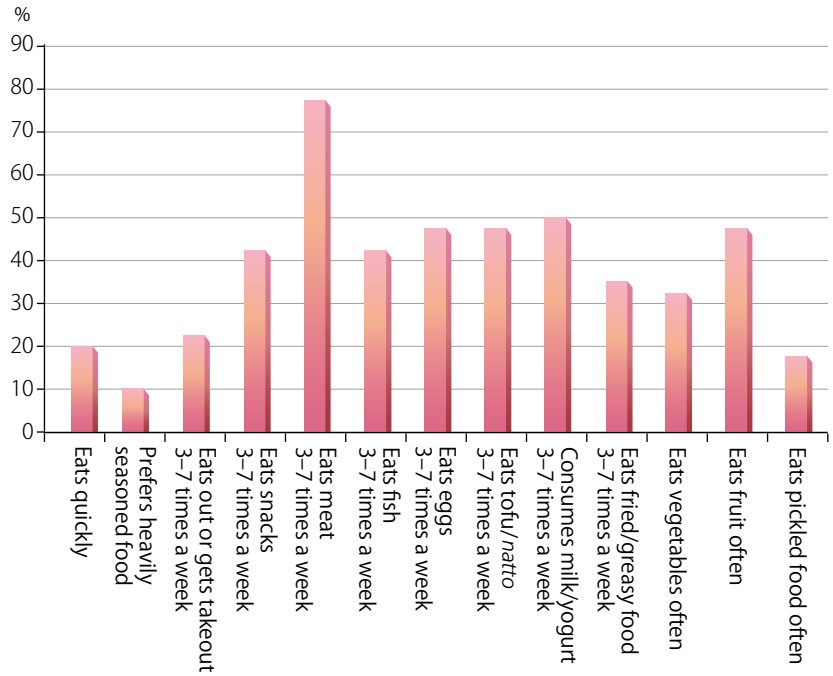

Figure 1 Eating habits

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

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

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

2 Gallbladder Agenesis

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

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[Tomoko Shiga]

V Internal Medical Care

2 Endocrine and Metabolic Disorders

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

1 Introduction

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

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

2 Lifestyle Diseases

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

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

3 Overweight

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

4 Hepatic Steatosis

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

5 Dyslipidemia

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

6 Abnormal Glucose Metabolism

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

7 Hyperuricemia

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

8 CKD

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

9 Osteoporosis

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

10 Endocrine and Metabolic Abnormalities

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

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

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

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[Tetsuya Tagami]

V Internal Medical Care

3 Kidney Disease, Hypertension, and Cardiovascular Disease

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

1 Chronic Kidney Disease (CKD)

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

(1) Definition and concept of CKD

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

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

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

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

(2) Diagnosing and scrutinizing CKD

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

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

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

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

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

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

(3) Significance and progression of CKD

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

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

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

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

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

(4) CKD-related findings from comprehensive medical examinations

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

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

2 Hypertension

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

Table Blood pressure categories for adults (mm Hg)

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

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

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

(1) Diagnosing hypertension

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

(2) Measuring and evaluating blood pressure

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

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

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

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

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

(3) More information about lower-limb blood pressure

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

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

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

(4) Hypertension-related findings from comprehensive medical examinations

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

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

(5) Treatment of hypertension

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

3 Cardiac Diseases

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

(1) Congenital heart disorders

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

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

(2) Ischemic heart disease and cardiac failure

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

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

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

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

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[Fumihiko Hinoshita]

V Internal Medical Care

4 Preventing Respiratory Diseases and Infections

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

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

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

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

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

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

2 Preventing Respiratory Infections

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

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

Figure 1 Mask with long straps

Figure 2 Strapless mask

Figure 3 Automatic hand sanitizer

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

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

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

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

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

3 Preventing Infectious Gastroenteritis

[Focusing on prevention strategies aimed at norovirus]

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

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

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

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

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

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

4 Commentary on Disinfection

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

5 The Importance of Smoking Cessation

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

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

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

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

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

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[Hiroyuki Nagase]

5 Esophagogastroendoscopy (EGD) and Gastrointestinal Diseases

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

1 Status

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

2 Determining Patient Information

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

3 Observable Areas in EGD

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

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

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

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

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

5 Sedation

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

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

6 Local Anesthesia

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

7 Informing the Patient before the Procedure

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

8 Endoscopic Pretreatment

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

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

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

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

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

9 Transnasal Insertion

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

10 Guidance

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

11 Diagnosis of helicobacter pylori (HP) Infections

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

12 Handling Epistaxis and Nose Pain from Transnasal Endoscopy

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

13 Findings

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

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

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[Nobuko Shima, Takama Maekawa]

1 Diagnosis and Assessment/Testing

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

1 Congenital Musculoskeletal Malformations

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

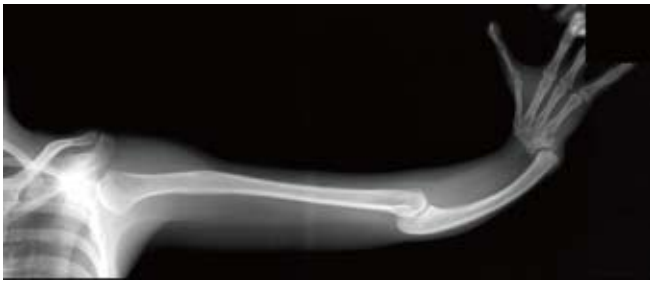

Figure 1 Severe preaxial longitudinal hypoplasia of the upper limbs
The radius is missing, the ulna is shortened, the thumb is missing, the index finger shows hypoplasia, and the carpal bones are hypoplastic and fused. The wrist is bent toward the radial. This is known as club hand. The elbow shows hypoplasia.

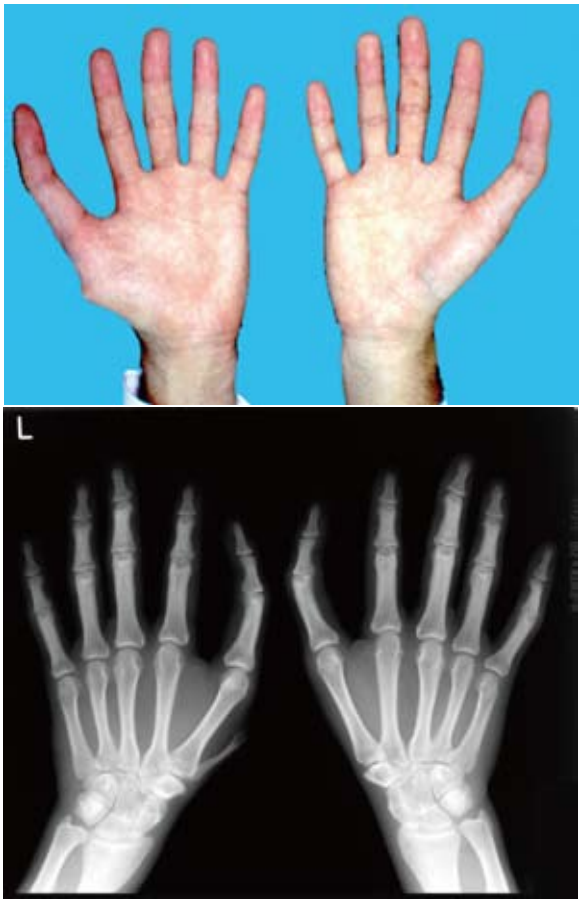

Figure 2 Mild preaxial longitudinal hypoplasia of the upper limbs
The thumbs are triphalangeal. The left hand has a rudimentary metacarpal on the radial side.

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

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

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

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

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

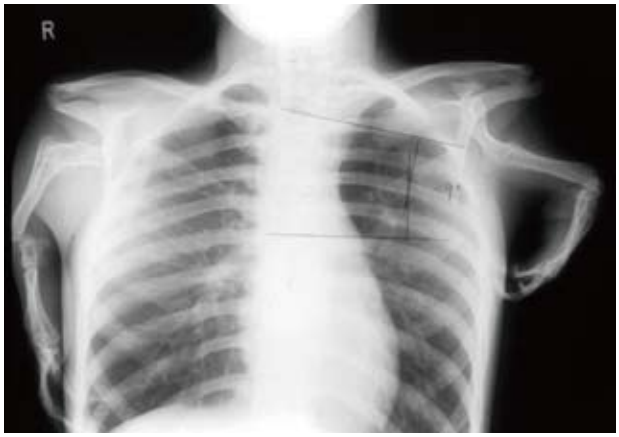

Figure 3 Phocomelia
Both humeri and radii show hypoplasia. Hands are present but have hypoplastic thumbs.

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

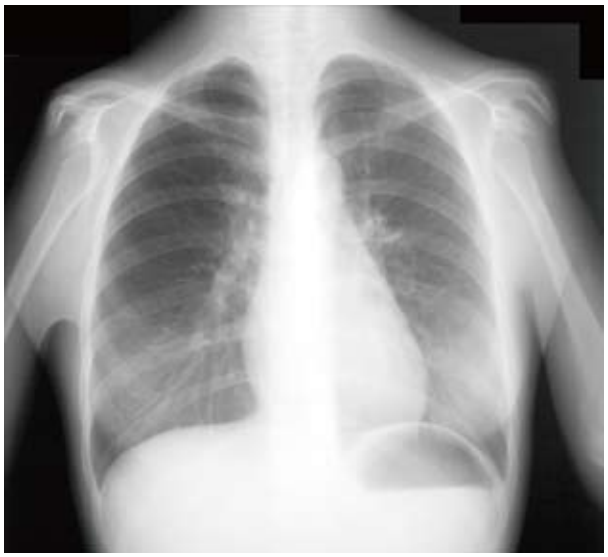

Figure 5 Shoulder subluxation and acromioclavicular joint protrusion caused by bilateral humeral hypoplasia

