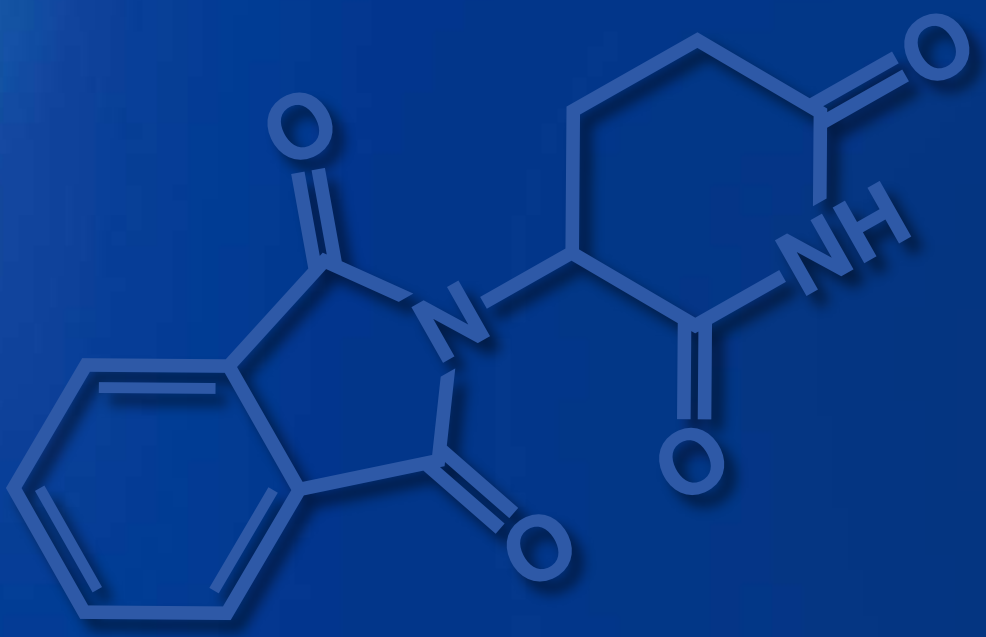

Guide for the Management of Thalidomide Embryopathy 2017

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

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

Fumiya Okabe

Director, Office for Drug-Related Damages, Pharmaceutical Safetey and Environmental Health Bureau, Ministry of Health, Labour and Welfare

In the 1950s, thalidomide, a drug developed and marketed as a hypnotic, tragically caused widespread upper limb and auditory defects in children exposed in utero. As a result of thalidomide-related litigation in Japan, the national government admitted responsibility and accepted mediation, and has since endeavored to meet the medical needs of victims.

A research team on thalidomide embryopathy (TE) was established in FY2011 when Dr. Atsuto Yoshizawa of the National Center for Global Health and Medicine (NCGM) was appointed as chair in response to an appeal from the Ishizue Foundation to the Minister of Health, Labour, and Welfare. The team was called the "National Study on the Health and Living Situations of Thalidomide-Impaired People". Dr. Yoshizawa's team was charged with investigating the health and living conditions of patients with TE to determine how these victims should be properly supported. As one of its activities, the team developed "Q&A on Thalidomide-Impaired People" together with medical doctors and other specialized healthcare professionals across relevant disciplines in 2014. This document is widely used in clinical settings to facilitate the proper management of thalidomide victims.

In FY2014, Dr. Fumihiko Hinoshita, also of NCGM, assumed leadership of the TE research group. The team was renamed the "Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-Impaired People in Japan". The responsibilities of Dr. Hinoshita's group, which operates under his initiative and works with many experts, include administering comprehensive medical examinations and questionnaires, networking with experts in other countries that have thalidomide victims, holding research meetings on TE, and actively engaging in other activities to better support victims. The group plays a central role in investigations of the health and welfare challenges and policies surrounding patients with TE. I am grateful for the many contributions of all who have worked on the group to present and the kind assistance of NCGM, which offered comprehensive medical examinations and allowed its staff to participate.

Post-retirement care for thalidomide victims is emerging as an issue now that many are in their 50s. Local medical institutions will have to properly meet their growing medical needs to allow victims to continue their lives fruitfully in the communities they call home. Many medical institutions, however, are not always experienced in managing TE. This lack of experience can be particularly problematic in areas such as dialysis and dentistry that victims will require more as they get older.

This "2017 Guide for the Management of Thalidomide Embryopathy," which covers many healthcare disciplines, was developed to help healthcare professionals inexperienced with TE patients properly treat this population.

I would like to encourage healthcare professionals throughout Japan to make use of this valuable guide to support these special patients. I sincerely hope that this guide will help thalidomide victims receive better care more smoothly and experience fulfilling lives through treatment.

2017 Guide for the Management of Thalidomide Embryopathy

Editor's Remarks

Shin Ohnishi

Hospital Director, Center Hospital of the National Center for Global Health and Medicine

You are reading this "2017 Guide for the Management of Thalidomide Embryopathy" thanks to the hard work of many people dedicated to researching and providing care for thalidomide embryopathy (TE). This guide is intended for doctors, nurses, and other healthcare professionals charged with the care of patients with TE. If you have TE and encounter a doctor inexperienced with this condition when you visit a medical institution, please tell them about this guide. If you are a busy doctor, browsing this guide will give you immediate access relevant to the care you will need to give.

This guide contains a wealth of the latest information on TE in chapters on the history and overview of TE, diagnostic procedures, medical treatment, orthopedic surgery and rehabilitation, radiology, otolaryngology, dentistry and oral surgery, ophthalmology, psychiatry, and many other clinical issues.

I am convinced that this guide, created more than 50 years after TE appeared, will help maintain health, prevent disease, and assist routine healthcare for patients with the disease throughout the world.

Note: This Guide was created under the FY2016 Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Health Labour Sciences Research Grants (under the title of "Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-Impaired People in Japan"). We express our gratitude to Secretary Aki Fujiwara for providing editing services for this Guide and administrative assistance and support for the team.

TABLE OF CONTENTS

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I Introduction

The marketing of the over-the-counter thalidomide drug Contergan® by 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 after. The German pediatrician, Dr. Widukind Lenz, eventually identified the cause of these disorders (which turned out to be thalidomide embryopathy), and on November 15, 1961, informed Heinrich Mückter, the chief scientist and lead thalidomide developer at Grünenthal. This later became known as Lenz's warning. Lenz's warning sparked alarm worldwide as people realized that this previously unexplained disorder was drug-induced.

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 thalidomide embryopathy (TE) had been born. The Ministry of Health and Welfare officially recognized 309 cases at the time. The children born with the consequences of embryopathy are now in their 50s. In addition to the orthopedic and auditory defects they have 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 [CKD]), and psychiatric issues. TE thus brings not only the congenital disorders this population has had for over 50 years, but also a wide range of other clinical conditions.

The Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-Impaired People in Japan created this management guide to allow healthcare professionals to better address the many problems faced by patients with TE. This guide expands on the aims and content of "Q&A on Thalidomide-Impaired People" developed by the previous group while widening the scope of medical disciplines covered to encompass all doctors, nurses, and other healthcare professionals responsible for managing TE. Patients with TE live throughout Japan and may therefore not receive care from doctors and healthcare professionals knowledgeable about TE, who tend to be clustered in Tokyo and other large cities. This guide is designed for doctors and healthcare professionals unfamiliar with TE to use to give patients satisfactory treatment, nursing, rehabilitation, and care.

This guide could be considered an English TE textbook not only for Japan but for other countries, and it is my sincere hope that it benefits doctors, nurses, and other healthcare professionals, researchers, bureaucrats, and others worldwide involved in one way or another with TE.

This guide was translated into English almost one year after the original publication in Japanese.

June 1, 2018

Fumihiko Hinoshita,
Head,
Research Group on the Various Problems Regarding the Health and Living Situations of Thalidomide-Impaired People in Japan and
Department of Nephrology, Center Hospital of the National Center for Global Health and Medicine

II History and Overview of Thalidomide Embryopathy

- Thalidomide embryopathy was the first drug-induced tragedy with worldwide 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-phthalimido-glutarimide, the true name of the compound.
- Brand names include Contergan (West Germany), Distaval (United Kingdom), 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 thalidomide embryopathy occurred during this 10-month lag.
- The withdrawal of thalidomide from the market stopped more cases of thalidomide embryopathy, demonstrating the importance of epidemiological investigations and academic scrutiny.

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 development. 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 the masses in 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 started being 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, seven in Africa, 17 in Asia, and 11 in the Western Hemisphere, but notably not in the United States.

In Japan, a researcher at Dainippon Pharmaceutical Co., Ltd., inspired after reading an article written by Grünental's Dr. Mückter in a pharmacology journal, independently developed a different process for synthesizing thalidomide. Under Japanese law, 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.

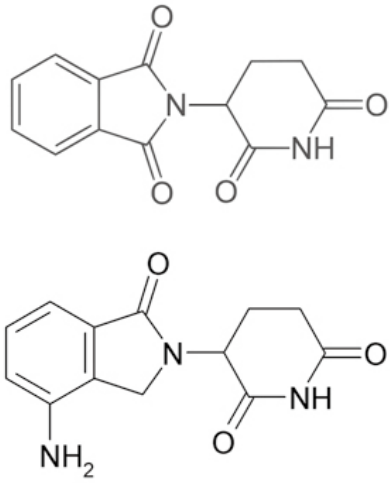

Figure 1 Chemical formula of thalidomide
The upper formula shows thalidomide, a shortened form of α-phthalimido-glutarimide. The lower formula shows the chemical formula of lenalidomide, a compound now used in multiple myeloma.

Thalidomide, embryopathy, Grünenthal, Contergan, Distaval, Isomin, Widukind Lenz, Carl Schulte-Hillen

Dainippon Pharmaceutical filed for a patent in November 1956 and began clinical development 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 for insomnia, tension and anxiety, and sedation before operations, 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 United Kingdom, Neurosedyn marketed in Sweden, and Kevadon and Talimol sold in Canada. Combination products included Grippex (gripp means cold), Algosediv (algo means pain, sediv means sedation), Enterodesiv (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. 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 (UPI), 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 Grünental'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 Journa*l. The letter reported four patients who had taken thalidomide for 18–24 months. The author stated that the patients complained of (1) marked paresthesia 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 leg muscles. These side effects improved but still remained with discontinuation, the author continued. Strangely enough, the author ended 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 mild in comparison to what came next. Evidence began to mount of a far worse side effect—deformed children born to mothers who took thalidomide during early pregnancy.

In 1960, Drs. Kosenow and Pfeiffer, pediatricians of the Institute of Human Genetics in University of Munster, presented on two babies with short limbs, facial hemangioma, and duodenal stenosis, which had been rarely reported until then, at a local meeting of the German Society of Pediatrics. 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 (Wiedemann, HR and Aeissen, K: Zur Frage der derzeitigen Häufung von Gliedmaßen Fehbildungen. Med Mschr 12; 816-818, 1961). 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 the 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 in May 1961, had the same deformities: short upper limbs, no 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 for 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 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 passed away (Figure 3).

Figure 2
Jan Schulte-Hillen, Dr. Ehrt, and members of the Thalidomide Research Team (photo taken on the roof of a hospital in Lucerne). Dr. Ehrt (front center), also a thalidomide victim, has bilateral thumb hypoplasia. She has a PhD in psychology.

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."

On November 24, representatives of Grünenthal met with Lenz in the provincial Ministry of the Interior in North Rhine-Westphalia. On November 25, the international press erroneously reported that thalidomide had been withdrawn 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.


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 Martinikirche in Siegen, Grabenstraße 27, 57072 Siegen statt.

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

Anstelle von Blumen bittet sich Carl-Hermann über eine Spende an den Bundesverband Contergangeschädigter e.V., Bank für Sozialwirtschaft Köln, IBAN: DE35 3702 0500 0007 0621 00, BIC: BFSWDE33XXX, "Carl-Hermann Schulte-Hillen"

Figure 3
A notice of the death of Mr. Carl Hermann Schulte-Hillen. He died after a long battle with Alzheimer's disease.

5 Avoidable Cases of Thalidomide Embryopathy

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 United Kingdom on December 2, and Sweden, somewhat later, on December 18.

UPI reported news about thalidomide embryopathy (TE) in Japan on November 17. The drug, however, was referred to mostly as thalidomide, the name of the component, 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 public interest incorporated 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 July 21, 1962 issue of the *Lancet*. This information was presented at a Sapporo regional meeting of the Japan Pediatric Society on August 26. An article on this presentation ran in the *Yomiuri* newspaper 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 removal and the recall (Figure 4). This proved the thalidomide theory, demonstrating the importance of epidemiological investigations and academic scrutiny.

Ryoji Kayamori,
Department of Physicotherapeutics, Teikyo Heisei University

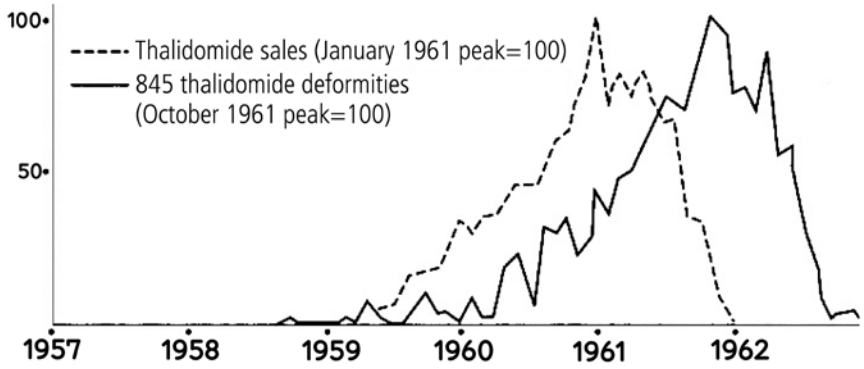

Figure 4 Thalidomide sales and the incidence of thalidomide deformities
Lenz W: A short history of thalidomide embryopathy. Teratology 38: 203-215, 1988

III Diagnostic Procedures for Thalidomide Embryopathy

Key Points

- Although 50 years have passed since the thalidomide tragedy, new claimers have emerged in certain countries, asserting that they were overlooked.
- A diagnosis of thalidomide embryopathy requires (1) proof that the mother took thalidomide, and (2) a date of birth coinciding with when thalidomide was marketed (i.e., 1958 to 1964).
- The World Health Organization (WHO) is of the position that "It is impossible to say with any certainty what constitutes a thalidomide deformity." The medical profession eagerly awaits new proposals.
- The Ministry of Health, Labour, and Welfare issued diagnostic criteria and severity classifications for thalidomide embryopathy in Japan.
- The physical manifestations of thalidomide embryopathy are broadly classified as upper-limb hypoplasia and auditory hypoplasia. These are often accompanied by arm domination, preaxial longitudinal hypoplasia, and, in auditory hypoplasia, Duane syndrome and facial paralysis.
- Thalidomide embryopathy must be differentiated from three to five syndromes, all of which are very similar. Differentiation based on physical signs alone is unfeasible. All of these syndromes are caused by a genetic anomaly.