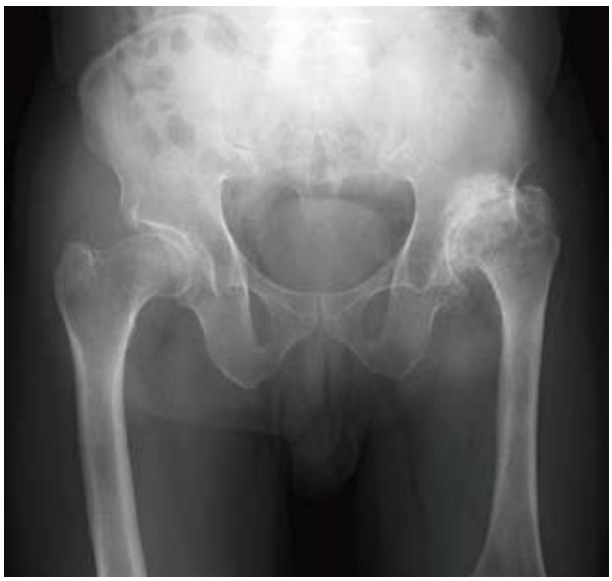

Figure 6 Bilateral hip hypoplasia and coxarthrosis

2 Age-related Musculoskeletal Disorders

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

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

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

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

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

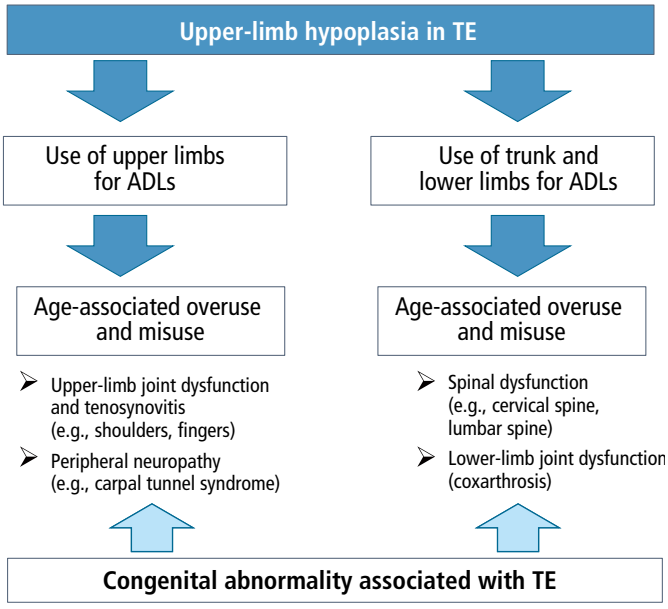

Figure 7 The mechanism of musculoskeletal dysfunction caused by upper-limb hypoplasia in TE

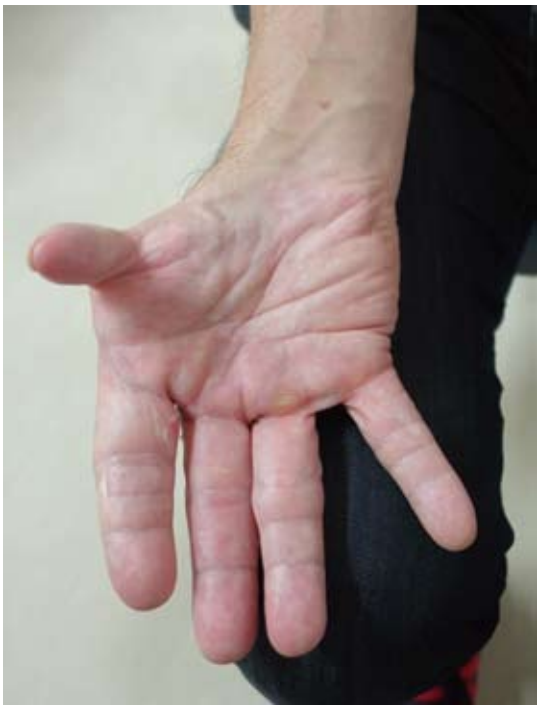

Figure 8 Thumb and thenar hypoplasia, with tenosynovitis of the other fingers due to overuse

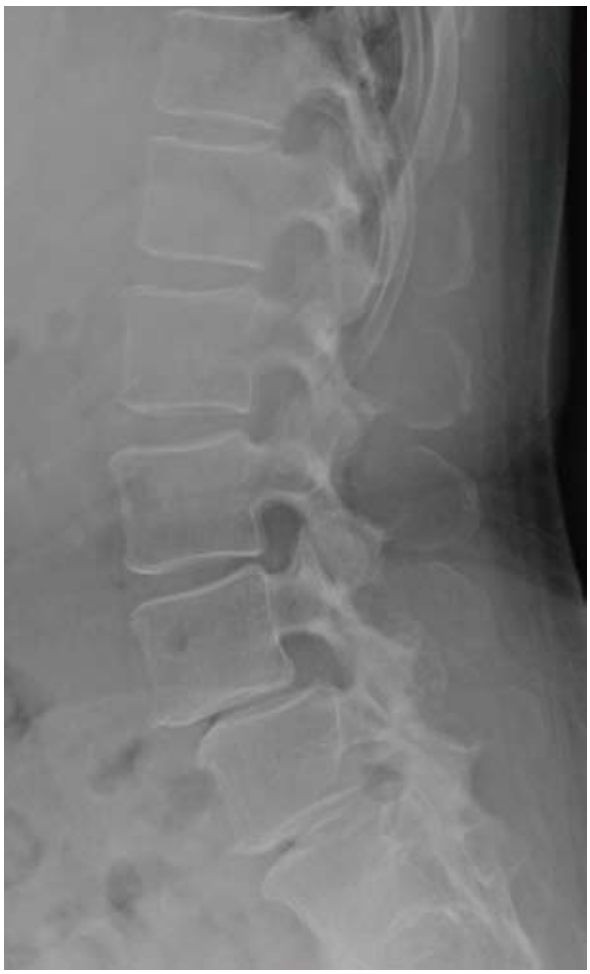

Figure 9 Narrowing of the intervertebral space and spondylolisthesis in the lower lumbar spine

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[Nobuhiko Haga]

2 Treatment and Support [1] Drug Therapy

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

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

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

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

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

[Nobuhiko Haga, Ryoji Kayamori, Yasuhiro Maehara]

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

2 Treatment and Support [2] Surgery and Indications

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

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

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

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

[Nobuhiko Haga, Ryoji Kayamori]

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Artificial joint replacement, carpal tunnel syndrome, carpal tunnel release

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

Key Points

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

1 Introduction

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

2 Characteristics of Upper-limb Defects and Approaches to Guidance

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

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

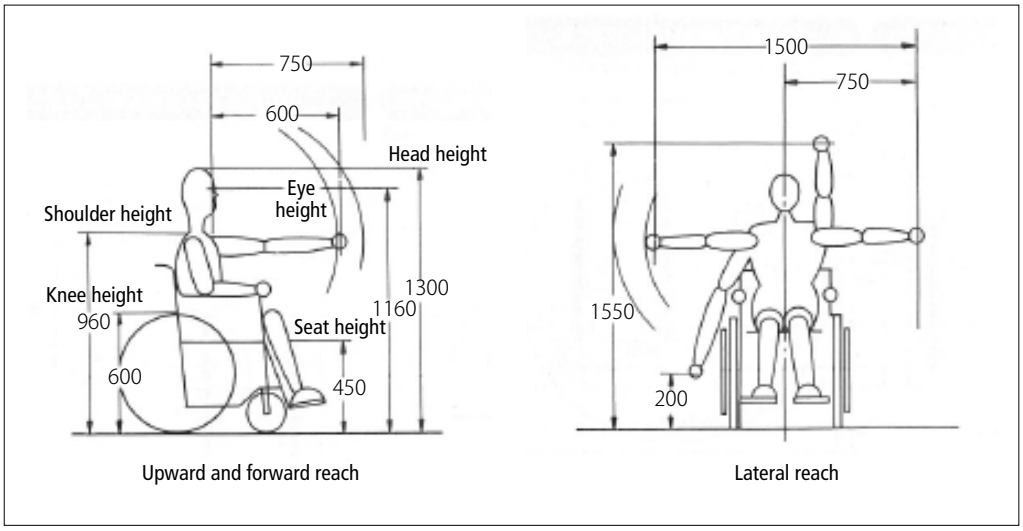

Figure 1 Reach of the upper limbs of a person seated in a wheelchair (TOTO Ltd.[2)], 1977) (dimensions are in millimeters)

Keywords

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

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

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

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

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

Figure 2 Using a reacher

Examples:

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

3 Characteristics of Finger Defects and Approaches to Guidance

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

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

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

Examples:

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

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

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

4 Characteristics of Auditory Defects and Approaches to Guidance

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

Examples:

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

5 Conclusions

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

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[Takeshi Kobayashi, Junko Fujitani]

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

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

1 Introduction

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

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

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

(1) Effects of shortened limbs

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

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

(2) Shoulder hypoplasia

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

(3) Hypoplasia of the upper-limb musculature

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

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

(4) Spinal column symptoms

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

(5) Wrist pain

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

3 Identifying Issues in Interviews

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

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

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

4 Ergonomic Remedies

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

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

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

Photograph 1 A computer mouse with a handle

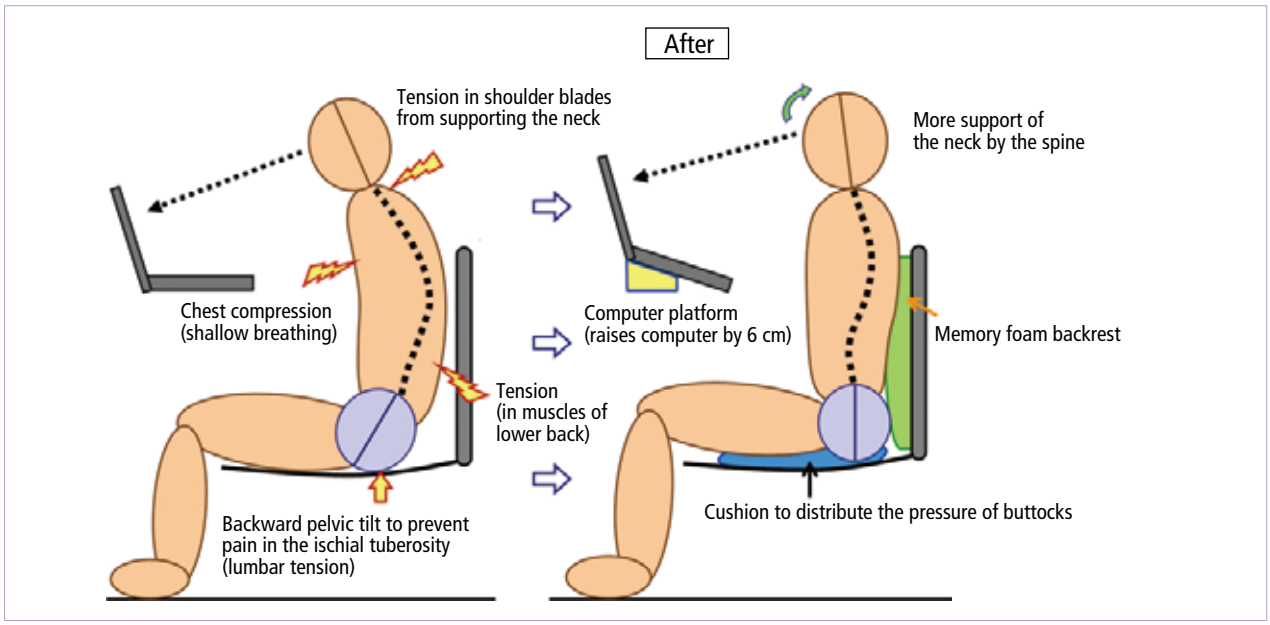
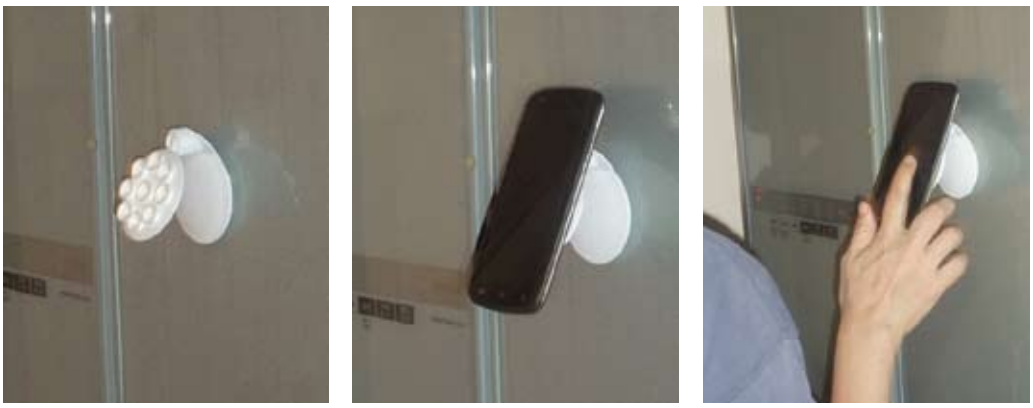


Figure An improvement of working environment for easier operation of a computer user



Photograph 2 A cellphone holder

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

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

5 Recommendations for Health Management

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

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

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

6 Conclusions

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

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[Hiroji Tsujimura, Shin-ichi Shirahosi]

VII Radiological Examination and Evaluation

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

1 Preparing for Radiological Procedures

(1) Interviewing and informing the patient before the procedure

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

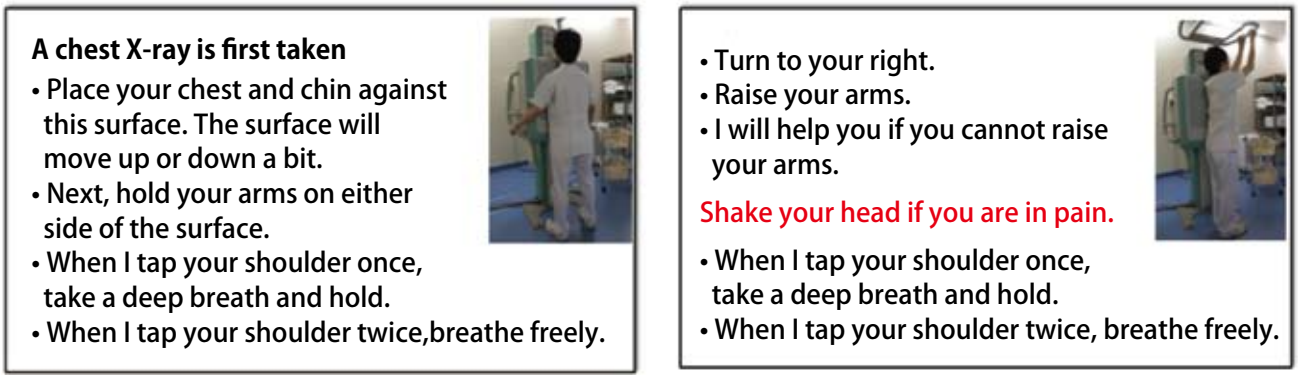


Figure 1 Signs with patient instructions for a chest X-ray

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

(2) Changing into gown and preparation

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

Figure 2 Front-tying gown

Figure 3 Slip-on gown

[Azusa Minagawa]

2 1. General Imaging: Chest X-rays

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

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

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

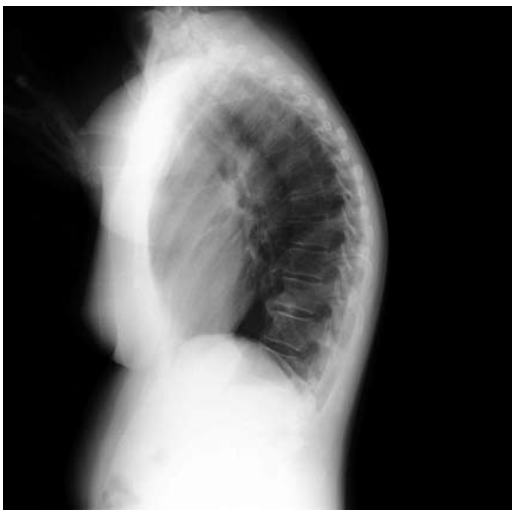


Figure 4 Lateral chest X-ray image

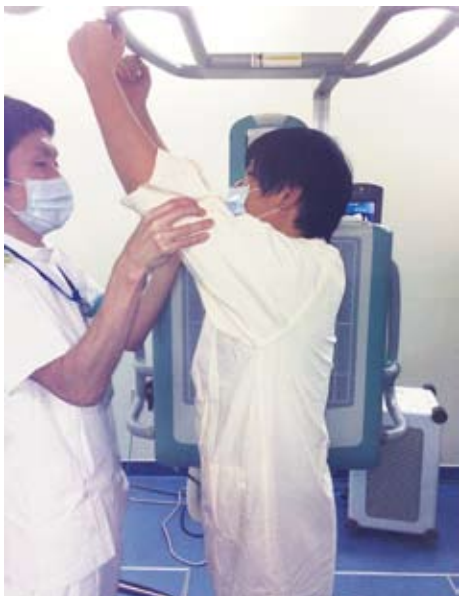


Figure 5 Upper-limb assistance for a patient undergoing a lateral chest X-ray

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

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

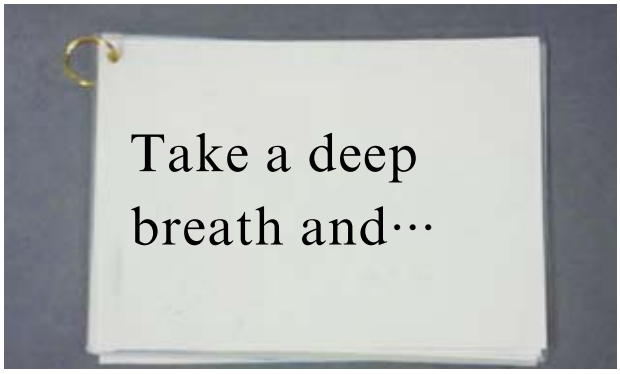


Figure 6 A sign with instructions

Figure 7 A patient is instructed with the sign

[Azusa Minagawa]

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

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

(1) Definition of osteoporosis

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

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

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

(2) BMD analysis

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

(3) Characteristics of BMD in patients with TE

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

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

(4) Considerations for BMD analysis for patients with TE

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

[Azusa Minagawa]

2 3. General Imaging: Mammography

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

(1) Mammography

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

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

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

(2) Mammography imaging techniques for patients with TE

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

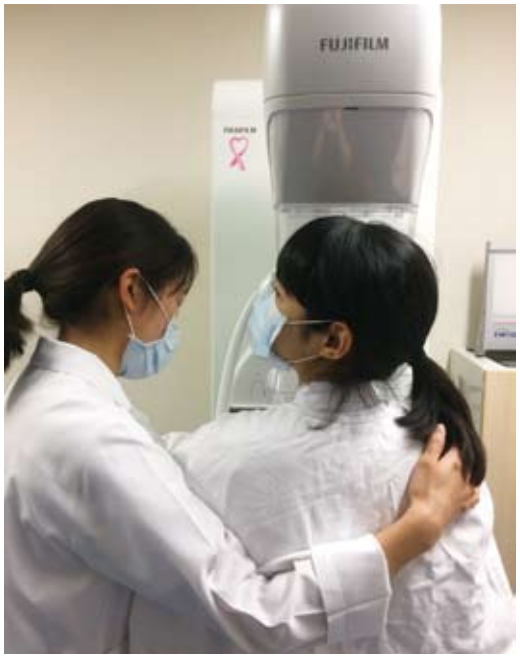


Figure 8 Craniocaudal imaging

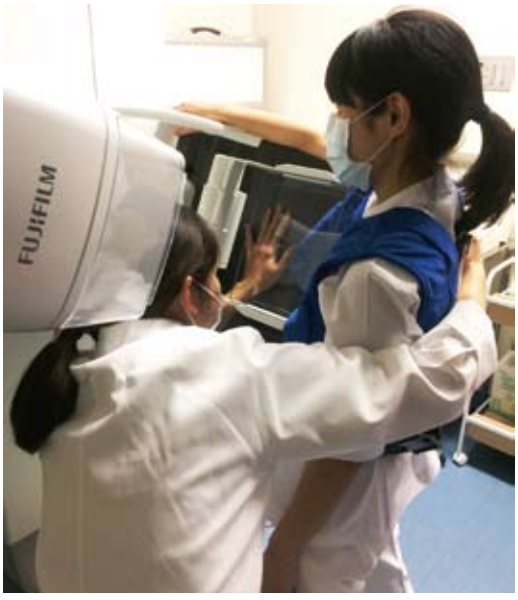


Figure 9 Medio-lateral oblique imaging

(3) Considerations for mammography for patients with TE

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

Figure 10 Patient chair for mammography

[Azusa Minagawa]

3 Computed Tomography (CT)

(1) Significance of CT

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

(2) Positioning

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

(3) Imaging protocol

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

Figure 11 shows proper positioning and the FOV.