1 Introduction

New claimers have emerged with the reintroduction of thalidomide or saying they were overlooked 50 years ago. This chapter explores the basics involved in diagnosing thalidomide embryopathy (TE).

2 Requirements for a Diagnosis of Thalidomide Embryopathy

TE is defined as a deformity in the offspring of a mother who took thalidomide 34 to 50 days after her last period. Genetic diseases are not included. Thalidomide was marketed in Japan from around 1959 to 1962 for morning sickness and insomnia associated with pregnancy.

To qualify as having TE, a new claimer must (1) show proof that the mother took thalidomide (although this is difficult as many medical records have been destroyed and prescribing doctors have died), and (2) have a date of birth coinciding with when thalidomide was marketed (i.e., 1958 to 1964) (Figure 1). Those not meeting these two requirements are examined for physical findings characteristic of TE.

3 Position of the World Health Organization (WHO)

The WHO held a meeting on diagnostic procedures for new claimers in 2014. It was concluded that "It is impossible to say with any certainty what constitutes a thalidomide deformity." A 4-grade scale of likelihood was proposed: (1) highly likely (at least 90%), (2) probable (about 65%), (3) possible (about 25%), and (4) highly unlikely (10% or less) (these percentages, from Volume 315, Issue 12 of the New England Journal of Medicine, are arbitrary). This proposal, however, lacks specificity. Although this proposal ranks patients based on the total

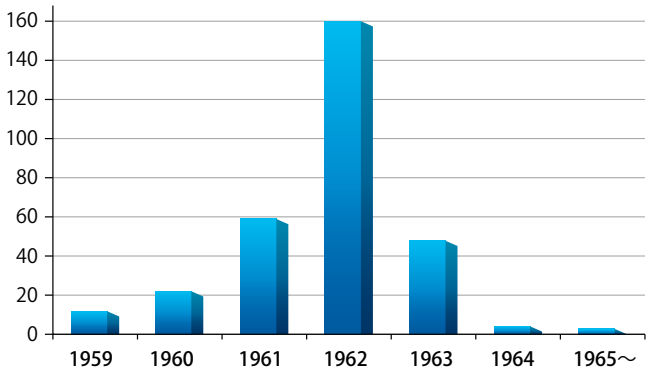

Figure 1 Numbers of thalidomide embryopathy babies born in Japan

Keywords

New claimer, thalidomide embryopathy diagnosis, diagnostic criteria and severities, upper-limb hypoplasia, auditory hypoplasia, Duane syndrome, facial paralysis, Holt-Oram syndrome, Okihiro syndrome

of several scores, patients with particularly high scores are likely to be classified as not having TE. This proposal was from the United Kingdom. The medical profession eagerly awaits an alternative.

4 Physical Manifestations of Thalidomide Embryopathy

The Japanese Ministry of Health, Labour, and Welfare provides a checklist for TE (Figure 2). TE victims are classified into two 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%). Thus, about three-quarters of the victims fall into the short-arm group, and the other quarter are in the hearing-loss group (Figure 3).

	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 2 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.

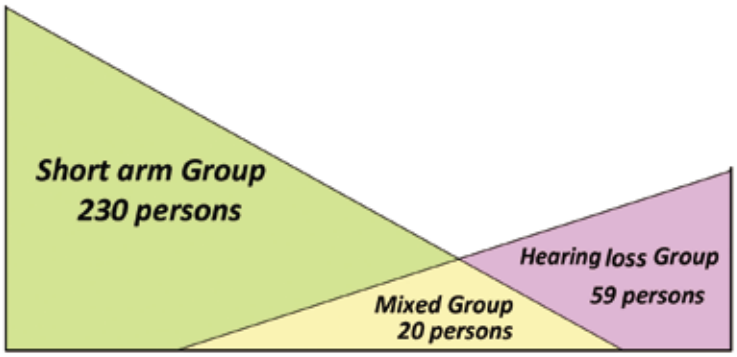

Figure 3 Physical manifestations of thalidomide embryopathy
Patients are classified into a short-arm or hearing-loss group.

(1) Preaxial longitudinal hypoplasia

Preaxial longitudinal hypoplasia is a feature of upper or lower limb reduction defects. Hypoplasia occurs in the order of the thumb, 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 4). Some victims have hypoplasia of the arm muscles despite having a normally formed humerus, scapula, and clavicle.

(2) Symmetry and arm domination

TE rarely features complete right–left symmetry. Upper-limb hypoplasia generally appears with certain right–left differences. This might be attributed to thalidomide's entry into the fetal circulation via placental blood after being taken by the mother. At the 2015 International Symposium on Thalidomide Embryopathy in Tokyo, Janet McCredie proposed that TE with unilateral manifestations was possible. Many of the Japanese victims appear to be normal on one side but, on closer observation, have slight thenar hypoplasia. Thenar hypoplasia must be factored in to diagnoses. None of the Japanese TE victims has unilateral manifestations.

The lower limbs are often unaffected, with manifestations limited to the upper limbs in Japan.

(3) Severity classifications for upper-limb hypoplasia

Upper-limb hypoplasia is classified into the four grades of most severe, severe, moderate, and mild (Table 1, Figure 5). Victims most typically fall into the severe category followed in decreasing order by moderate, mild, and most severe.

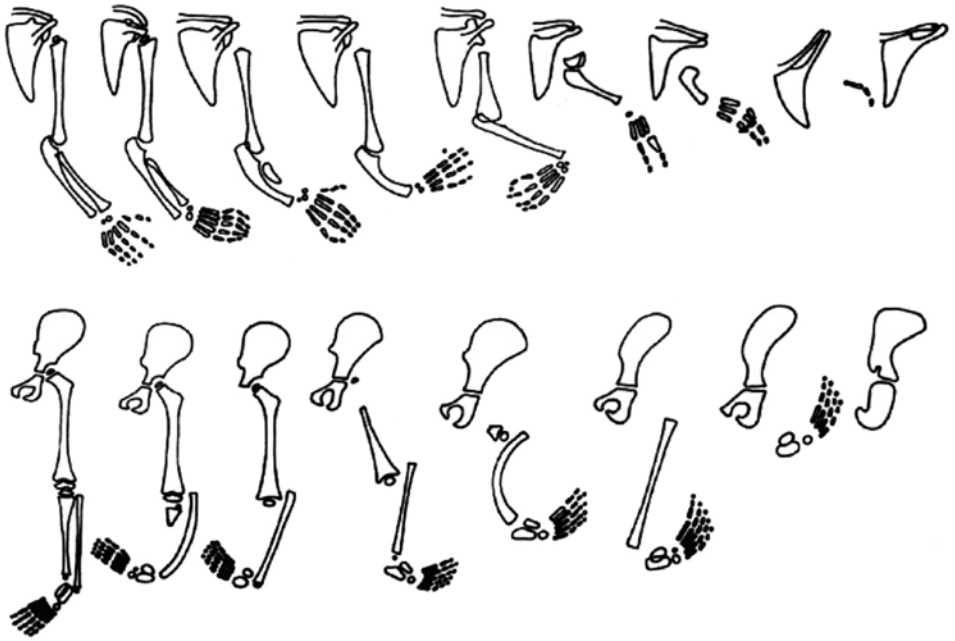

Figure 4 Pattern and severity classification of hypoplasia in thalidomide embryopathy

Table 1 Severity classification criteria for upper-limb hypoplasia

Most severe	Most severe upper limb defects a) Bilateral amelia or phocomelia b) Amelia or phocomelia plus severe ectromelia
Severe	Severe upper limb defects a) Phocomelia plus ectromelia b) Severe bilateral ectromelia c) Severe ectromelia plus ectromelia
Moderate	Forearm defects a) Severe ectromelia plus hand abnormalities b) Bilateral ectromelia c) Ectromelia plus hand abnormalities
Mild	Hand defects a) Bilateral hand abnormalities b) Unilateral hand abnormalities

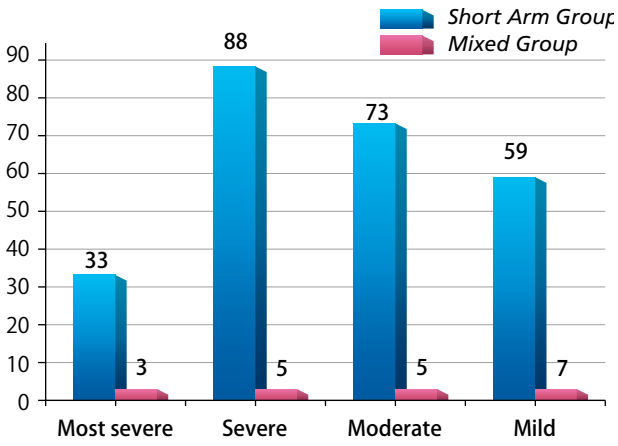

Figure 5 Severity classifications of upper-limb hypoplasia

(4) 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 nerve in the 8th cranial nerve (Figure 6, Table 2). Other frequent manifestations include Duane syndrome with defects of the sixth cranial nerve nuclei, facial paralysis with hypoplasia of the seventh cranial nerve nuclei, and crocodile tears syndrome. Upper-limb hypoplasia occurred in just 20 of the 309 (6%) victims in the hearing-loss group. Auditory hypoplasia severity is typically classified according to the degree of deafness.

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

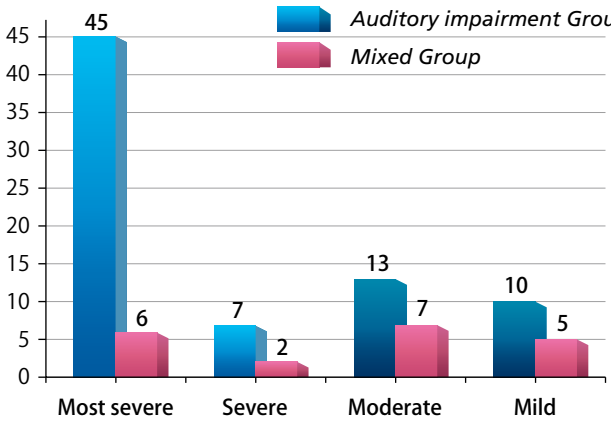

Figure 6 Distribution of TE victims with deafness according to severity categories

Table 2 Types and classifications of auditory hypoplasia

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 Tanaka Y 1987)

Legal evidence is based on the severity of deafness at the ages of 12 to 14.

Classification therefore does not factor in worsening of deafness with age, such as in a patient with moderate deafness progressing to most severe deafness in the fourth to fifth decade of life.

5 Diagnosing Thalidomide Embryopathy

Can a diagnosis of TE be assigned to a new claimer? Or can a diagnosis of TE be made in someone with upper-limb hypoplasia and auditory hypoplasia with organ defects factored in? Unfortunately for the diagnostician, multiple syndromes that are very similar to TE must be considered in the differential diagnosis. These syndromes, which include Duane syndrome and organ defects, all involve preaxial longitudinal hypoplasia. They also feature otological manifestations resembling those of TE. Characteristically, all are genetic diseases.

They are (1) Holt-Oram syndrome, which has a *TBX5* gene abnormality; (2) Duane-radial ray syndrome (Okihiro syndrome), which involves a *SALL4* mutation; (3) Townes–Brocks syndrome, an autosomal dominant genetic disorder featuring imperforate anus, auricular malformation, thumb malformation, and kidney malformation and 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 defects (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.

*All of the concepts mentioned above are specifically applied in Japan

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IV 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 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 test 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

As with the general Japanese population, patients with thalidomide embryopathy (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 thalidomide embryopathy

The frequency of lifestyle diseases in patients with TE is shown in Table 1. Hepatic steatosis and hypertension

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)

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

were common, affecting about half of both sexes. In decreasing order of prevalence, other common 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. An HOMA-R score of ≥3.0 therefore indicates insulin resistance. Female hormones are believed to be interrelated with metabolic syndrome pathogenesis because women with polycystic ovaries, 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 onset of hepatic steatosis, as was the case with metabolic syndrome. 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 test 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 screening 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 meat 3–7 times a week (Figure 1). Although no statistically significant correlations were found between eating habits and lifestyle diseases, the high prevalence of dyslipidemia

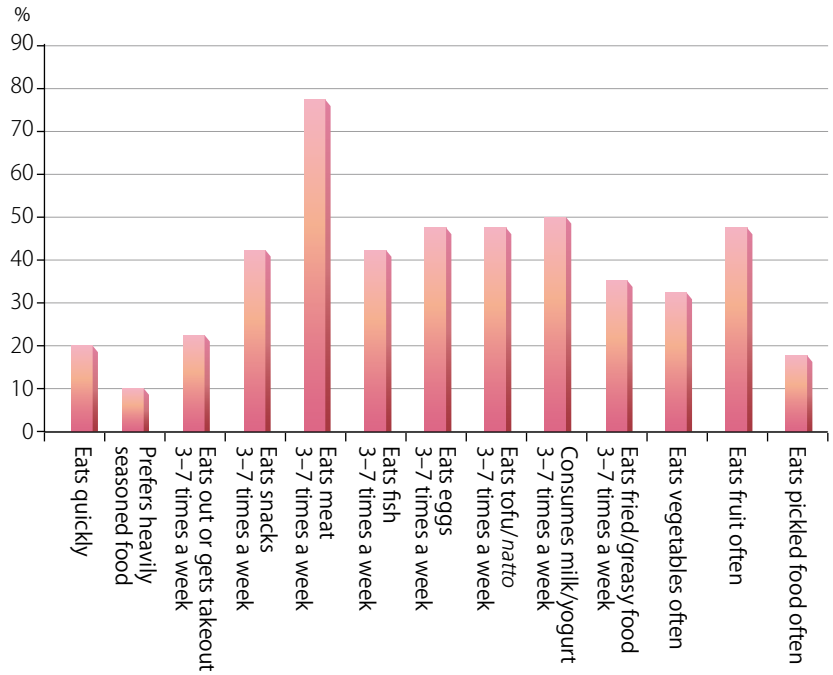

Figure 1 Eating habits

indicates the need for diet therapy in which patients are advised to reduce meat consumption.