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

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

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

Figure 13 shows reconstructed images of the inner ear.

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

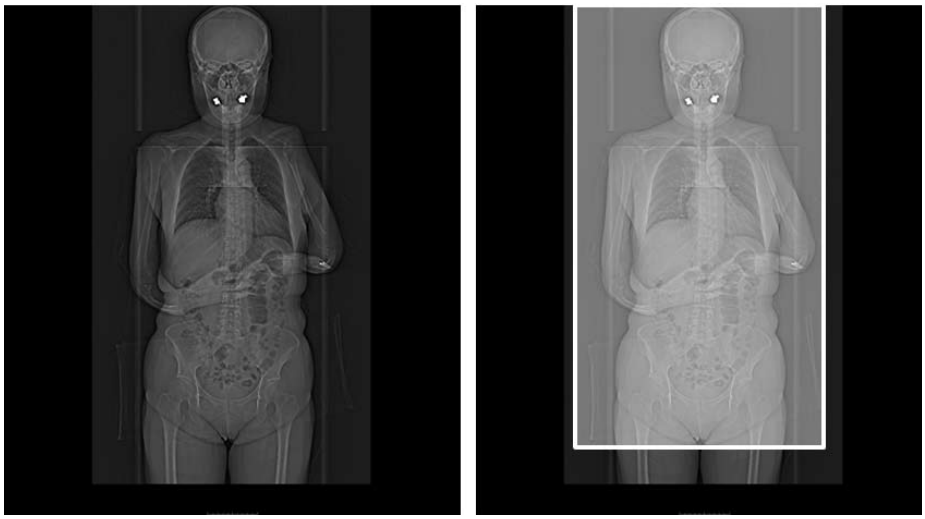
Figure 14 shows reconstructed images of the cervical vertebrae.

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

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

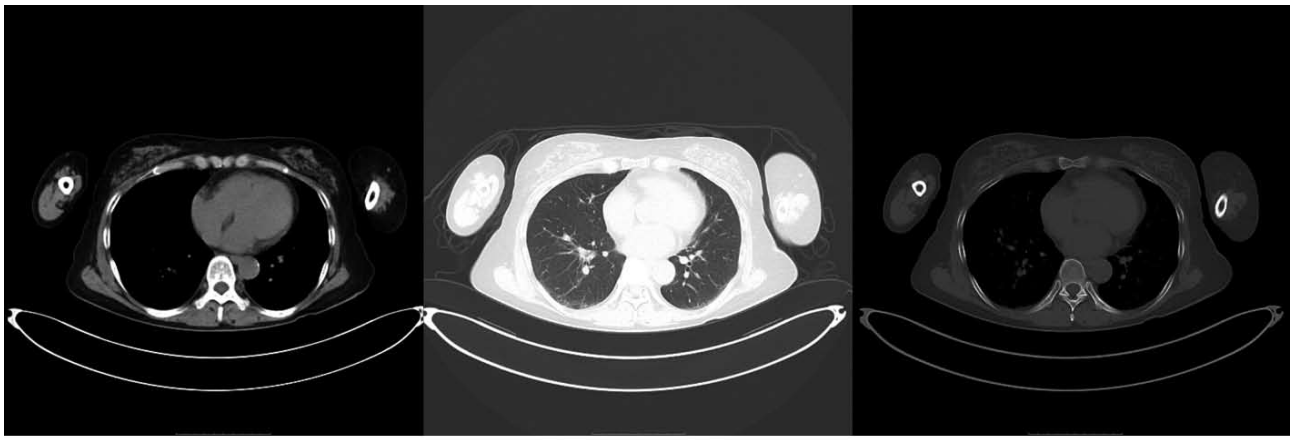
The FOV includes all thoracic, lumbar, and sacral vertebrae. A 1-mm axial slice and 1-mm sagittal and coronal slices are shown. Attenuation coefficients for bone reconstruction were used.

[Masafumi Shinozaki]



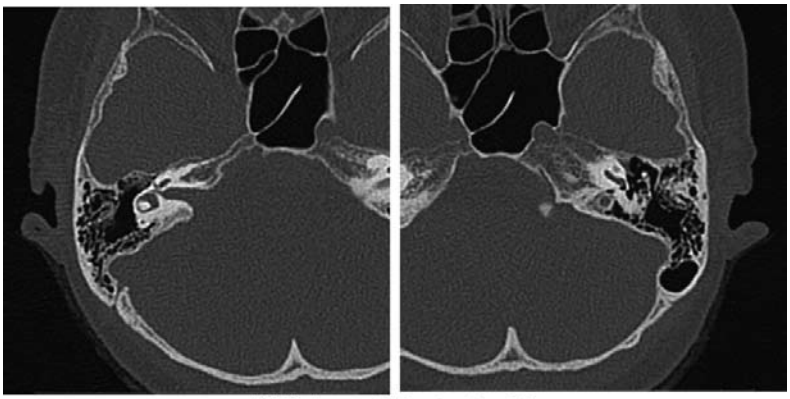
Positioning Field of view (within white rectangle)

Figure 11 Positioning and field of view

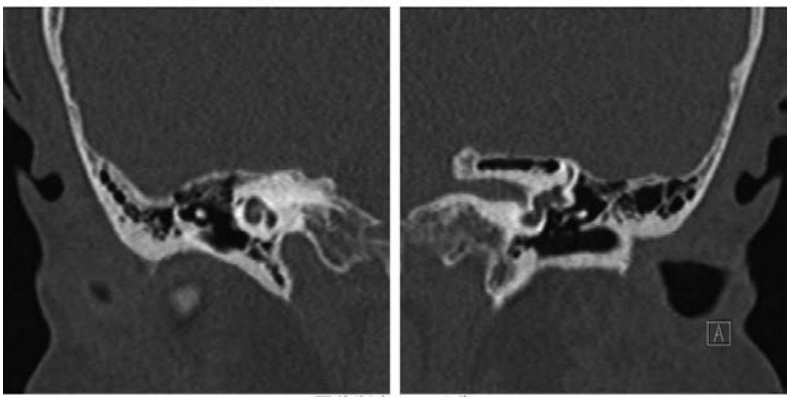


Soft tissue conditions (5 mm thickness) Lung tissue conditions (5 mm thickness) Bone conditions (5 mm thickness)

Figure 12 Reconstructed images of the trunk

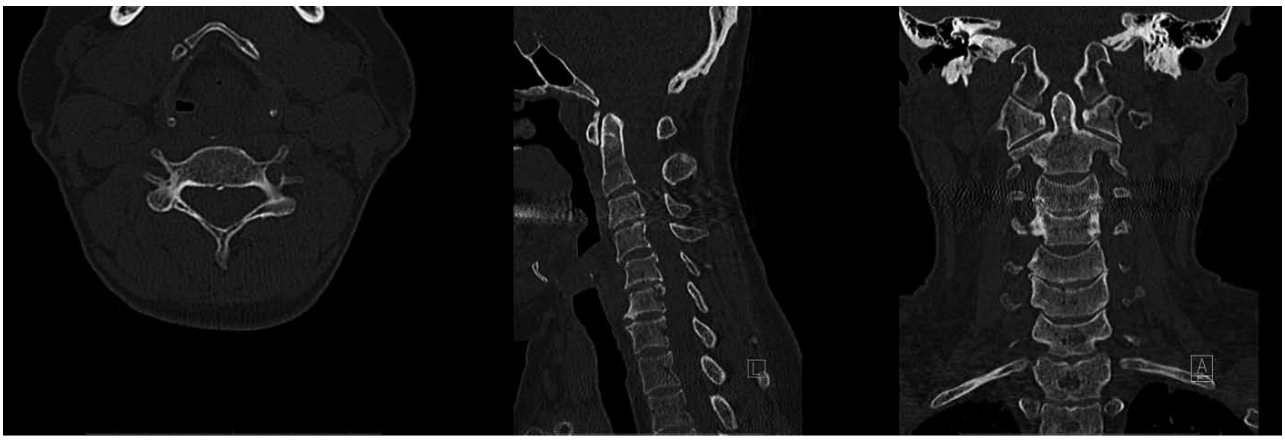


Axial (0.5 mm or 0.6 mm thickness)



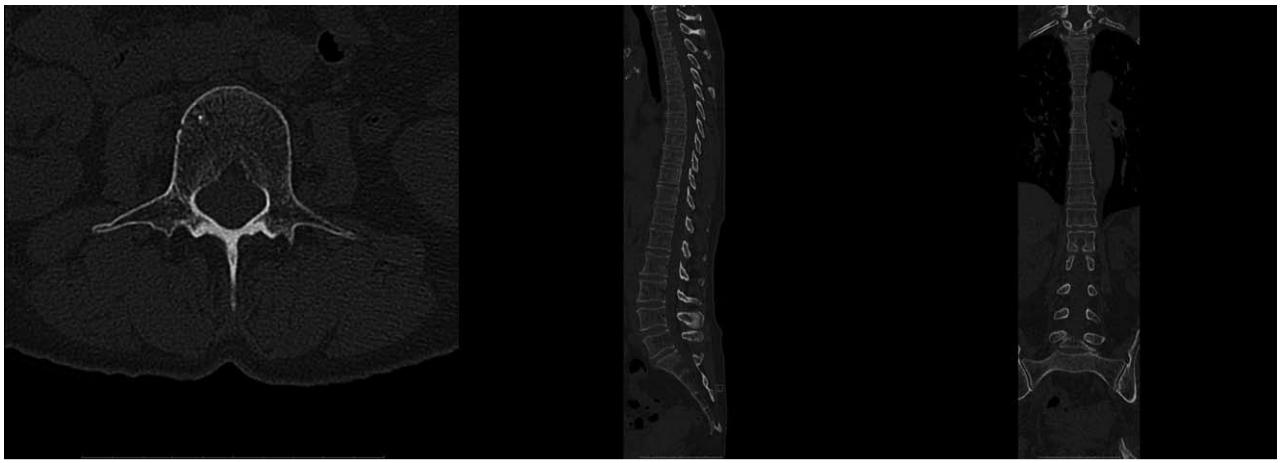
Coronal (1.0 mm thickness)

Figure 13 Reconstructed images of the inner ear



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

Figure 14 Reconstructed images of the cervical vertebrae



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

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

4 Magnetic Resonance Imaging (MRI)

(1) Interviewing the patient before the procedure

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

(2) Informing the patient before the procedure

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

(3) Changing clothes and preparation

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

(4) During the procedure

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

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

[Jun Harada]

5 Diagnostic Imaging: Tips and Warnings for Radiographic Evaluation

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

(1) MRI of head and sinuses

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

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

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

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

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

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

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

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

(5) Presentation of radiology images

Following are radiaology images typical of TE.

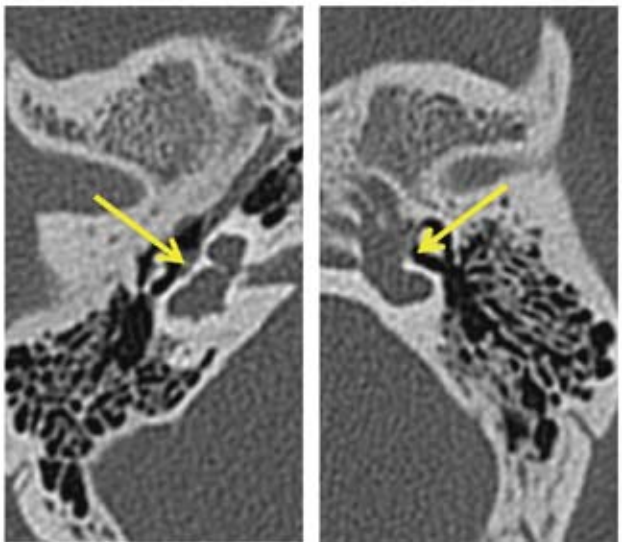


Figure 16 Bilateral hypoplasia of the semicircular canals, vestibule, and cochlea
Axial CT scans of the temporal bone. The images show bilateral hypoplasia of the semicircular canals, vestibule, and cochlea, with one cystic area (arrow).

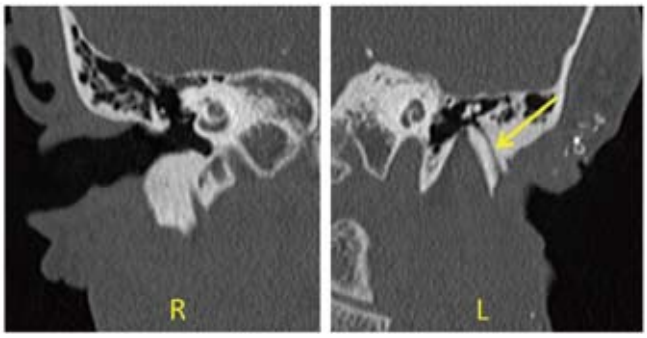


Figure 17 Stenosis of the outer ear canals
Coronal CT scans of the temporal bone. The left outer ear canal (arrow) features much more stenosis than the right.

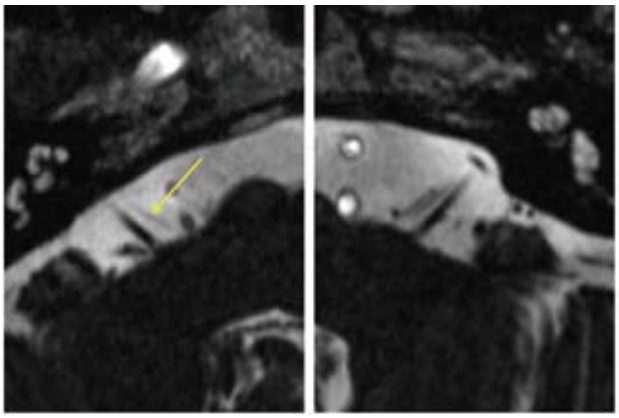


Figure 18 Facial nerve hypoplasia
Axial T2-weighted MRI scans. The right facial nerve (arrow) features more hypoplasia than the left. Both auditory nerves are normal.

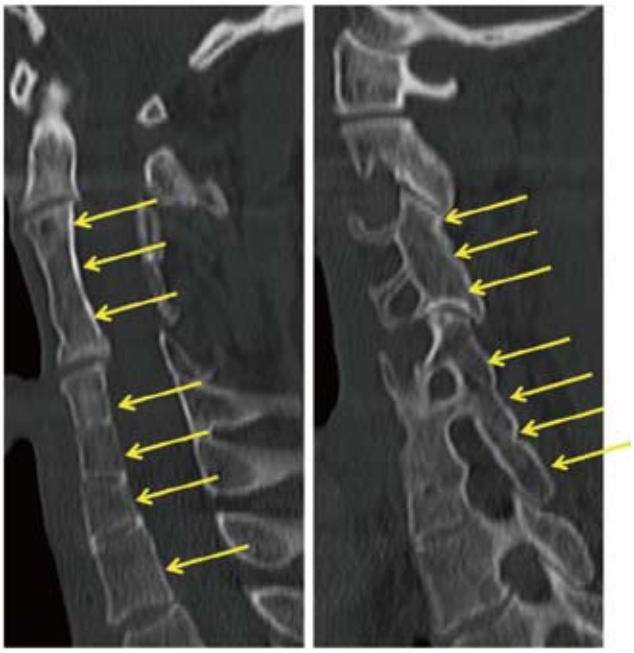


Figure 19 Block vertebrae
Reconstructed sagittal CT scan without contrast. The bodies and arches of the cervical and thoracic vertebrae (C3–C5 and C6–T2) are fused (arrows).

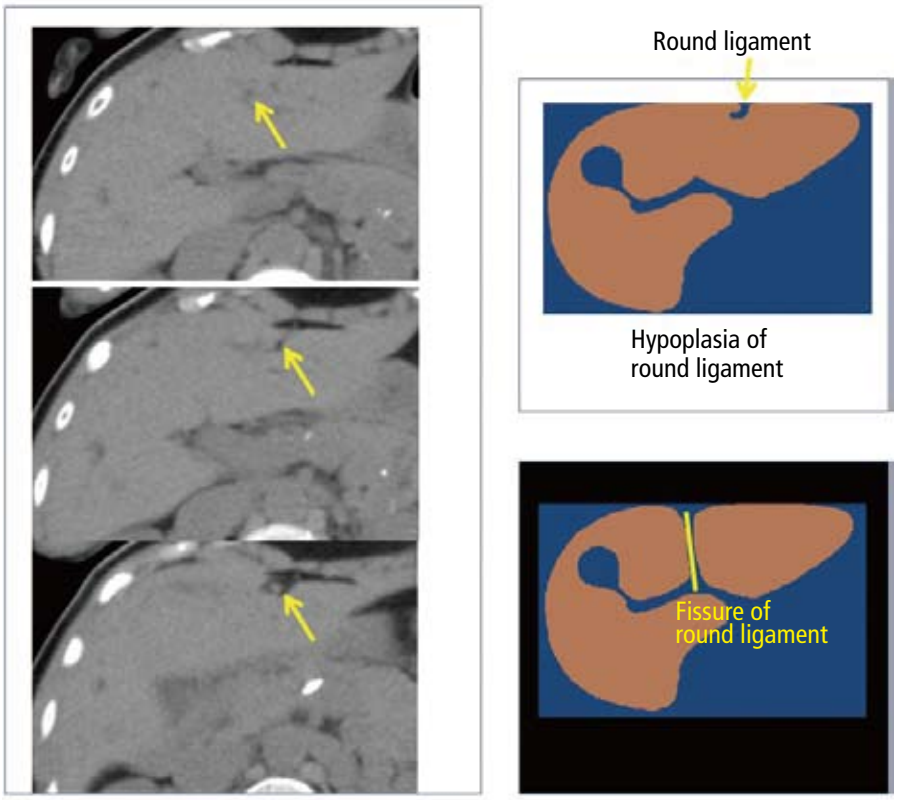


Figure 20 Lobulation defect of the superior and inferior lateral segments of the left lobe of the liver
Axial image of unenhanced CT. The barely visible fissure of round ligament indicates hypoplasia (arrow).

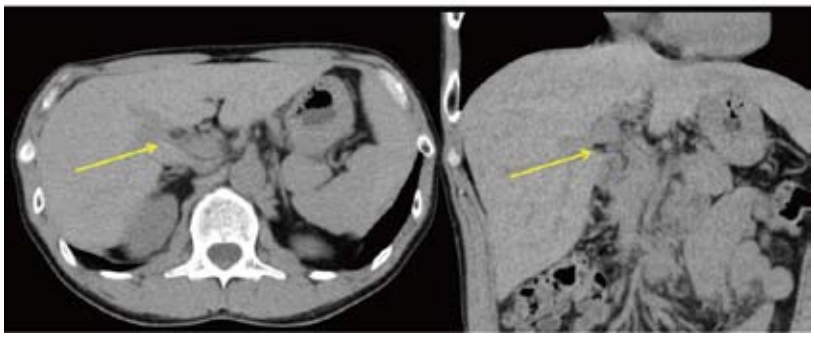


Figure 21 Gallbladder agenesis
Axial and coronal CT scans without contrast. No gallbladder is present (arrow). No gallbladder fossa is visible (arrow). Biliary dilatation is indistinct. These findings indicate gallbladder agenesis.