Hyperuricemia is known to contribute to chronic kidney disease (CKD) via the renin-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 TE patients 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 the latest round of health examinations of TE patients, 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 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 TE patients 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.

2 Gallbladder Agenesis

A substantial proportion of thalidomide victims have cardiac malformations, gallbladder agenesis, and other internal disorders, 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[3]. An investigation of the interrelation of these internal defects with a focus on gallbladder agenesis revealed block vertebrae in about 40% of the TE patients 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, cervical vertebra 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 involves impaired neovascularization, it follows that block vertebrae sometimes appear in TE upper-limb defects[4].

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IV 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.
- Thalidomide and its derivatives cause thyroid dysfunction and endocrine and metabolic abnormalities.

1 Introduction

We have examined 10 men and 23 women with thalidomide embryopathy (TE) (33 patients; mean age: 52 years) at our medical institution, National Hospital Organization Kyoto Medical Center. A summary of our findings follows.

* One man (10%) and six women (26%) had mild obesity (i.e., body mass index [BMI] = 25–30 kg/m^2).
* Two men (20%) and three women (17%) had high alanine aminotransferase (ALT) levels.
* About half of the patients (16 of 33) had hyper-low density lipoprotein (LDL) cholesterolemia (>120 mg/dL). Four men (40%) and three women (13%) had hypertriglyceridemia (>150 mg/dL). No patient had hypo-high density lipoprotein (HDL) cholesterolemia.
* The hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program) level was 6.5% in one patient (a woman) but did not exceed 6.2% in the others.
* Five men (50%) and one woman (4%) had hyperuricemia (>7.0 mg/dL).
* CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) was seen in one man (eGFR = 55) and two women (eGFR = 17, 59).
* BMD analysis revealed a lumbar spine density of less than 70% of the young adult mean (YAM) in two patients (one man and one woman) and 70% to 80% of YAM in five patients (one man and four women). Femoral neck density was less than 70% of YAM in three patients (one man and two women) and 70% to 80% of YAM in 11 patients (two men and nine women).
* Among the seven patients who underwent measurements, blood thyroid stimulating hormone levels were slightly high in one and slightly low in another.

2 Overweight

Patients with TE are prone to becoming overweight not only because of developmental limb disorders, but also because many find going outside a hassle. Although no patient we examined at our hospital had severe obesity (BMI >30), one of five patients 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.

3 Hepatic Steatosis

High ALT levels were not the only liver-related concern. Ultrasonography revealed findings of hepatic steatosis (high hepato-renal echo contrast) in 14 patients (42%, five men [50%] and nine women [39%]). At-risk patients would benefit from a better diet (2014 Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis, ed. by Japanese Society of Gastroenterology).

4 Dyslipidemia

Blood LDL cholesterol levels were 140–149 mg/dL in one man and one woman, 150–159 mg/dL in one man,

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

and 170–179 mg/dL in one woman. Blood triglyceride levels were 200–299 mg/dL in one man and two women and 300–399 mg/dL in one woman. Persisting lipid disorders exacerbate arteriosclerosis. At-risk patients would benefit from proper eating habits and appropriate pharmacotherapy (2012 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases: ed. by Japan Atherosclerosis Society).

5 Abnormal Glucose Metabolism

None of the patients had obvious signs of diabetes mellitus (DM). We did not assign a diagnosis of DM to the woman with an HbA1c level of 6.5% because her blood glucose was in the normal range, but the patient had high ALT (50–59 IU/L) and mild hyper-LDL cholesterolemia as findings of hepatic steatosis. Accumulating risk factors, which ultimately lead to atherosclerosis, should be addressed through diet and exercise therapy (2016 Treatment Guide for Diabetes: ed. by Japan Diabetes Society).

6 Hyperuricemia

Hyperuricemia not only causes gout flare-ups but is now also considered a risk factor for arteriosclerosis. One male patient had a blood uric acid level on the order of 8 mg/dL. Pharmacotherapy would be recommendable in such a patient if urinary calculus, renal disorders, hypertension, ischemic heart disease, DM, metabolic syndrome, or another such comorbidity were present (Second Edition of the Guideline for the Management of Hyperuricemia and Gout 2012, ed. by Japanese Society of Gout and Nucleic Acid Metabolism).

7 Chronic Kidney Disease (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 in an ultrasound examination. Solitary kidney and other deformations are reported in patients with TE. Caution in the form of regular examinations is needed, even when no clear evidence of deformation is present, because these patients may experience age-related decreases in renal function more quickly than healthy people (2013 Evidence-based Clinical Practice Guideline for CKD, ed. by Japanese Society of Nephrology).

8 Osteoporosis

Two men (20%) and three women (13%) had confirmed osteoporosis. One man (10%) and 10 women (43%) had confirmed osteopenia. Endogenous risk factors for osteoporosis include (1) being a postmenopausal woman at least 55 years of age, (2) being underweight, (3) being on a corticosteroid, (4) having 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 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.

9 Endocrine and Metabolic Abnormalities

Although we did not perform any diagnostic tests focusing on endocrine function, the adverse reactions to thalidomide listed below suggest that embryonic exposure could possibly affect the development of endocrine tissues.

Secondary effects of thalidomide and the thalidomide derivative lenalidomide on endocrine and metabolic function:

(1) Increased insulin resistance[1)]
(2) Hypothyroidism[2 - 5)]: Incidence of 0.9% (per package insert), thyroiditis (thyroid toxicity)[6,7)]
(3) Hypoparathyroidism[8)]
(4) Hypogonadism[9)]

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IV 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.
- Measure blood pressure per the suggestions in this Guide and "Q&A on Thalidomide-Impaired People"
- When a patient is unsuited to arm blood pressure measurement, measure blood pressure near the medial malleolus and estimate arm systolic blood pressure using an estimating equation.
- Do not overlook congenital heart disease.
- Refer patients with a clinically significant electrocardiographic abnormality or abnormal echocardiographic finding to a cardiologist at a hospital familiar with thalidomide embryopathy.

1 Chronic Kidney Disease (CKD)

Patients with thalidomide embryopathy (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 indicates the presence of a renal disorder. The presence of proteinuria 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 creatinine and GFR less than 60 mL/min/1.73 m^2.

GFR is determined according to serum creatinine, age, and sex. In adults, eGFR is determined using a formula for estimating GFR in Japanese people (2013 Evidence-based Clinical Practice Guideline for CKD, ed. by Japanese Society of Nephrology). 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. TE patients require no special attention when renal function is G1 or G2 (i.e., eGFR ≥60); however, when renal function is G3a or above (i.e., eGFR <60), they should be referred to a nephrologist to maintain renal function.

TE patients often have congenital organ abnormalities in addition to congenital limb malformations. Ultrasonography, CT, or MRI should be performed in a medical examination to check for not uncommon renal and urinary tract malformations (embryopathy patients

Chronic kidney disease, glomerular filtration rate, kidney/urinary tract malformation, undescended testicle, hemodialysis, shunt, hypertension, blood pressure measurement technique, lower-limb blood pressure, upper-limb blood pressure estimate, peripheral artery disease, Guidelines for the Management of Hypertension, congenital heart disease, ischemic heart disease, cardiac failure, electrocardiography, echocardiography, auditory disorder

enrolled in the detailed health examination program of the Ministry of Health, Labour, and Welfare's Thalidomide Embryopathy Research Group are required 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 United Kingdom 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 relative 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 cardiovascular disease than patients with CKD caused by nephritis[1)]. TE patients will be prone to these diseases as they age. Management and treatment are therefore very important. Now that they are in their 50s, TE patients should all have a doctor to routinely monitor for and control these lifestyle diseases.

Doctors identifying a TE patient 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) 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 TE patients and should therefore be done at an experienced medical institution. Specifically, patients with upper- or lower-limb defects often find keeping still 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 signs or sign language. 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 TE patients with end-stage renal failure are placed on HD. Although exact figures are unavailable, at least two to three or more TE patients in Japan, Germany, and the United Kingdom are on HD. Patients who begin maintenance HD must be shunted to allow needle insertion for each session. Shunting in TE patients 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 difficult. Whenever possible, careful up-front evaluation with angiography, ultrasonography, or a vein imaging device should be performed. Even with the best preparations, however, shunting is difficult and 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, but also to all vascular procedures for TE patients because of the inherent difficulty involved.

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 cardiovascular deaths and more than half of strokes are attributable to blood pressure exceeding the optimal range. The prevalence of hypertension in Japan is thought to exceed 60% in men in their 50s or older and women in their 60s or older. Hypertension is therefore a concern in people with TE now that they are in their 50s.

(1) Diagnosing hypertension

Consecutive hospital-measured blood pressure readings exceeding the upper limit (<140/90 mmHg) constitute hypertension (see table). The blood pressure of patients with TE, if they have upper limbs, 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

Blood pressure categories for adults (in mmHg)

	Category	Systolic blood pressure		Diastolic blood pressure
Normal blood pressure	Optimal	<120	and	<80
	Normal	<130	and/or	<85
	High normal	130–139	and/or	85–89
Hypertension	Hypertension I	140–159	and/or	90–99
	Hypertension II	160–179	and/or	100–109
	Hypertension III	≧ 180	and/or	≧ 110
	Systolic hypertension	≧ 140	and	<90

2014 Guidelines for the Management of Hypertension, Japanese Society of Hypertension

described below can be corrected with a formula to arrive at an estimated 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 TE patients whose upper-arm circumference is obviously <20 cm.

When lower-limb blood pressure measurement is necessary, the pulse of the posterior tibial artery should be identified by palpation near the medial malleolus[1]. 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 slowly and calmly take a deep breath. Two or more blood pressure measurements should be obtained. If a medium cuff is used, the upper-limb systolic blood pressure can be estimated using the following formula (developed by the previous research group)[1]:

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

The German physician Dr. Jan Schulte-Hillen 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 limbs compared with the upper limbs, although the exact difference may differ between Japanese 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)[1]:

- Measuring ankle brachial pressure should be considered for patients with severe arteriosclerosis but is not possible in TE patients 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 use to attempt measuring systolic blood pressure in the dorsalis pedis and posterior tibial arteries via a Doppler blood flow monitor. 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 monitor is available, an attempt can be made to measure systolic blood pressure in the dorsalis pedis and posterior tibial arteries by auscultation.

(4) Treatment of hypertension

Hypertension should be treated by giving guidance on daily habits such as reducing sodium intake and selecting antihypertensive drugs according to the Guidelines for the Management of Hypertension. 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 TE patient with diseases other than hypertension because pharmacotherapy will require them to take more drugs. Since many TE patients resist taking drugs, the physician must conscientiously convince the patient of the significance of medication and select an antihypertensive drug that does not require the patient to take many dosage units. Pharmacotherapy must be selected to facilitate compliance in those few TE patients with facial paralysis 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, strategies to combat these diseases in patients with TE are a subject of intense concern among specialists there.

(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 when visiting for a medical examination. 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. Some investigators have even identified 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 cardiovascular disease 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. Even though many cases are treatable with simple pharmacotherapy, patients requiring cardiac catheterization or another invasive procedure should be sent to a hospital with experience treating TE patients 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 the National Hospital Organization Kyoto Medical Center or Teikyo University Hospital. This is because some TE patients have difficulty with stress electrocardiographic examinations owing to upper or lower limb defects that impair their balance or limit their mobility. Communication disorders impair routine stress electrocardiographic examinations in TE patients with an auditory disorder. 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 difficult in those with moderate or severe defects. Moreover, damage to the artery of an upper limb could severely restrict the activities of a TE patient. Such damage could also adversely affect shunt creation when needed in patients 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 selected in those TE patients with femur malformation or hip abnormality. 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 (of the bones and body). Since these anomalies would seriously complicate treatment if cardiac diseases were 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.

Reference
1) Shiga Y, Maehara Y, Yoshizawa A, et al: 6. Measuring and evaluating blood pressure. In: Q & A on Thalidomide-Impaired People (Yoshizawa A. ed), pp59-63, Tokyo, 2014

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

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4. Preventing Respiratory Diseases and Infections

- No respiratory diseases or dysfunctions specific to thalidomide embryopathy patients have emerged.
- Thalidomide embryopathy patients with upper-limb defects tend to have lower forced expiratory volume in 1 second and should therefore avoid smoking.
- 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 thorough heating of clams 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 50-Year-Olds

No respiratory diseases or dysfunctions specific to thalidomide embryopathy (TE) patients have emerged. Pulmonary function tests performed in TE patients with a mean age of 50 years indicated that function was maintained. Percent vital capacity (%VC) was 89.6±2.6% and forced expiratory volume in 1 second (FEV_1%) was 81.7±1.4% (mean±standard error, n=28 [14 men and 14 women], Results of FY2012-2013 Health Screening Project for Thalidomide Embryopathy Patients).

Five of the patients, however, had a restrictive ventilatory defect (%VC<80%) [four men and one woman], and four of these patients had upper-limb defects. Diagnostic imaging showed cardiomegaly in one patient and bilateral discoid atelectasis in another, but two other patients had no abnormal findings in chest X-rays and computed tomography (CT).

Two men had an obstructive ventilatory defect (FEV_1%<70%). Both had upper-limb defects. One was one of the patients with discoid atelectasis mentioned above, and the other had no abnormal imaging findings.

Moreover, %VC did not differ according to whether an upper-limb reduction defect was present (89.3±3.3% in 18 patients with a defect vs. 90.1±4.5% in 10 patients without a defect), while FEV_1% tended to be lower in the patients with an upper-limb defect (80.2±1.5% vs. 84.5±2.9%).

The proportions of abnormalities were higher in the patients with an upper-limb defect (%VC: 14.3% vs. 3.6%, FEV_1%: 7.1% vs. 0%). No obstructive ventilatory defects were observed in the patients without an upper-limb defect.

This suggests that obstructive ventilatory defects could be related to upper-limb defects, and while upper-limb defects could be related to respiratory muscle weakness, further investigation that factors in smoking history is needed to identify the cause. The takeaway message is that TE patients with upper-limb defects may be at greater risk for developing chronic obstructive pulmonary disease if they continue to smoke and should therefore strive to abstain from smoking.