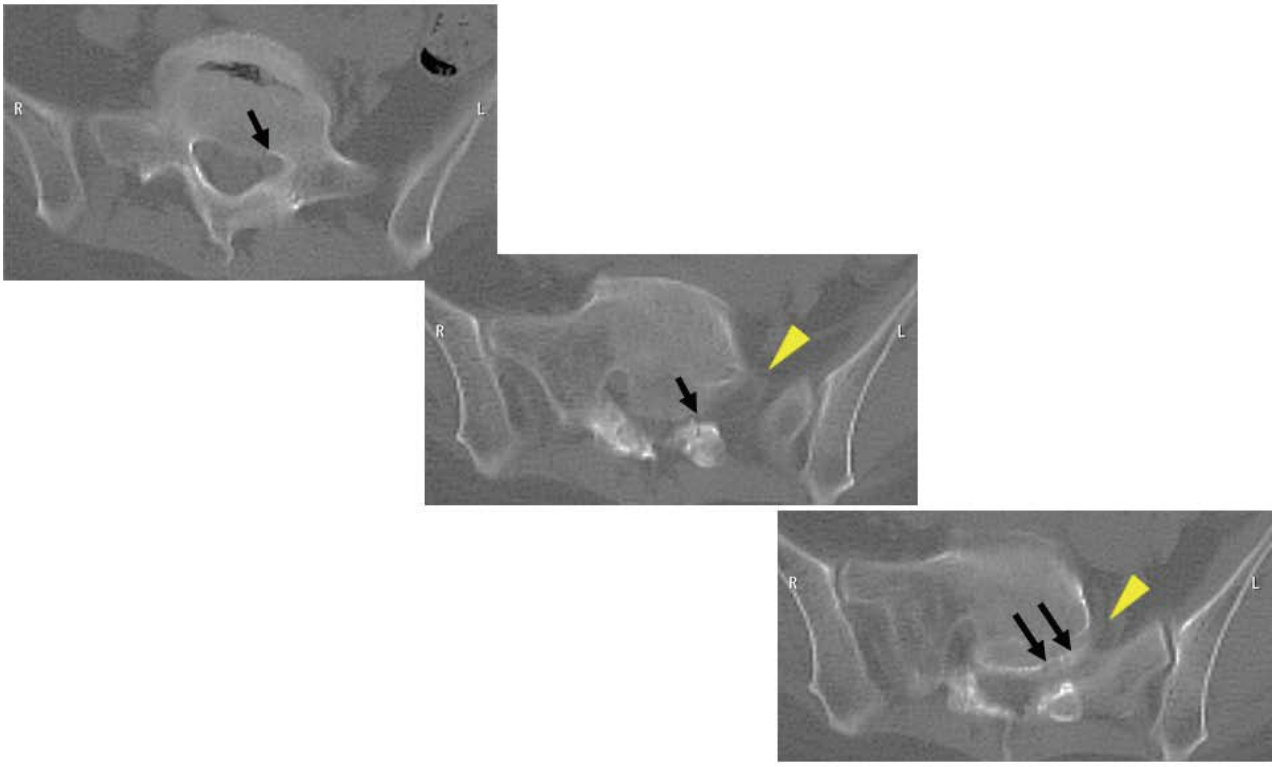
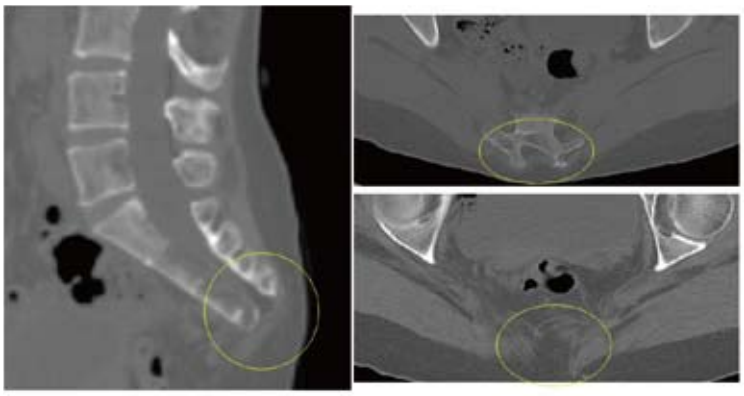


Figure 22 Sacral vertebra aplasia

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



Sagittal MPR scan　　Axial CT scan

Figure 23 Aplasia of the sacrum and coccyx

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

[Tsuyoshi Tajima]

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4) Tajima T, Wada T, Yoshizawa A, et al:Internal anomalies in thalidomide embryopathy: results of imaging screening by CT and MRI. Clin Radio 71:1199.e1-7, 2016

VIII Otorhinolaryngology

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

1 Auditory Defects

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

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

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

(1) Outer ear malformations

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

(2) Middle ear malformations

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

(3) Inner ear malformations

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

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

have severe hearing defects that impair communication during examinations.

2 Facial Nerve Palsy

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

3 Abducens Nerve Palsy

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

4 Vestibular Dysfunction

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

5 Orofacial Abnormalities

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

6 Other Comment

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

7 Relationship Between Otolaryngological Deformation and Limb Malformation

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

8 Other Considerations for Patient Care

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

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[Niro Tayama]

IX Dentistry and Oral Surgery Examination

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

1 Oral Examination

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

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

(1) Teeth

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

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

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

(2) Tooth alignment

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

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

(3) Fillings, artificial teeth, and dental implants

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

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

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

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

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

(4) Periodontal tissues

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

(5) The tongue, lips, and oral mucosa

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

2 Jaw and Other Bone Disorders

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

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

(1) Jaw

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

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

(2) Temporomandibular joint

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

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X Ophthalmologic Care

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

1 Introduction

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

2 Malformations of the Eyes and Their Symptoms

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

(1) Microphthalmos

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

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

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

(from reference 1).

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

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

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

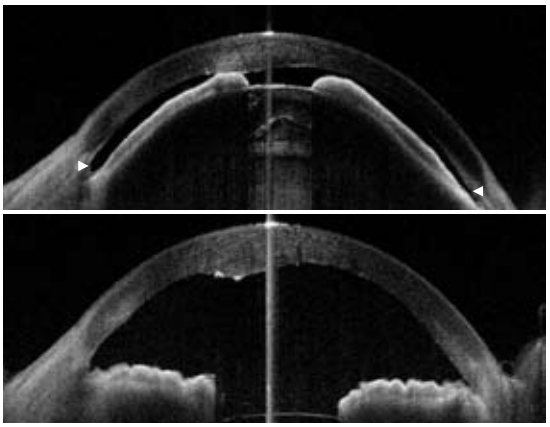

Figure 2 Cross-sections of the anterior eye of a patient with microphthalmos
The axial length of the eye is 17 mm, higher lens volume results in severe narrow angle (arrow heads), and the iris and cornea are adhered around the pupil (top). In lens reconstruction, the ≥4-mm thick lens was replaced with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

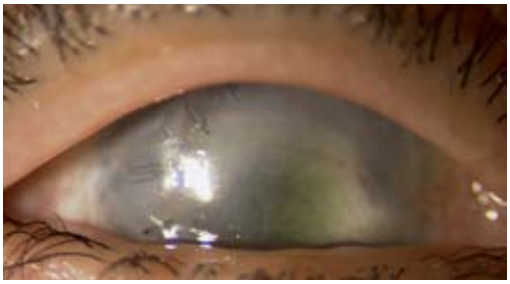

Figure 3 Postoperative complications in a patient with microphthalmos
The abnormal eye structure in microphthalmos makes surgery risky. Blindness may result from complications such as retinal detachment and corneal opacity (bullous keratopathy).

(2) Uveal coloboma

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

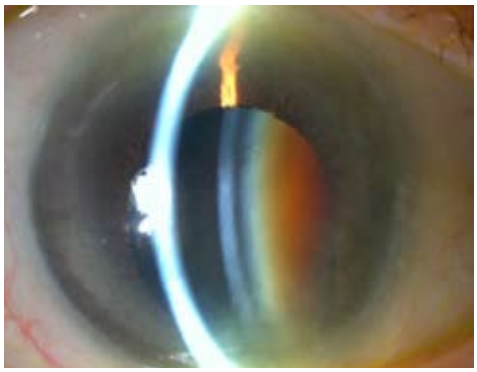

Figure 4 Uveal coloboma (iris coloboma)
Uveal coloboma always affects the lower half of the eye. Those with iris coloboma are often photophobic because the pupil is larger than normal. When ciliary body coloboma is present, the equator of the lens becomes deformed.

(3) Congenital aniridia

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

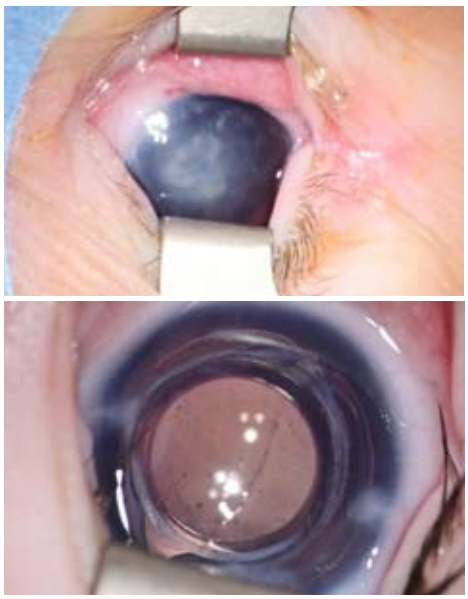

Figure 5 Aniridia (with congenital cataracts)
This 3-month-old patient has bilateral cataracts (top). Six months after lens reconstruction, the artificial lens is fixed within the capsule (bottom).

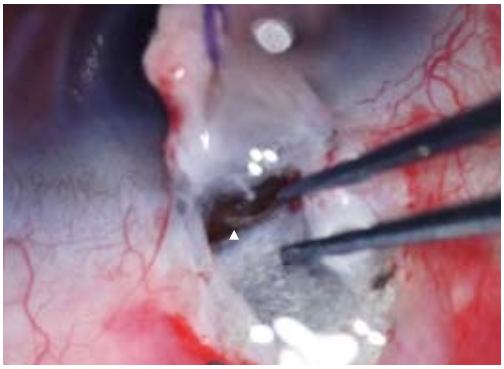

Figure 6 Glaucoma surgery (trabeculectomy)
Schlemm's canal is opened from the outside of the eye, and the trabecular meshwork (arrow head), which is the primary resistance to aqueous humor outflow, is removed. The procedure may be modified according to findings made during surgery.