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 aimd at the influenza virus]

Influenza virus infections generally peak around February of each year. Infections are generally transmitted via two routes. Droplet transmission occurs when someone inhales virus particles contained in droplets coming from the cough of an infected person. Contact transmission occurs when someone touches a doorknob or other surface touched by an infected person and then touches their nose or mouth. 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 disinfection is highly effective against the influenza virus. Disinfecting the hands with an alcohol product is useful for people unable to rub their hands together. Alcohol sprays, such as Welpas, and gels, such as Softy Hand Clean, are available. Gel products can be dispensed and applied with one hand. Automatic hand sanitizers can be purchased for several thousand yen (search for "automatic hand sanitizer," Figure 3). They can be operated with one hand and can also be used for 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 vaccination: Influenza vaccination reduces the chance of getting the flu and prevents influenza infections from worsening. Flu shots require about 2 weeks to become effective and should therefore be given by mid-December. Only one shot is needed. A shot is needed every year because the effects wear off after about 5 months and prevalence strains change from year to year. Flu shots contain an inactivated vaccine free of pathogens and therefore cannot cause influenza. Adverse reactions, which include redness and swelling at the injection site, fever, headache, and fatigue, normally resolve within 2–3 days. Shock and other severe adverse reactions are rare. Expert review revealed no death clearly causally related to vaccination. Most deaths occurred in elderly people with severe heart or kidney disease.

3 Preventing Respiratory Infections

[Focusing on prevention strategies aimd 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. Acute viral gastroenteritis can occur (1) by infection from virus particles that get on the hands from the feces or vomit of an infected person, or (2) by 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 can occur (3) after eating contaminated food handled by an infected person, (4) after eating contaminated clams without heating, 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 or eliminate 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 wiped away after cleaning so that it does not remain on the skin or get inhaled.

(3) Thorough heating of clams: Since most viruses are highly susceptible to heat, heating is an excellent way to inactivate virus particles. Clams and other foods should be heated so that the internal temperature reaches 85°C to 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

It is important that those with TE who smoke 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 chronic obstructive pulmonary disease and peptic ulcers. Smoking also has aesthetic effects. By promoting melanin pigment production and breaking down collagen fibers, smoking can cause "smoker's face," which features sallow skin and darkened 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 TE patients as of 2017 was 54 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 also 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 for the 30% out-of-pocket costs for a 3-month course is in the 20,000-yen range, which amounts to about 250 yen a day. This is less than 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.

*These data are based on the results of medical examination for thalidomide victims carried out at Teikyo University Hospital.

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IV Internal Medical Care

5. Upper Gastrointestinal Tract Endoscopy (Oral Insertion) and Gastrointestinal Diseases

- A relaxing environment should be created to relieve tension and anxiety.
- Normal pharyngeal anesthesia is acceptable.
- The sedative dose for patients with an upper-limb reduction defect must be carefully chosen.
- Intravenous injections for patients with an upper-limb reduction defect should be given in the lower limb.
- The upper gastrointestinal tract endoscopy procedure itself should be performed as with general patients.

1 Introduction

Upper gastrointestinal tract endoscopy (in which the endoscope is inserted through the mouth) for thalidomide embryopathy (TE) patients is discussed in this section. There is no medical literature on endoscopy for patients with TE.

2 Initial Preparation

(1) Determining patient information

The specific physical characteristics of the patient to undergo endoscopy must be determined in advance. Specific characteristics to check for include upper-limb reduction defects and deafness. If the patient is deaf, explanatory signs and cards should be prepared in advance to show the patient before and during the procedure.

(2) Exam room

A normal exam room should be used. No special considerations are required for lighting or monitor placement.

3 Preparation for Endoscopy

(1) Pharyngeal anesthesia

Pharyngeal anesthesia may be performed as it is normally done at the medical institution. Anesthesia with xylocaine spray alone, which is used at the medical institution of the authors, provides satisfactory results. Since many patients are very anxious about using drugs, carefully inform them in advance about the purpose of pharyngeal anesthesia and that the procedure will involve irritation and a bitter taste in the mouth. Speaking quickly or forcefully should be avoided, since it will only increase their anxiety.

(2) Use of a sedative (conscious sedation)

The use of a sedative in gastrointestinal tract endoscopy provides the two benefits of (1) reducing procedure-related pain and discomfort and easing pre-procedural stress in the patient, and (2) making the patient more receptive to the endoscope to assist with the early identification of gastrointestinal cancers. Many medical institutions in Japan now follow the guidance in the "Guidelines for Endoscopy Sedation" of the Japan Gastroenterological Endoscopy Society. Sedatives can be used in TE patients as they are in patients in general.

Many patients with TE are anxious and tense about not only medical procedures, but also the use of drugs. Patients should therefore be carefully informed about sedatives before undergoing the procedure. Those requesting sedation should be given a sedative, but sedation should not be forced on those with a strong fear of drugs. If the patient is unsure, do not insist on sedation. Intravenous injection must be given in a lower limb if the patient has an upper-limb reduction defect. Patients with a strong fear of needle jabs require emotional care. Finally, the sedative dose must be selected in consideration of the fact that patients with bilateral upper-limb reduction defects weigh about 13% less than their peers.

Upper gastrointestinal tract endoscopy, upper-limb reduction defect, deafness, pharyngeal anesthesia, sedative, conscious sedation, endoscope

(3) Endoscope selection

Any normally used endoscope may be used. Since certain patients will be very nervous, a narrower endoscope should be used to reduce patient burden for times when a sedative is not used or bilateral upper-limb reduction defects prevent the patient from remaining balanced. The Q260, Q240X, and XQ240 endoscopes by Olympus Corporation are used at Center Hospital of the National Center for Global Health and Medicine. Certain situations may require the physician to consider switching to transnasal endoscopy (discussed elsewhere) or to orally insert a narrow endoscope intended for transnasal endoscopy. Ultimately, the endoscope should be selected in overall consideration of the level of nervousness and build of the patient, whether upper-limb reduction defects are present, and whether a sedative will be used.

(4) Posture of the patient during the procedure

Patients are normally fitted with a mouthpiece and placed in a left lateral decubitus position. Often, patients with bilateral upper-limb reduction defects may have their shoulder roll forward and can experience pain when placed in a left lateral decubitus position for an extended time. A rolled-up towel or other item should be gently placed against the back so that they may lean back slightly.

4 During the Endoscopy Procedure

(1) Techniques

The endoscope should be inserted as usual while checking for malformations. No special considerations are required for performing image enhancement, dye scattering, biopsy, or clipping. When an endoscope is difficult to insert, a narrower endoscope should be immediately switched to.

During the procedure, assistants should call to the patient and rub their back to provide reassurance. For deaf patients, procedural instructions written in a large font on cards should be prepared and shown in sequence during the procedure.

(2) Endoscopic findings and gastrointestinal diseases

The literature reports bilateral tonsil agenesis and hypoplasia, but no other malformations relevant to endoscopy beyond the pharynx further down the esophagus or in the stomach or duodenum.

5 Post-procedural Considerations

(1) Patient monitoring

The level of consciousness of sedated patients should be carefully evaluated. Patients normally wake in about an hour but should not be rushed home because they could fall and hurt themselves if not fully awake. Patients should be instructed to resume eating and drinking as with other patients.

(2) Informing patients of findings

As with the pre-procedural discussion, be considerate when telling the patient about the findings. Any necessary treatment should be given during follow-up outpatient visits.

6 Gastrointestinal Diseases

No endoscopically-identified gastrointestinal diseases specific to patients with TE have been reported. We have seen constipation, gastric ulcers, colon polyps, and other common diseases in our patients with TE, but we have not needed to adjust drug therapy or make other special considerations.

7 Summary

In general, routine endoscopy is possible in patients with TE. However, flexibility is required because the mental state and physical characteristics of the patient may require the injection site, dose, endoscope used, and procedural instructions to be changed.

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V Orthopedic Surgery and Rehabilitation

1. Orthopedic Disorders and Rehabilitation

- The critical period in thalidomide embryopathy involves thalidomide exposure by the mother 36–49 days after the last period (i.e., gestational age of 22–35 days or 4–5 weeks).
- Typical manifestations include preaxial longitudinal hypoplasia of the upper and lower limbs and arm domination with left–right symmetry.
- Dislocations of the hips and shoulders occur frequently. Hypoplasia of the ball and socket of the hip could lead to age-related osteoarthritis of the hip, but no reliable statistics on this are yet available.
- Thumb defects, thumb hypoplasia, or thumb triphalangia are hallmarks of thalidomide embryopathy.

1 Organ Susceptibility during Embryonic Development

Why is thalidomide embryopathy (TE) classified into two groups in Japan? There are two TE patient groups. One is made up of patients with upper-limb hypoplasia, and the other is composed of deaf patients. These groups find communicating with each other difficult as a third-party sign language interpreter is needed. The timing of embryonic organogenesis defects caused by thalidomide exposure is relevant to the makeup of these two groups (Figure 1). The critical period is 36–49 days after the last period (i.e., gestational age of 22–35 days or 4–5 weeks), which is the period of embryonic development when the organs are most susceptible and prone to malformation. Exposure before this period often leads to embryonic death. Exposure after this period often causes functional disorders in the period of fetal development, leading to a condition called fetopathy. The following discussion involves the group with upper-limb hypoplasia.

2 Characteristic Morphology

Henkel L and Willert HG developed a classification system for TE patients based on 287 primarily German patients (557 affected upper limbs and 136 affected lower limbs) (see Figure 4 in "III. Diagnostic Procedures for Thalidomide Embryopathy" [1]). The morphologies characteristic of TE patients are discussed below in reference to this figure.

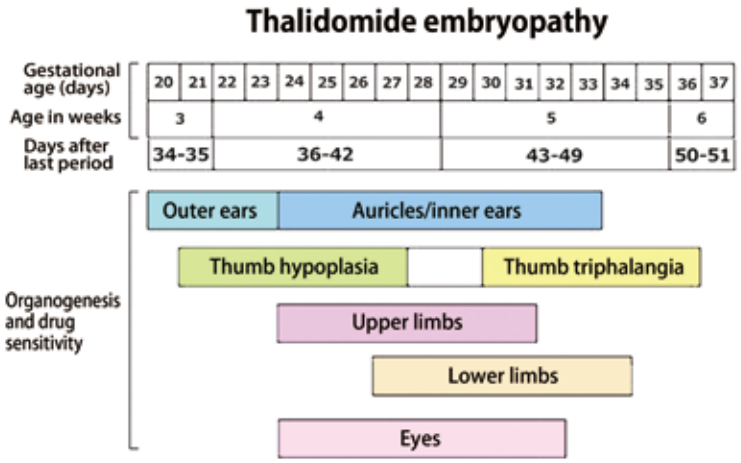

Figure 1 Thalidomide exposure and organogenesis defects

Upper and lower limb preaxial longitudinal hypoplasia, hip ball and socket hypoplasia, hallmarks, thumb defect or hypoplasia, thumb triphalangia

(1) Preaxial longitudinal hypoplasia

Preaxial longitudinal hypoplasia of the upper and lower limbs is a hallmark morphological feature of TE. The axis of the body is determined by the position of the limbs of the fetus in the uterus (Figure 2). The upper and lower limbs have a central axis. In the context of the upper limbs, the term "preaxial" refers to the thumbs and radius. In the context of the lower limbs, "preaxial" refers to the big toes and tibia. Slightest hypoplasia results in thumb defect/hypoplasia. Moderate hypoplasia causes radius hypoplasia or defect. This type of malformation is called ectromelia and appears morphologically as club hand.

Severe hypoplasia leads to hypoplasia or defect of the humerus. This condition is referred to as phocomelia. The ulnar fingers and ulna hypoplasia are present but nonetheless conserved. People with the most severe form, called amelia, have no upper limbs.

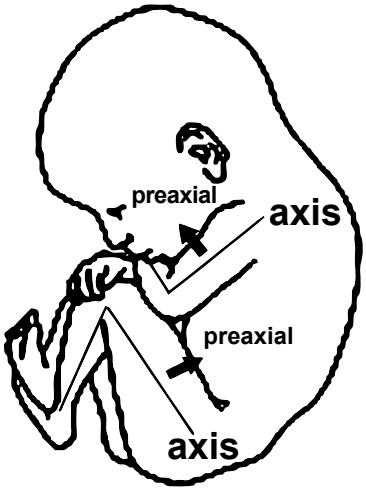

Figure 2 Fetal limb positioning and central axes
The central axis of the body is determined by the position of the limbs of the fetus in the uterus. Everything forward of the central axis of the limbs of a fetus in the uterus is described as preaxial. Everything behind is described as post-axial.

(2) Left–right symmetry

Janet McCredie, at the first International Symposium on Thalidomide Embryopathy in Tokyo 2015, noted that most but not all patients display symmetry, claiming that unilateral hypoplasia had been reported[2]. Many Japanese TE patients, however, appear to have normal upper limbs, but actually have thenar muscle hypoplasia (Figure 3). Thalidomide absorbed by the mother reaches the fetal circulation via the umbilical cord. The limb buds form alternately on the left and right sides during fetal development, which explains left–right differences. Further evaluation is needed to show whether the limbs on one side could form completely normally at the time that left–right differences emerge.

(3) Arm domination

The upper limbs are dominantly affected in German, British, and Japanese thalidomide victims. Only two of the 309 Japanese victims (≤1%) have lower-limb hypoplasia. About 150 of the 2397 German thalidomide victims (6%) have lower-limb hypoplasia. This is about 65 of 467 (14%) among the British thalidomide victims (Figure 4). Why Japan has a smaller proportion of patients with lower-limb hypoplasia is unclear. Cultural habits about taking drugs to treat morning sickness or as sleep medications may contribute. In Japan, only one 25-mg tablet of thalidomide may have been taken for a short period as a sleep medication. These cultural habits, resulting in the use of smaller doses of thalidomide compared with Western countries, may have limited effects on upper limbs, but not on lower limbs.

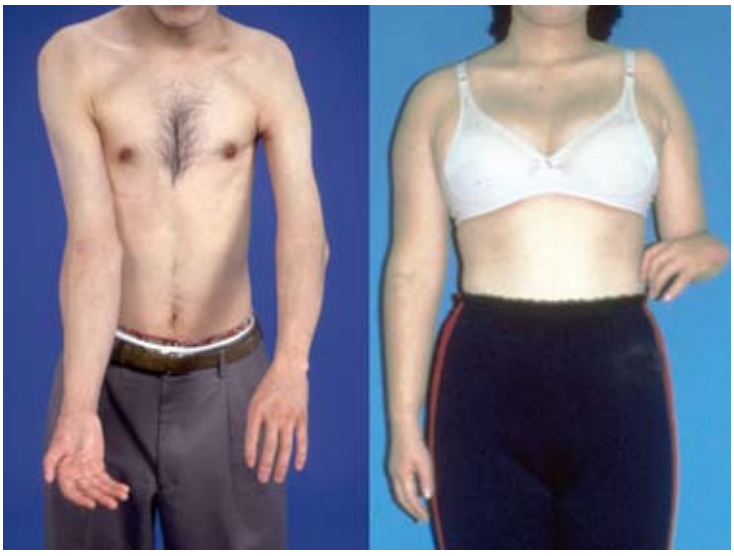

Figure 3 Patients that appear to have unilateral hypoplasia

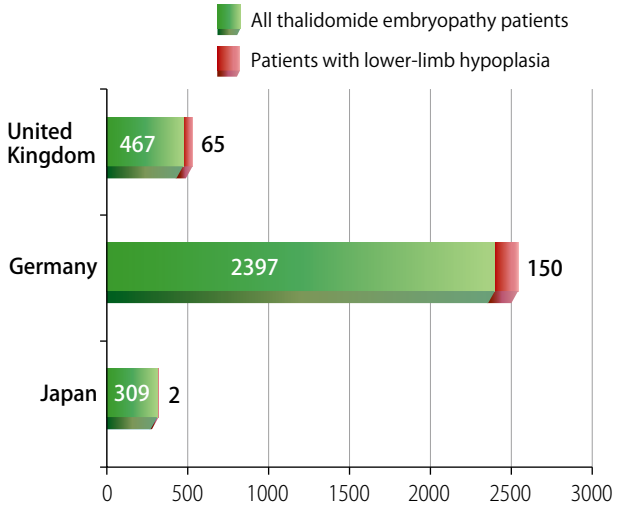

Figure 4 Numbers of thalidomide embryopathy patients and patients with lower-limb hypoplasia

(4) Joint dislocations can occur

1. Shoulder dislocations

Shoulder dislocations are the most frequent type of dislocation. Hypoplasia of the humeral head and arm muscles leads to joint dislocation (Figure 5). But possibly because patients do not carry heavy things as part of a conservative treatment regimen, they do not complain of extreme pain, even though the range of motion is limited, as with other joints.

2. Hip dislocations

Although few Japanese TE patients have lower-limb hypoplasia, hip dislocations and hypoplasia of the hip ball and socket are not uncommon. This hypoplasia of the hip ball and socket could lead to age-related osteoarthritis of the hip (Figure 6).

(5) Joint fusion can occur

Commonly observed types of fusion are proximal radioulnar synostosis and, in those without a radius, elbow fusion (Figures 7 and 8). Both severely limit the range of motion of the elbow.

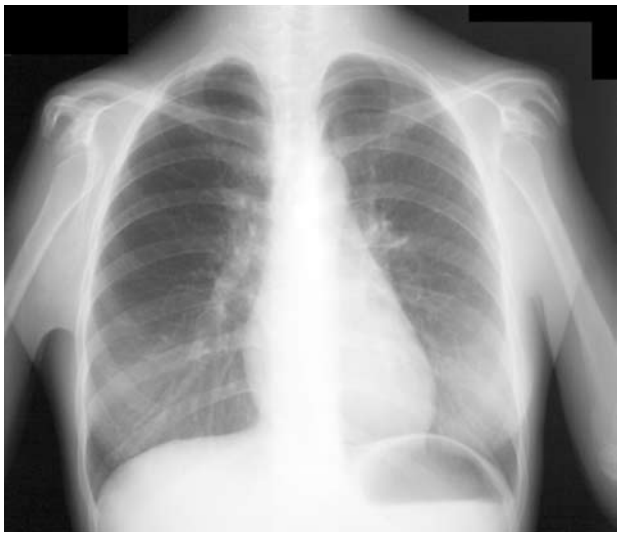

Figure 5 Shoulder subluxation caused by bilateral humeral hypoplasia

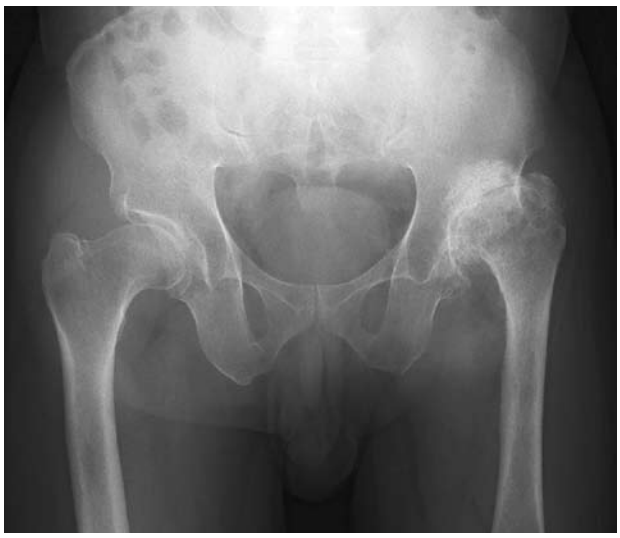

Figure 6 Bilateral hip hypoplasia and osteoarthritis

3 Hallmarks and Thumb Hypoplasia

The mildest dysfunction involves thumb defect or hypoplasia followed by thumb triphalangia. A diagnosis of TE can be confidently made for those with no genetic diseases who were exposed *in utero* to thalidomide and have these features. Preaxial longitudinal hypoplasia occurs in the thumb, radius, and humerus, from the periphery to the center. Importantly, the ring and little fingers (ulnar fingers) are conserved to the end. Hand and thenar muscle hypoplasia are seen even in those with radial hypoplasia (ectromelia) or humeral hypoplasia (phocomelia, Figure 9).

Like thumb defects, thumb triphalangia is a common characteristic (Figure 10). These conditions are rare in other types of deformities. The thumb is generally missing in thumb triphalangia, which is more accurately classified as polydactyly.

References

1) Henkel HL, Willert HG：Dysmelia: A classification and a pattern of malformation in a group of congenital deformities of the limbs. J Bone Surg 51: 399-414, 1969
2) McCredie J：Pathology, radiology and pathogenesis. In: Proceedings of the International Symposium on Thalidomide Embryopathy in Tokyo, 2015 (Final Edition) (Hinoshita F. ed), pp19-30, Tokyo, 2017

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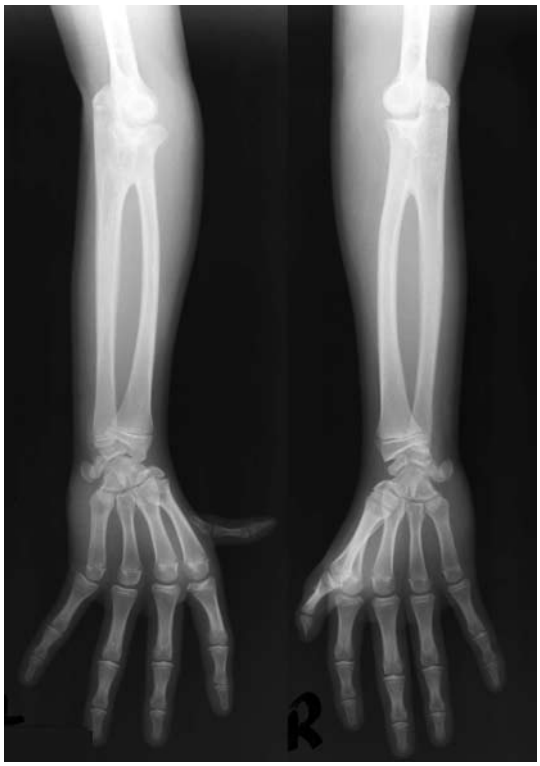

Figure 7 Proximal radioulnar synostosis
This X-ray shows fusion of the bilateral proximal radioulnar joint and elbow. Both thumbs show hypoplasia.

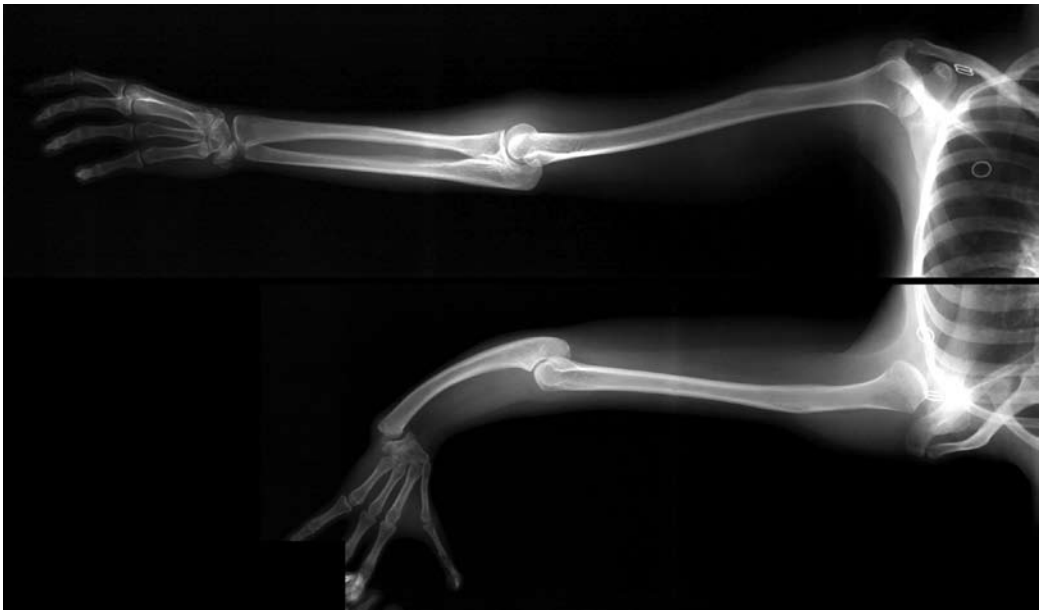

Figure 8 Elbow synostosis
The patient has club hand on the left side because the left radius is missing. The elbow has fused with the humerus. The right limb shows radial shortening and proximal radioulnar joint synostosis. Both humeri are relatively well conserved. This condition is known as ectromelia.

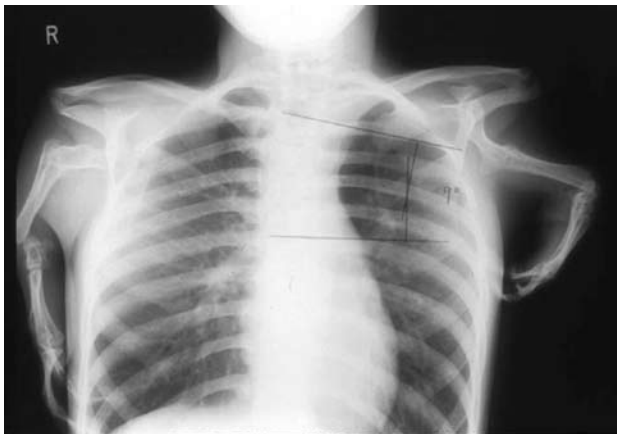

Figure 9 X-ray of a patient with phocomelia
The patient has bilateral radial defect, humeral hypoplasia, and hands that remain but have thumb hypoplasia.

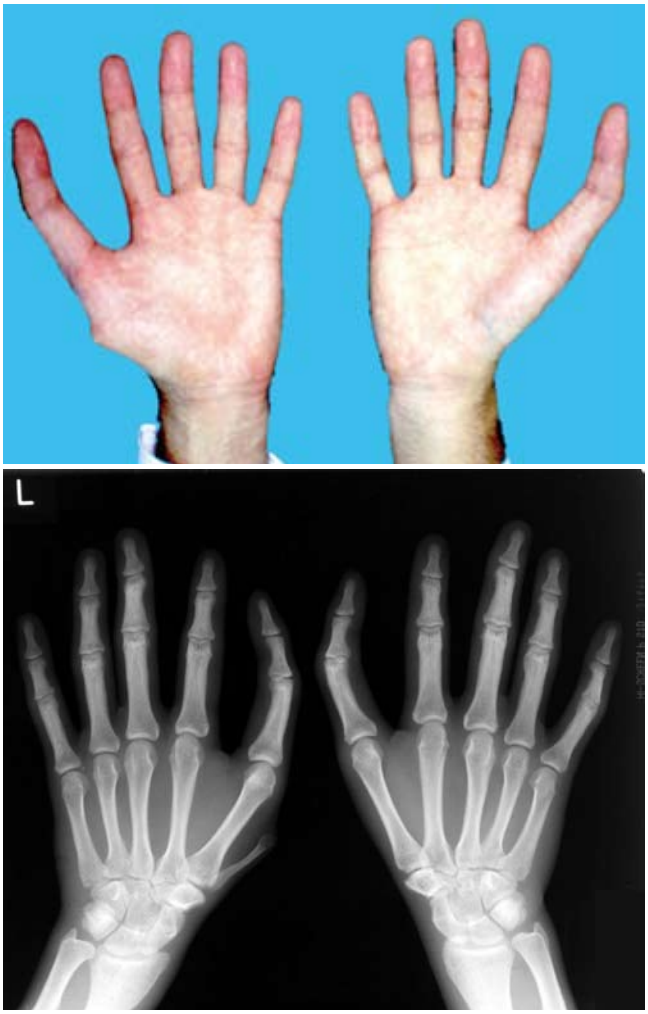

Figure 10 Photograph and X-ray of patient with thumb triphalangia
Thumb triphalangia are present on both sides (top). The X-ray shows a rudimentary left thumb (bottom).

2. Pain Management

- Shoulder pain and lumbago were the most common physical complaints among both types of thalidomide embryopathy patients. Other complaints were painful joints in the hands and feet and numbness in the hands and feet.
- Pain was the most noted problem facing daily life followed by impairment of activities of daily living (ADL).
- Anxiety, fear, depression, and other emotional states can modify the severity of chronic pain. Pain-related behaviors such as inactivity, withdrawal from society, and frequently visiting the hospital are learned and can make pain refractory.
- Some relief may be gained from traditional heat therapy or another type of physical therapy, stretching or another type of physiotherapy, and treadmill use or other full-body workouts to complement a relaxed lifestyle.