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[Miyuki Nagahara]

XI Psychiatric Care

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

1 Psychiatric Issues in Patients with TE

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

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

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

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

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

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

2 Quality of Life (QOL) of Patients with TE

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

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

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

3 Tips for Caring for Patients with TE

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

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

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

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

XII Problems Encountered in Clinical Settings

1 Blood Sampling

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

1 Blood Collection: Being Prepared

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

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

2 Technical Challenges of and Techniques for Collecting Blood

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

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

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

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

Blood collection, being prepared, blood sampling kit

3 Blood Sampling Kits

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

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

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[Fumihiko Hinoshita]

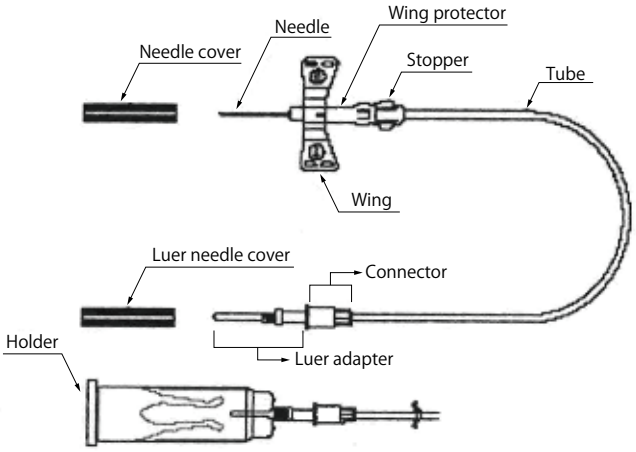

Figure 1 Names of the components in the Safe-touch PSV Set with Luer Adapter

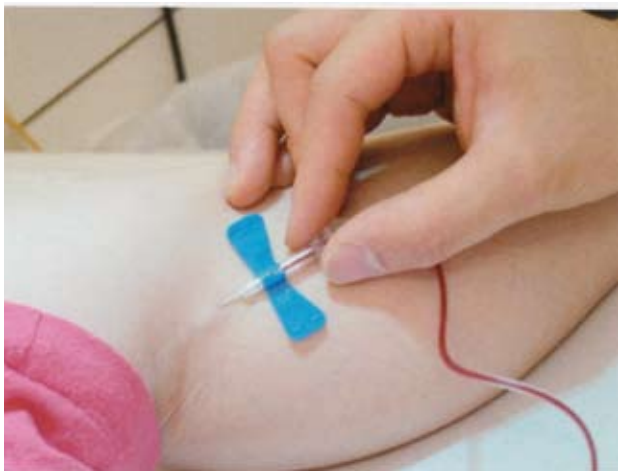

Figure 3 Patient from whom blood can be collected only from behind the left knee (24 gauge)

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

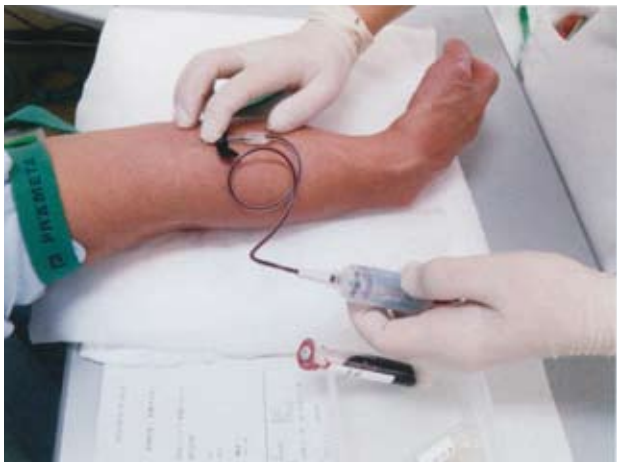

Figure 4 Patient from whom blood was successfully collected from a vein of the upper right limb (22 gauge)

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

XII Problems Encountered in Clinical Settings

2 Measuring Blood Pressure

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

Measurement by Healthcare Professionals

1 Before Measuring Blood Pressure

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

2 Selecting a Site to Measure Blood Pressure

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

3 Cuff Placement on the Upper and Lower Limbs

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

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

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

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

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

5 Evaluating Lower-limb Systolic Blood Pressure

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

6 Evaluation When peripheral arterial disease (PAD) Is Suspected

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

7 Recommendations of an Overseas Expert on Blood Pressure Measurement

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

8 Other Information

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

Home-based Blood Pressure Measurement Procedures

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

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

References

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

URL

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

[Fumihiko Hinoshita]

XII Problems Encountered in Clinical Settings

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

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

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

1 General Preoperative Issues

First, know what type of abnormality the patient has.

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

2 What Range of Preoperative Tests is Possible?

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

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

3 Issues Facing Anesthesia and Intraoperative Management

(1) Measuring blood pressure and ensuring venous access

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

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

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

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

(2) Airway management and intubation

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

(3) Options other than general anesthesia

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

(4) Maintaining body positioning during surgery

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

4 Postoperative Management

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

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3) Kumar CM. Anesthesia and thalidomide-related abnormalities. Anaesthesia 43: 613-614, 1988
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5) Shiga Y, Nojiri F, Yoshizawa A, et al. Measurement of blood pressure in a thalidomide-impaired patient who required ovarian cystectomy: A case report. Int J of Surg Case Reports 5:428-430, 2014
6) Earle R, Vaghadia H, Shanahan E, et al. Real-time measurement of blood pressure with Nexfin in a patient with thalidomide-related phocomelia. J of Clinical Anesth 34: 244-246, 2016
7) Imai K, Iida T, Yamamoto M, et al. Psychological and mental health problems in patients with thalidomide embryopathy in Japan. Psychiatry and Clinical Neuroscienses 68: 479-486, 2014

URL

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

[Yasuhiro Maehara]

XII Problems Encountered in Clinical Settings

4 Nursing

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

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

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

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

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

1 Urinalysis

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

2 Abdominal Ultrasonography

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

3 Electrocardiography

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

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

4 Computed Tomography (CT)

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

5 Hearing Tests and Otolaryngology Examinations

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

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

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

6 Gynecological Examinations

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

7 Breast Surgery Examinations

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

8 Upper Gastrointestinal Endoscopy

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

9 Examinations and Nutritional Guidance

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

10 Others

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

[Keiko Tanaka, Chika Kuge]

5 Information on Supporting Patients with Auditory Defects

Information on Hearing Aids

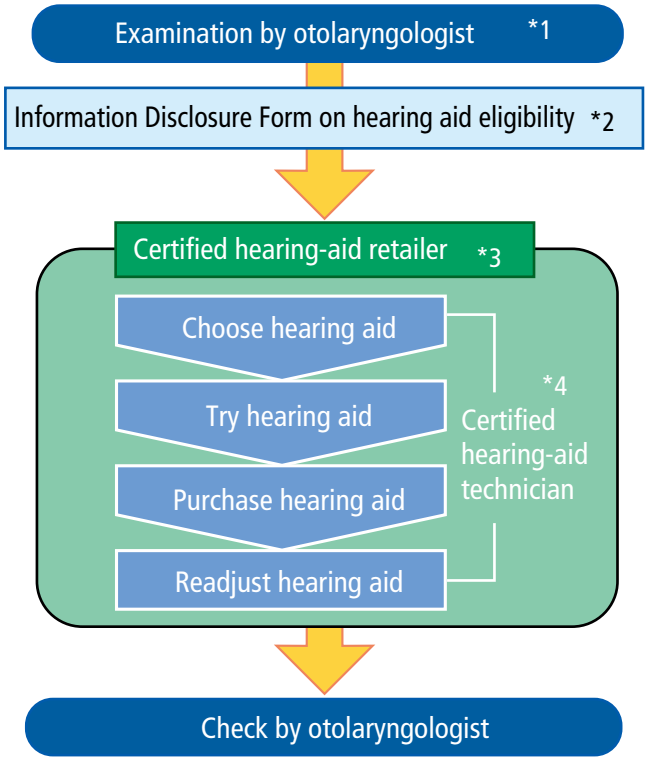
1. The Oto-Rhino-Laryngological Society of Japan, Inc.:
   :http://www.jibika.or.jp
   Easy explanation of hearing aids:
   http://www.jibika.or.jp/citizens/hochouki/yasasii.html
   List of hearing-aid specialized ENT doctors:
   http://www.jibika.or.jp/members/nintei/hochouki/hochouki.html
2. Japan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

Smartphone Apps

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

[Niro Tayama]

Process of purchasing a hearing aid



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

XIII Care for Thalidomide Embryopathy (TE) in Germany

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

Members of the TE research group visited Germany and the UK as the "Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-impaired People in Japan" in August 2016 and the "Research Group on Grasping the Health and Living Situations as well as Creating the Support Infrastructure for Thalidomide-impaired People in Japan" in September 2018. While in Germany, they visited two facilities that provide focused care for many thalidomide victims[1,2]. One facility, located in Nordrhein-Westfalen, is the Dr. Becker Rhein-Sieg-Klinik, which provides care in central Germany, where more patients with TE live than anywhere else. The other is Thalidomide Clinic Hamburg (Contergansprechstunde Hamburg), which offers comprehensive care for patients with TE in Hamburg and other areas in northern Germany. Each clinic is dedicated to supporting patients with TE. To inform TE care in Japan, the services they offer are presented here.

1 Dr. Becker Rhein-Sieg-Klinik

The Dr. Becker Rhein-Sieg-Klinik is located in Nümbrecht, a suburb of Cologne in Nordrhein-Westfalen. It opened the Outpatient Center for Contergan Victims in September 2017. There to cut the ribbon at the opening ceremony was Udo Herterich, the leader of the International Contergan Thalidomide Alliance (ICTA), a group of about 800 thalidomide victims in the state of Nordrhein-Westfalen (Figure 1).

The leader of the Center is Dr. Kraus M. Peters (at the left in Figure 1). Patients receive outpatient care 4 days a week from Monday to Thursday, with an optional examination by a psychotherapy specialist at the University Hospital of Cologne on Wednesday. Patients can opt for a 3-day schedule without the Wednesday examination (Table 1). The services include a welcome address by the coordination team, a doctor examination, acupuncture, moxibustion and other evaluations, as well as routine physical therapy (which includes aquatic therapy in a large pool), physiotherapy, and occupational therapy (Table 2).