1 Introduction

Questionnaires were sent by mail to thalidomide embryopathy (TE) patients in 2012 when their mean age was 49.9 years. In total, 201 of the 286 patients to whom a questionnaire was sent responded, for a response rate of 70%. A total of 154 patients were in the short-arm group and 35 were in the hearing-loss group. The other six were in another category. The concerns of TE patients are discussed here based on the results of the questionnaire survey.

2 Physical Problems

The physical problems of shoulder pain and lumbago were reported by a majority of the patients in the short-arm group (Figure 1). Shoulder pain (44%) and lumbago (44%) were also the first and second most common complaints reported by the patients in the hearing-loss group (Figure 2). Shoulder pain and lumbago were the most common physical complaints among both types of TE patients. Other complaints were painful joints and numbness in the hands and feet.

3 Problems in Daily Life

Pain was the problem most noted in the questionnaire, which focused on problems the patients faced in daily life (Figure 3). The next most commonly reported problem was impairment of ADL.

	Problems	N=95	%
1	Shoulder pain		63
2	Lumbago		57
3	Painful joints in hands and feet		44
4	Numbness in hands and feet		36
5	Headache		36
6	Fatiguability		34

Figure 1
Physical complaints by patients in the short-arm group

	Problems	N=27	%
1	Shoulder pain		44
2	Lumbago		44
3	Hearing deterioration		37
4	Blurred vision		37
5	Sight impairment		33

Figure 2
Physical complaints by patients in the hearing-loss group

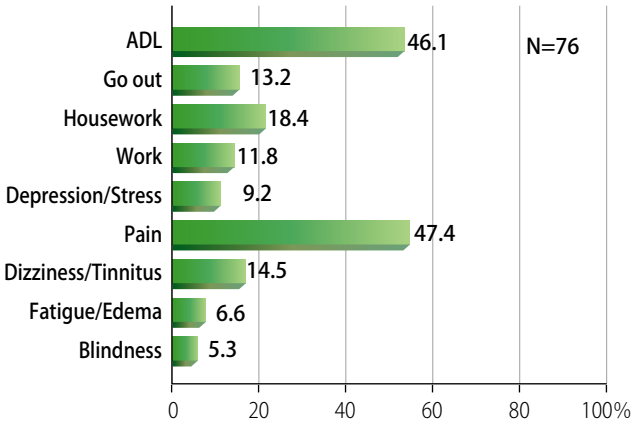

Figure 3
Problems faced in daily life

Keywords: Shoulder pain, lumbago, chronic pain, relaxed lifestyle, heat therapy, physical therapy, stretching, treadmill, full-body workout

4 Musculoskeletal Problems

(1) Shoulder hypoplasia

It can be difficult to pinpoint the source of shoulder pain, which can come from the glenohumeral, acromioclavicular, or sternoclavicular joint. Multiple factors, such as cervical spondylosis, block vertebrae, and poor posture, may contribute.

(2) Hypoplasia of arm muscles

Patients may have hypoplasia of the arm muscles in addition to humerus hypoplasia or shoulder dislocation. The muscles are easily fatigued by the weight of the upper limbs or when something is carried. This is another cause of shoulder pain.

(3) Lumbago

Patients may have spina bifida occulta in addition to spinal deformities such as kyphosis and scoliosis. Excessive twisting of the trunk to compensate for a reach disorder can exacerbate vertebral changes to a level beyond those expected from aging.

(4) Wrist pain

Problems in this area include carpal tunnel syndrome from overuse of the relatively healthy limb as well as tenosynovitis, medial humeral epicondylitis, and humeral epicondylitis attributable to muscle and tendon hypoplasia. Patients unable to use one upper limb because of hypoplasia or club hand may experience exacerbated tenosynovitis and chronic pain.

5 Chronic Pain

The questionnaire showed pain to be the biggest concern among TE patients. This was in agreement with the results of previous questionnaires, which indicate that conventional medical approaches often do little to alleviate pain, which becomes chronic.

Acute pain is a biological symptom of nociception in a tissue affected by disease or trauma. By contrast, chronic pain is pain that persists beyond the time normally required for tissue damage to heal. Detailed tests normally fail to reveal organic lesions or pathophysiological mechanisms to explain the pain. Even when they do, the degree of pain or ADL disabilities it causes far exceed the degree expected based on physical findings. Anxiety, fear, depression, and other emotional states and psychogenic reactions begin to appear secondary as pain becomes chronic. These conditions modify how the pain is felt and manifested. Pain-related behaviors such as inactivity, withdrawal from society, habitual drug dependence, and frequently visiting the hospital are learned and can make pain refractory.

6 Approaches

Conventional NSAIDs, local steroid injections, nerve block injections, and other approaches are largely ineffectual. The profession now realizes that pain will not improve without lifestyle changes. Some relief may be gained from traditional heat therapy or another type of physical therapy (Figure 4), massages, stretching, or another type of physiotherapy, or treadmill use or other full-body workouts (Figure 5) to complement a relaxed lifestyle. Ongoing, relaxed balneotherapy or water therapy to relieve stress should help.

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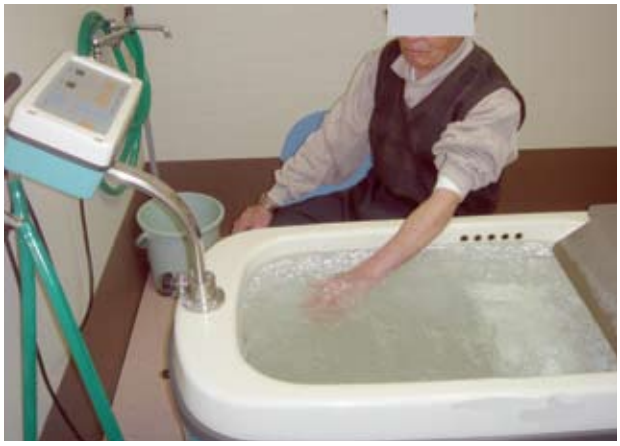

Figure 4
Hand pain is treated using water therapy (Vibra Bath)

Figure 5
A patient gets a full-body workout on a treadmill

3. Properly Interacting with Thalidomide Embryopathy Patients: An Occupational Therapy Perspective

- Give guidance to improve poor posture.
- Predict age-related changes to help patients plan for the future.
- Aim to reduce anxieties about individual daily activities to allow patients to live independently.

1 Introduction

Building on the detailed explanation of the manifestations of thalidomide embryopathy (TE) presented in sections V1 and V2, this section considers the condition from an occupational therapy approach.

2 Accurate Evaluation

As with patients with other diseases and disorders, patients with TE have disorders at different sites and of different severities. Not all disorders are visually apparent aplasia or defects. Some are organ-related, and patients have a wide range of social backgrounds and living environments. Since childhood, thalidomide victims have generally been treated at many medical institutions where they have had to undergo X-ray imaging in awkward postures and have blood collected from unusual sites. This has instilled a fear of and resistance to tests and measurements in some patients and must be adequately dealt with. What is needed is an approach based on accurate evaluation that factors this in.

(1) Physical functionality

In addition to gripping disorders caused by thumb hypoplasia, TE features shortened upper limbs. Patients tend to slump forward when working to compensate for their impaired reach. Patients with left and right upper limbs of different lengths obviously have to move their trunks laterally and horizontally (rotate) in addition to back and forth. These movements could lead to scoliosis and hunchback (kyphosis). Some have poor posture as a result of using the lower limbs beginning early in development to compensate for impaired upper-limb function. This poor posture may have contributed to joint pain. The lower limbs, overused since early childhood, begin to lose muscle strength and range of motion with aging. This will only accelerate as TE patients age.

Massages, stretching, and other general exercises for increasing the range of motion are given to patients with joint contracture and limited range of motion, but these exercises could injure joint components if not carefully administered with a full understanding of the patient's hypoplasia. Caregivers must therefore work closely with orthopedic surgeons, rehabilitation therapists, and other specialists.

(2) Psychiatric and psychological functionality

In a lifestyle questionnaire, many patients reported having depression and other mental diseases and listed health issues and anxiety about the future as worries and troubles in their lives. Patients are also likely anxious about having bad experiences in tests and exercises as stated above. Caregivers must support these special patients with a realization that they may have not only issues regarding physical functions, but also psychiatric and psychological functions, working with a psychiatrist or other relevant specialist when identifying issues.

Thumb hypoplasia, upper-limb length, poor posture, joint range of motion (restricted), anxiety, independent living, age-related decline in function, welfare equipment

3 Supporting Patients' Efforts to Live Independently

The goal of therapy should be to provide guidance and support for better approaching and training for activities of daily living (ADL) rather than to strengthen muscles or extend the range of joint motion. Patients with joint pain of the lower back or hip may require guidance to correct poor posture and thereby reduce the pain that it causes. Although prosthetic limbs and braces are options for serious disorders, self-help tools and welfare equipment offered or fine-tuned for the needs of the individual TE patient may turn out to be more useful.

4 Aiming to Reduce Anxiety in Later Life

Respondents to the above-mentioned questionnaire noted being anxious about lifestyle issues, such as further loss of function through aging and having to care for parents. Physicians must confront these concerns of TE patients, specifically identifying all the motions and functions involved when physical function is an issue. Through an iterative or trial-and-error approach, caregivers need to design procedures or self-help tools or consider the use of welfare equipment that factor in the situations in which patients with TE carry out their activities (see figure). Sometimes, redesign of the living environment is in order.

Figure A patient uses a reacher
Patients with thalidomide embryopathy find self-help reachers very useful for compensating for their short reach.

5 Conclusions

The main objective of occupational therapy for TE patients must be to individually help patients develop ways to live independently in their current situation, not to recover from disability. Caregivers must properly evaluate psychiatric and psychological functionality and social situations instead of focusing only on physical functionality in order to truly help these victims live well despite the problems they face.

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VI 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 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 an 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 continuously 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 with thalidomide embryopathy (TE) before the procedure

Radiological procedures require a cooperative patient. Radiology technicians must know the physical characteristics of individual TE patients 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 TE patients must assume awkward postures or limb positions for imaging. Patients with upper-limb hypoplasia may find raising their upper limbs or holding their upper limbs 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.

A chest X-ray is first taken

- Place your chest and chin against this surface. The surface will move up or down a bit.
- Next, hold your arms on either side of the surface.
- When I tap your shoulder once, take a deep breath and hold.
- When I tap your shoulder twice,breathe freely.

- Turn to your right.
- Raise your arms.
- I will help you if you cannot raise your arms.

Shake your head if you are in pain.

- When I tap your shoulder once, take a deep breath and hold.
- When I tap your shoulder twice, breathe freely.

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 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 TE patients with upper-limb hypoplasia because they may not be able to tie a front-tying gown.

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Figure 2 Front-tying gown

Figure 3 Slip-on gown

2 1. General Imaging: Chest X-rays

Chest X-rays are the most commonly performed radiological procedure. This is also true for TE patients. 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. Position the patient comfortably, 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).

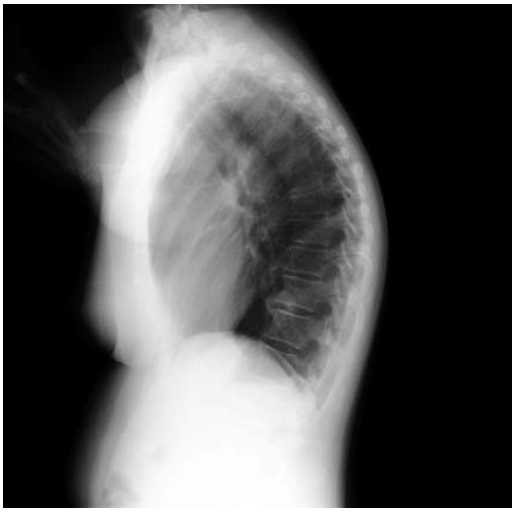

Figure 4 Lateral chest X-ray

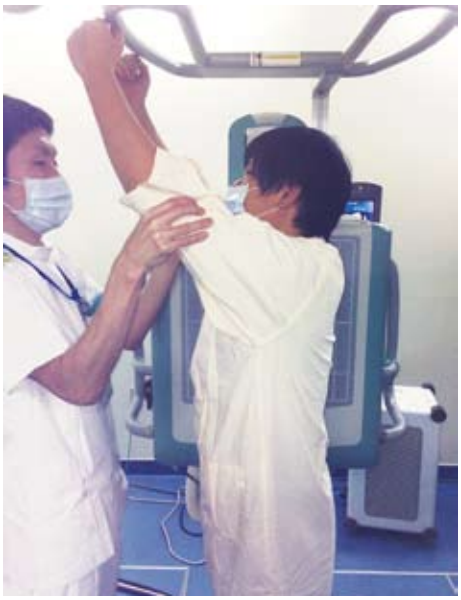

Figure 5 Upper-limb assistance for a patient undergoing a lateral chest X-ray

(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 5 and 6).

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.

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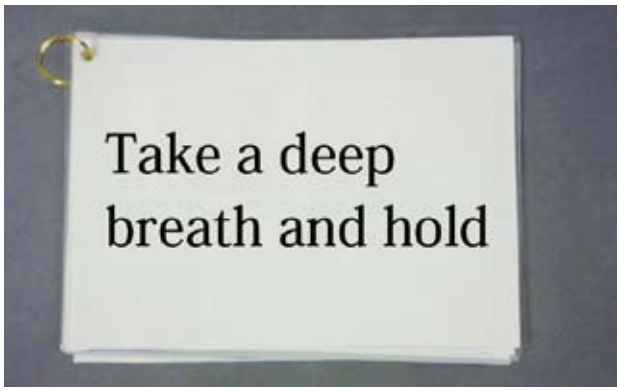

Figure 5 A sign with instructions

Figure 6 A patient is instructed with the sign

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 regularly determine in order to help prevent fractures that reduce QOL. Monitoring for risk factors and lifestyle guidance are also necessary.

(1) Definition of osteoporosis

The 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 based on WHO BMD

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), Dual-energy X-ray absorptiometry (DXA), quantitative ultrasound (QUS), and other procedures are used to determine BMD. TE patients 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. Our medical institution determines BMD using DXA of L1–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 BMD in TE patients by K Mochiki et al.[1]) in "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 TE patients 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 TE patients 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 that the patient can be imaged in an identical position to ensure reproducibility.

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2 3. General Imaging: Mammography

Breast cancer has a growing 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, a growing number of women in their 60s develop breast cancer. Breast cancer is therefore a concern in TE patients. Patients are often the first to discover their breast cancer, but some TE patients with upper-limb hypoplasia may not be able to do a 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 40 years of age or older
* Frequency: From left or right once every 2 years (from left and right for women in their 40s)
* Parameters: Interview, inspection, palpation, mammography

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

Mammography for patients with TE should be performed per the Third Expanded Edition of the "Mammography Guideline" (published in Japan). For CC imaging of TE patients with upper-limb hypoplasia, the patient should be instructed to stand with the trunk squarely against the device and the face out of range so that it does not interfere with imaging[2] (Figure 7). Patients should be quickly positioned when 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 closely parallel to the breast support platform, but this is difficult for TE patients with upper-limb hypoplasia since their arms narrow distally. This can result in wrinkles near the pectoralis at the armpits (Figure 8).

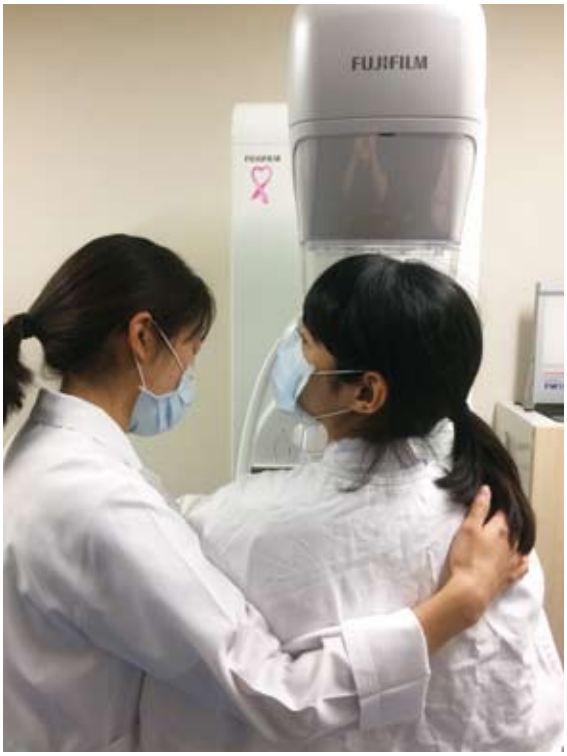

Figure 7 Craniocaudal imaging

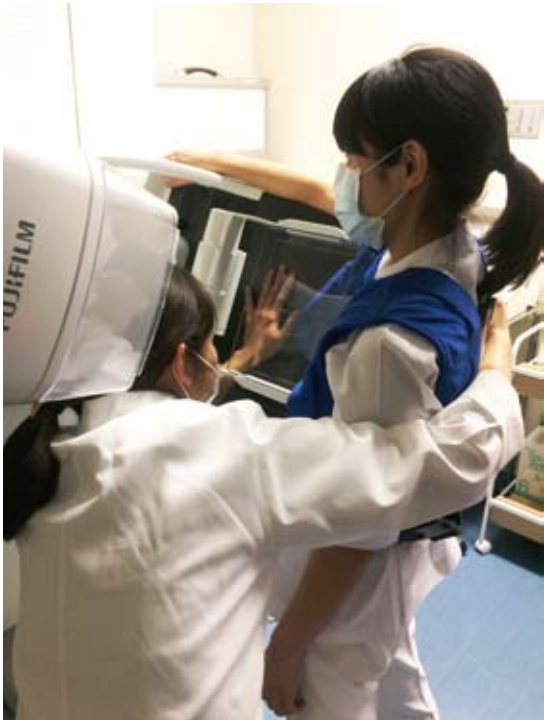

Figure 8 Medio-lateral oblique imaging

(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 9). 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.

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Figure 9 Patient chair for mammography

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.

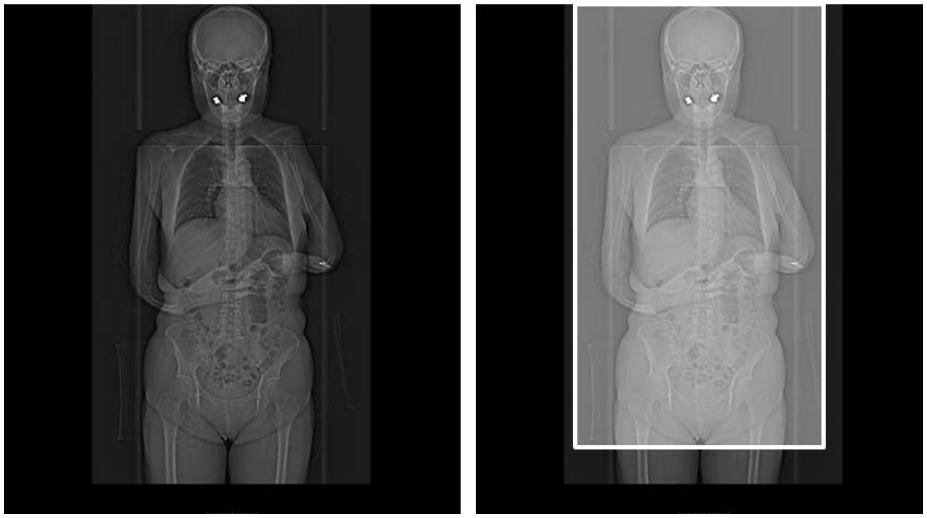
(3) Imaging protocol

Figure 10 shows proper positioning and the field of view (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 arms, held at the sides, are in the FOV.

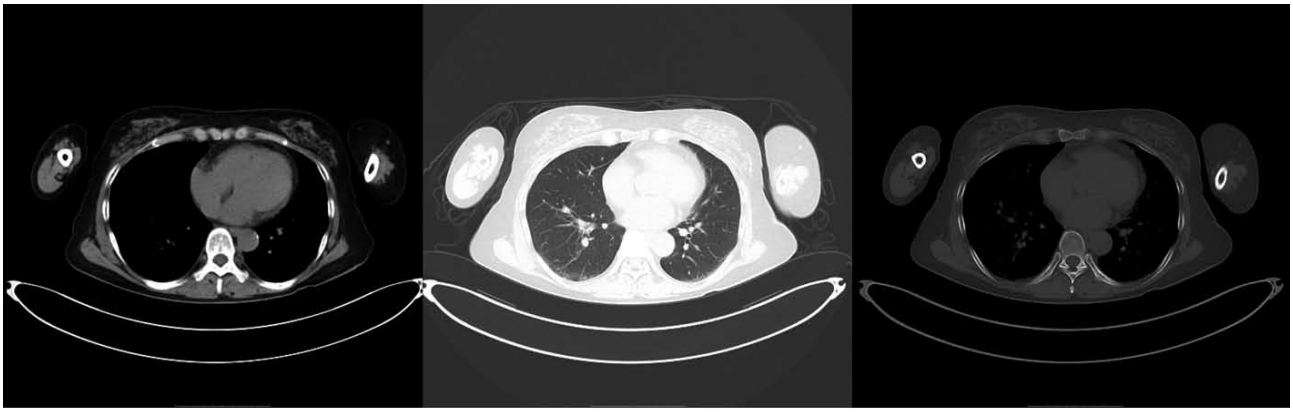
Figure 11 shows images reconstructed from a full-body CT scan.

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



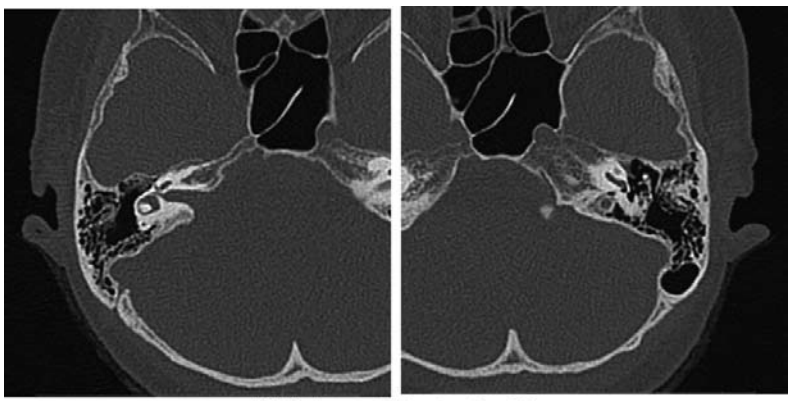
Positioning　　Field of view (within white rectangle)

Figure 10 Positioning and field of view

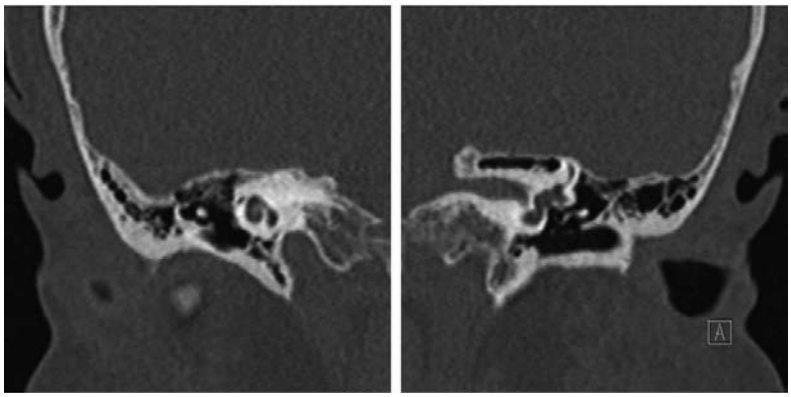


Soft tissue conditions (5 mm thickness)　　Lung tissue conditions (5 mm thickness)　　Bone conditions (5 mm thickness)

Figure 11 Reconstructed images of the body



Axial (0.5 mm or 0.6 mm thickness)



Coronal (1.0 mm thickness)

Figure 12 Reconstructed images of the inner ear

Figure 12 shows reconstructed images of the inner ear.

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

Figure 13 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 coronal slices are shown. Attenuation coefficients for bone reconstruction were used.

Figure 14 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.

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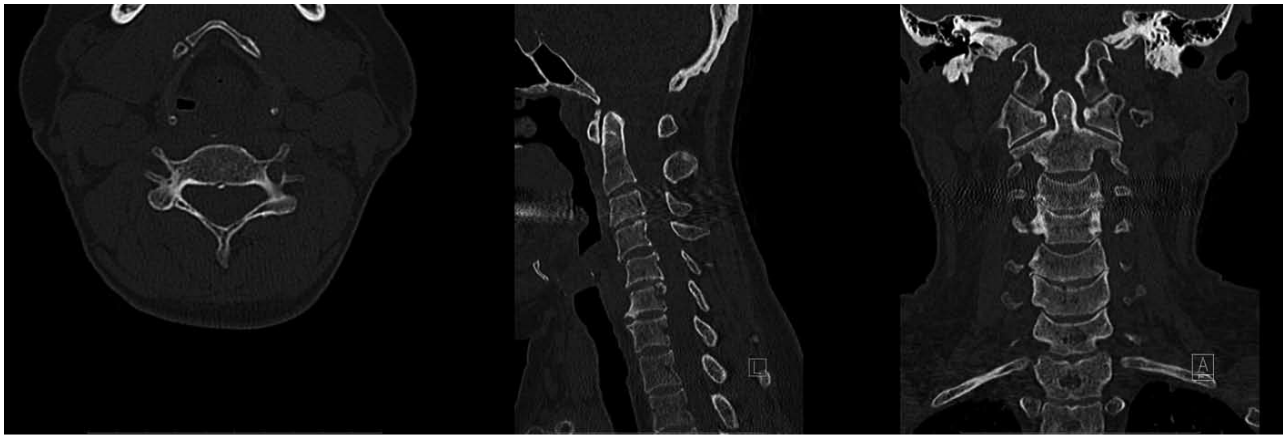
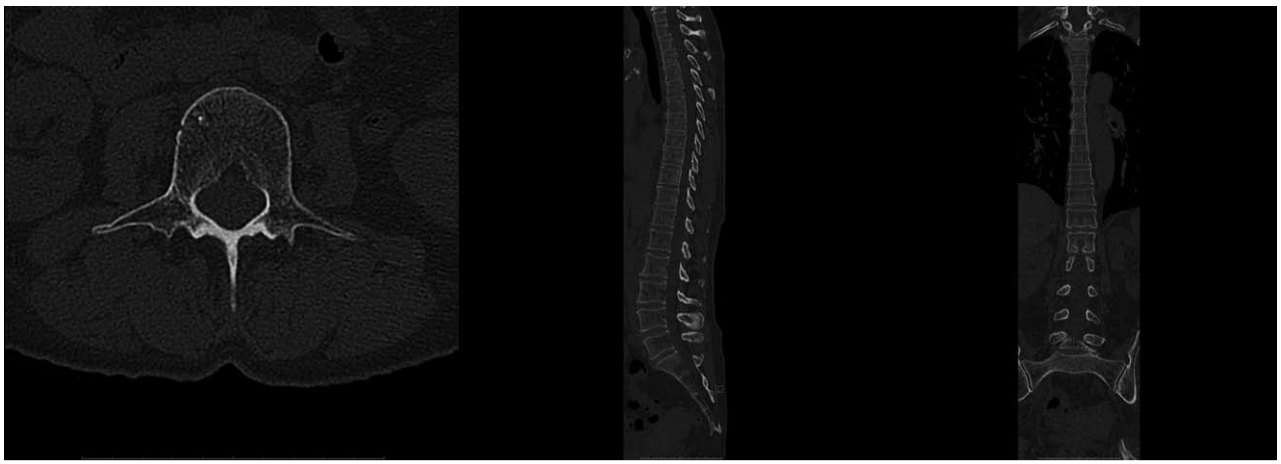


Axial (1 mm thickness) Sagittal (1 mm thickness) Coronal (1 mm thickness)

Figure 13 Reconstructed images of the cervical spine



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

Figure 14 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 depends on the manifestations in the particular patient. The TE 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 TE 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, the need to change clothes, a description of the procedure, the time needed, the fact that the device will make noise, the need to restrain the patient, position, 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 defects.

(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 falling because of muscle weakening.

A gown that facilitates visual inspection should be used to speed the process when metal is detected. At our medical institution, we have the caregiver clothe for TE patients and others in a front-tying gown when they need to change for an MRI scan.

(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 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 TE patients 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 people with serious CKD.

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5 Diagnostic Imaging: Tips and Warnings for Radiographic Evaluation

Tips and warnings for the image-based diagnosis of TE patients are presented here based on the findings health screenings performed by this and the previous research team[2].