Figure 1 Ribbon cutting ceremony at the launch of the Outpatient center for thalidomide-damaged people in the Dr. Becker Rhein-Sieg-Klinik (Ambulantes Zentrum für contergangeschädigte Menchen in der Dr. Becker Rhein-Sieg-Klinik)

Nordrhein-Westfalen, Hamburg, Outpatient Center for Contergan Victims, alternative medicine

In Germany, physical therapy is called *physiotherapie* (English: physiotherapy). Dr. Becker's facility distinguishes physiotherapy from physical therapy.

*Sling table (Figure 2): A sling table is used to bear some of the weight of the body to facilitate exercise of the limbs and trunk.

Table 1 Schedule of the Outpatient Center for Contergan Victims

	Category	Caregiver
Monday	Welcome address	Coordination team
	Physical examination	Doctor
	Lunch	
	Physical therapy	PT
	Physiotherapy	PT
	Occupational therapy	OT
	Acupuncture, moxibustion	Doctor
	Follow-up	Coordination team
Tuesday	Consultation	Visiting specialist
	Lunch	
	Physiotherapy	PT
	Occupational therapy	OT
	Physical therapy	PT
Wednesday	Psychotherapy consultation	University of Cologne
Thursday	Physiotherapy	PT
	Physical therapy	PT
	Occupational therapy	OT
	Lunch	
	Acupuncture, moxibustion	Doctor
	Closing discussion	Doctor
	Farewell remarks	Coordination team
	PT = Physical therapist	
	OT = Occupational therapist	

PT = Physical therapist
OT = Occupational therapist

Table 2 Therapeutic treatments

Physiotherapy	Mobilization, sling table*, cognitive and motor training/physical exercise
Physical therapy	Craniosacral therapy, foot reflexology (foot acupressure), interstitial massage, ultrasound therapy, aquatic therapy, acupuncture, moxibustion
Occupational therapy (ergotherapy)	Mobilization of the hands, upper limbs, and shoulders, brace consultations
Evaluation	Evaluation + recommended approaches

Figure 2 A patient is treated on a sling table

• Following is a list of questions we asked Dr. Peters and his staff along with their answers.

1) What do your conferences involve?

We begin by telling the patient about their condition and our approach. We then write a prescription for therapy with our team of physical and occupational therapists. We evaluate the effects of the therapeutic approach at the next visit. Since some patients are unable to make a follow-up visit, we can pass along our recommended approach and prescriptions to the referring doctor.

2) Do you offer telemedicine?

Having considered the comments of our psychologist Mr. Alexander, we do not offer it now because of problems in the system for connecting individual patients with TE, but we will offer it in the future. Dr. Peters was asked in 2019 to diagnose a new claimer from Brazil. From faraway Germany, Dr. Peters confirmed that the patients satisfied the diagnostic criteria in the British diagnostic algorithm for thalidomide embryopathy based on the dates of birth, affected limbs, other disease characteristics, and family history of the claimers.

3) How do you psychologically evaluate chronic pain?

Since our patients are so susceptible to psychosomatic pain, we work hard on our evaluations in this area. On Wednesdays, we offer psychotherapy consultations at the University of Cologne. Holding meetings for thalidomiders to exchange opinions about pain and anxiety have been found to be effective.

4) Are there any new approaches to pain?

Thalidomiders in general (1) do not like medications, (2) have bones and tissues different from healthy people, and (3) have chronic pain. For these reasons, here in Nümbrecht, we focus on acupuncture, moxibustion, and aquatic therapy, and use a range of other approaches (see Table 2).

2 Thalidomide Clinic Hamburg

(Contergansprechstunde Hamburg) at Schön Klinik Hamburg Eilbek

In Hamburg, Dr. Rudolf Beyer (of the Schön Klinik Hamburg Eilbek) established the Thalidomide Clinic Hamburg (Contergansprechstunde Hamburg) in the Schön Klinik Hamburg Eilbek in 2013. There, patients are treated through a comprehensive, multidisciplinary approach (Figure 3). The Center served fewer than 20 patients in 2014, but more patients began to visit as word spread. A total of 181 patients visited a total of 309 times from 2014 to 2017. The data of patients who have visited even once are stored in electronic medical records so that they can be easily retrieved if the patient must be hospitalized. Although Dr. Beyer is an anesthesiologist, visiting patients can be seen by specialists, including a pain specialist, orthopedic surgeon, psychiatrist, and physical therapist, as well as an internist or surgeon when needed. The Center uses X-ray devices, computed tomography (CT), and magnetic resonance imaging (MRI) to identify problems that are treated with the necessary medication, pain therapy, physical therapy, psychotherapy, and rehabilitation. When indicated, patients are referred for care to an otolaryngologist, ophthalmologist, or dentist. Patients can also receive hospitalized care managed by a surgeon, physical therapist, or psychologist when needed. The focuses of the Center are (1) orthopedic issues, (2) pain, (3) hypertension and cardiovascular risk factors, (4) entrapment neuropathy, (5) digestive diseases, and (6) psychiatric diseases. The Center caregivers organically partner and work with other hospital departments to address these conditions. Instruction in yoga, Pilates, and other alternative therapies are also offered. These programs appear to be arranged for patients with TE because even healthy people find them difficult.

- Research activities

1) Application of digital health apps for TE

In partnership with the Institute of Technology and Innovation Management at the Hamburg University of Technology, the Center is using an Internet survey service called Survey Monkey to determine what kinds of digital health apps are needed for TE. They identified a certain amount of interest in individualized yoga and Pilates instruction and remote instruction for rehabilitation and exercise. Unexpectedly, however, the greatest amount of interest was expressed in flexible home care. Specifically, survey respondents expressed interest in a digital app they could use to seek a supporter when they require care (e.g., for shopping or going to the movies). Such an app would help thalidomiders live more independently.

2) Evaluation of congenital vascular and organ anomalies using non-contrast-enhanced magnetic resonance angiography

The Center evaluated 78 patients with TE in partnership with the University Hospital Hamburg Eppendorf. The investigators found a higher incidence of double renal arteries and other renal vascular anomalies than in healthy individuals, but noted that these vascular malformations did not cause renal impairment[3)].

3) New attempts to measure blood pressure

Investigators are studying methods for measuring blood pressure by looking at changes in pulse oximetry determined with a finger cuff and measuring blood pressure at the buccal artery, but these methods have not yet been applied for patients with TE because the former method requires reference measurements and is expensive, and the latter method requires mathematical modeling to produce blood pressure values.

4) Other studies

In a partnership with the University of Hannover Medical School, the Center began investigations in June

Figure 3 Schön Klinik Hamburg Eilbek (left) and Dr. Rudolf Beyer giving a presentation (right)

2016 to serve as a foundation for helping patients with TE maintain their range of motion and be independent, and, under an initiative called the "E-Health Project," is developing a way to allow easy, on-demand access to the healthcare information of thalidomide victims when they visit other medical institutions by importing digitized healthcare information into computers. The Center is also working with the Hamburg University of Technology to provide remote instruction for rehabilitation and exercise via the Internet.

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2) Hinoshita F, Haga N, Kayamori R, et al. II. General Report 3. Visit to Europe Report: Visit / Visit to Europe, Exchange with Experts. Health and Labor Science Research Grant (Pharmaceutical / Medical Equipment Regular Science Research Project) "Study on understanding the health and living conditions of patients with salidamide embryos and building a support base (H29-Pharmaceutical-Designation-006)" 2018 Summary / Shared Research Report. 2019 (in Japanese)
3) Weinrich JM, Beyer R, Well L, et al: Assessment of Congenital Vascular and Organ Anomalies in Subjects With Thalidomide Embryopathy Using Non-Contrast Magnetic Resonance Angiography. Circ J 82(9):2364-2371, 2018

[Ryoji Kayamori, Fumihiko Hinoshita]

XIV Related Information

1. Network of Healthcare Providers Serving Thalidomide Survivors

The Network of Healthcare Providers Serving Thalidomide Survivors was established in 2015 by the previous research group, the Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-impaired People in Japan. This network consists of dozens of members who are physicians, nurses, physiotherapists, researchers, pharmacists and other healthcare professionals, with experience providing care for or otherwise involved in activities with thalidomiders. This network aims to facilitate access to healthcare for thalidomiders even in local areas. Moreover, this network is useful for consultations among physicians, caregivers and researchers and for the exchange of clinical and research information.

The list of this network is omitted here because it is written in Japanese.

2. Website of the Thalidomide Embryopathy Research Group

The website of the Thalidomide Embryopathy Research Group of Japan was created in March 2016, and is available at http://thalidomide-embryopathy.com/.

3. Information on the Ishizue Foundation

The Public Interest Incorporated Foundation, the Ishizue Foundation, was founded in 1974 for thalidomide victims living in Japan, and continues to actively work on various issues.

（http://ishizue-twc.or.jp/）

4. Notable Sites for Information on Thalidomide Embryopathy Outside Japan

- Conterganstiftung für behinderte Menschen. Contergan Infoportal. (Germany)
  https://www.contergan-infoportal.de/
- Contergan. Wiederholt durchzuführende Befragungen zu Problemen, speziellen Bedarfen und Versorgungsdefiziten von contergangeschädigten Menschen (A survey on the living situations of German thalidomiders)
  https://silo.tips/download/wiederholt-durchzufhrende-befragungen-zu-problemen-speziellen-bedarfen-und-verso
- Damage to Health, Psychosocial Disorders and Care Requirements of Thalidomide Victims (Survivors?) in North Rhine Westphalia from a Long-Term Perspective. Expert opinion commissioned by LZG.NRW.
  https://www.thalidomidetrust.org/wp-content/uploads/2016/10/The-Cologne-Report.pdf
- The Thalidomide Trust (The UK)
  https://www.thalidomidetrust.org/
- A Securer Future - Evaluation of the Health Grant to Thalidomide-Impaired People Year 3 Final Report – July 2013
  http://www.fiftyyearfight.org/images/Health_Grant_Evaluation_Year_3_Final_Report_July_2013_.pdf
- The Swedish Thalidomide Society (Sweden)
  http://www.thalidomide.org/web/welcome/
- EX-Center (Sweden)
  http://www.ex-center.org/web/home/
- Thalidomide victims association of Canada (Canada)
  http://www.thalidomide.ca/the-canadian-tragedy/

* The information above was obtained in 2020.

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