(1) MRI of head and neck

1. As with evaluations of normal individuals, first evaluate the scan in T1WI, T2WI, FLAIR, and T2*WI primarily to screen for intracranial 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 the present research team). Patients may have narrow or missing inner ear canals, which should be checked for with temporal bone CT with thin-slide multi-planar reconstruction.
3. In head-and-neck magnetic resonance angiography (MRA), TE 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 arterial 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: Evaluation in 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 spinal CT: Evaluation 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 the 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 disks in this aging population of patients with TE.

(4) Body CT: Evaluation with a focus on reconstructed axial images

1. Gallbladder agenesis is a frequently observed abnormality (reported incidence of 27% by the present research group).
2. Abnormal fusion of the liver (e.g., fusion of the left lobe lateral segment and quadrate lobe, agenesis/hypoplasia of round ligament, right 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 (duplicated superior vena cava, directional abnormality of azygos vein)
7. Heart malformations: These are often difficult to evaluate in non-contrast-enhanced CT.

References

1) Mochiki K, Sasaki T, Wada T, et al. 3. Comments from radiologists. Q3-3 What points should be considered when measuring bone mineral density? In: Q&A on Thalidomide-Impaired People (Yoshizawa A. ed), pp39-48,Tokyo, 2014
2) 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

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VII Otorhinolaryngology

- Ear canal stenosis and upper-limb hypoplasia can complicate earwax removal. Intervention is required.
- Patients with thalidomide embryopathy might have varying degrees of deafness. Speak clearly and slowly, allowing the patient to see your mouth.
- Communication with thalidomide embryopathy patients with severe deafness can be achieved through sign-language interpreting, written communication, or lip reading.
- Little is known about the clinical course of deafness in patients with thalidomide embryopathy. 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 thalidomide embryopathy (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 deafness. Tanaka identified an auditory defect of some type in 83 (about 60%) of 137 patients. He explains that auditory defects begin at 8 kHz, 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 (reported in a paper in Japanese, 1986).

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 deafness, aging will likely impact the auditory defects of patients as they grow older. Patients should undergo regular hearing follow-up because the clinical course of deafness in TE is unclear.

(1) Outer ear malformations

Auricle deformations take many forms. A substantial number of patients have 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 ear canal, a cause of conductive deafness, are unsuited for normal hearing aids and require the attention of a specialist.

(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 may also be present. Temporal bone CT imaging 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 typically have severe auditory defects that impair communication during examinations.

Auditory defect, outer ear malformation, ear canal stenosis, external auditory canal atresia, middle ear malformation, inner ear malformation, abducens nerve palsy, Duane syndrome, facial paralysis, crocodile tears syndrome, vestibular dysfunction

2 Facial Nerve Palsy

Facial nerve palsy occurs as a result of failure of the facial nuclei to develop or stenosis 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 severe limitation of 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 nerve palsy patients with an auditory anomaly, Takemori identified deafness in 15 and vestibular hypofunction or afunction in 15[1)].

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.

6 Others

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

7 Relationship between Otolaryngological Malformation 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 have may hamper communication. Sign language, gesticulating, writing, lip reading, 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.

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VIII Dentistry and Oral Surgery

- Patients have difficulty maintaining oral hygiene. Concerns go beyond just cavities, extending to loose and chipped teeth and tooth loss.
- Check artificial teeth for cleanliness.
- Check the color and condition of the gums, tongue, lips, and mucosa.
- Thalidomide embryopathy sometimes involves trismus, joint clicking and other conditions of the temporomandibular joint, and articulation disorders.

1 Oral Examination

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

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 (Yoneyama, 1999)[1].

(1) Teeth

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

People who hold items with their teeth to assist upper limb movement are prone to dental wear 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 baby 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 crown prosthesis are applied to treat dentin damage from dental caries, wear, or chipping. The resin used to secure fillings and cement used to attach prosthesis, however, degrade 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 as needed but must

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

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. A greater level of oral hygiene management, moreover, is required to properly maintain them.

(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 gums should be evaluated, and bleeding, gingival recession, and tooth looseness should be also checked for.

(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.

2 Jaw and Other Bone Disorders

The manifestations of TE include poor 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 clicking, and other temporomandibular symptoms. Training the patient to properly open the mouth and fitting the patient for a mouthpiece should prove effective.

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

Reference
1) Yoneyama T, Yoshida M, Matsui T, et al : Oral care and pneumonia. Oral Care Working Group. Lancet. 354: 515, 1999

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IX Ophthalmologic Manifestations

- Ophthalmologic manifestations specific to thalidomide embryopathy include Duane syndrome, facial paralysis, and crocodile tears syndrome.
- Many thalidomide embryopathy patients with auditory hypoplasia or deafness also have ophthalmologic manifestations.
- Duane syndrome often appears bilaterally as type III.

1 Ophthalmologic Conditions

Ophthalmologic dysfunction is nonspecific but involves visual impairment. Absence of the uvea is a common structural deficiency. Some patients have retinal coloboma, while others do not. Eye hypoplasia, when involving a coloboma, appears as anophthalmos or microphthalmos. Iris coloboma and microphthalmos occur frequently and are typically bilateral. Dermoid cysts on the eyeball surface are generally rare but are common in patients with auricle anotia or microtia. The defects listed above involve reduced visual acuity, which can also occur in patients without these structural anomalies.

Eye malformations in short-arm thalidomide embryopathy (TE) patients include microphthalmos, uveal hypoplasia, cataracts, and corneal opacity. In these patients, the severity of these eye conditions tends to increase with increases in the severity of upper-limb hypoplasia. By contrast, malformations of the eye adnexa are specific to hearing-loss type TE patients.

Duane syndrome, facial paralysis, crocodile tears syndrome, vertical gaze palsy, and dermoid malformations are common (Table 1)[1].

2 Abnormalities of the Extraocular Muscles

Duane syndrome is the most common ophthalmologic manifestation of TE. This syndrome is an abnormality of the extraocular muscles caused by aberrant regeneration of motor neurons associated with congenital hypoplasia of the abducens nuclei. An investigation of 31 TE patients with Duane syndrome revealed that 27 had deafness, one had upper-limb hypoplasia, and three had mixed manifestations. The clinical classification of the cases was overwhelmingly bilateral type III (Table 2). Since complete facial paralysis occurs with Duane syndrome, testing often showed no eyelid narrowing during adduction (Figure 1).

The comorbidities in these 31 patients included facial paralysis (26 patients) and crocodile tears syndrome (23 patients) (Table 3).

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 (from reference 1).

	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 paralysis	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

Table 2 Types of Duane syndrome (from reference 1)

Type	Abduction	Adduction	Bilateral	Unilateral	Total
I	+	-	7	2	9
II	-	+	1	0	1
III	+	+	21	0	21

Duane syndrome, congenital facial paralysis, crocodile tears, thalidomide embryopathy with deafness

Table 3 Comorbidities of Duane syndrome (from reference 1)

	Hearing-loss group	Short-arm group	Mixed group	Total
Crocodile tears syndrome	20	1	2	23
Facial paralysis	24	0	2	26
Vertical gaze palsy	2	0	0	2

3 Facial Nerve Palsy

Aplasia or hypoplasia of the facial nuclei is seen in congenital peripheral facial paralysis. The severity determines the degree of facial nerve hypoplasia and associated clinical symptoms (Figure 2). Some aberrant regeneration by the facial nerves is noted in electrophysiological testing, but unlike acquired facial paralysis, there is no clinically apparent pathological conjugate eye movement.

4 Crocodile Tears Syndrome

One sequela of acquired facial paralysis involves aberrant regeneration of the nerve fibers of the parasympathetic salivary and lacrimal glands such that a greater amount of tears than saliva is secreted when the affected person eats. This condition is called crocodile tears syndrome. Another feature of this condition is the absence of tear secretion when the affected person "cries." Some TE patients may have crocodile tears syndrome even though they do not have facial paralysis. Crocodile tears syndrome often occurs with Duane syndrome and auditory malformations. Caregivers must remember, however, that crocodile tears syndrome is not specific to TE.

Reference
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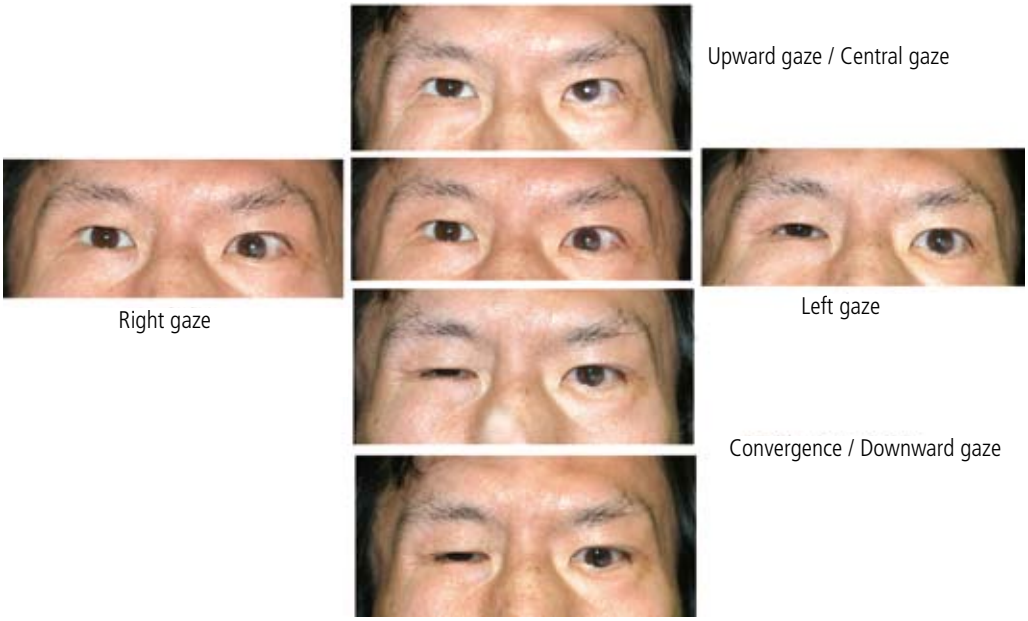

Figure 1 Bilateral Duane syndrome
The eyes do not move in either left or right gaze. Palpebral fissure narrowing is normally seen in the adducting eye but does not occur even in right gaze in this patient because of severe left facial paralysis.

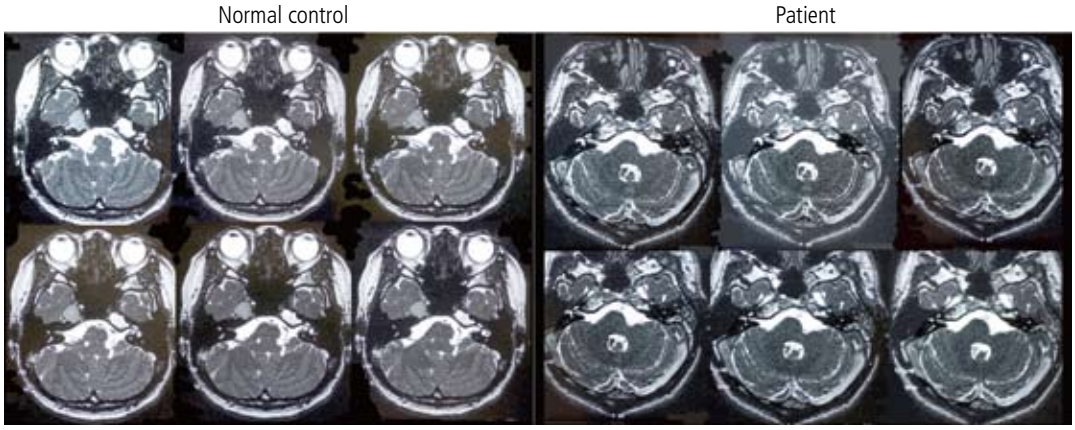

Figure 2 MRI scans of the facial nuclei and nerves
The patient imaged is the patient appearing in Figure 1. When compared with the control, the right facial nucleus shows atrophy. Defects are also seen in the left facial nucleus and facial nerves.

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X Psychiatric Care

- Patients with thalidomide embryopathy should be examined with the realization that a higher proportion of this population receives outpatient care for depression or another mental illness compared with the general population.
- Thalidomide embryopathy patients with auditory defects often have poor mental health because of the difficulty they experience communicating with others. The risk of anxiety, insomnia, and somatic symptoms is high in this population.
- It must be remembered that patients with thalidomide embryopathy have a much lower QOL than the general population.
- People with thalidomide embryopathy are expected to face more difficulty performing ADL as they age.
- Patient care must be flexibly handled in consideration of affected areas, disorder severity, and patient lifestyle and personality.

1 Psychiatric Issues in Patients with Thalidomide Embryopathy (TE)

The "National Study on the Health and Living Situations of Thalidomide-Impaired People" was conducted in Japan in 2012 (Yoshizawa, 2013)[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%) reported insomnia, 21 (10.4%) reported irritability, and 18 (9.0%) reported forgetfulness. A total of 21 respondents (10.4%) responded that they were "visiting a medical institution for depression or another mental illness." This is 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 (50–54 years of age, n=7,659).

Saito (2005) used the General Health Questionnaire-28 (GHQ-28), an instrument designed to evaluate mental health, to follow long-term outcomes among people with TE in Japan[2]. Higher scores on this instrument indicate poorer health. Around 20–35% of healthy people in the general population have a high GHQ-28 total score (cutoff point 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 healthy people in the general population. By contrast, 56% of thalidomide victims with auditory defects were above this cutoff. It indicates that this group has 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, which suggests that victims with auditory defects have poorer overall mental health (Table 1). The thalidomide victims with auditory defects had significantly poorer scores on the anxiety/insomnia and somatic symptom subscales of the GHQ-28, as well as poorer scores on the depression

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

subscale. Saito (2005) attributed this to the double punch of communication disorders caused by auditory defects and difficulty showing expressions, reasoning that many of the people in this group have relatively severe auditory defects and facial paralysis[2].

The 12-Item Short Form Health Survey (SF12) was conducted to evaluate quality of life (QOL) in 50 thalidomide victims in the United Kingdom (Newbronner et al., 2012)[3]. Compared with the general public, the thalidomide victims had much worse scores on questions related to physical functioning and bodily pain. A questionnaire survey using the World Health Organization quality of life (WHOQOL) was conducted to evaluate QOL in 900 thalidomide victims in Germany (Kruse et al., 2012)[4]. The thalidomide victims had much poorer QOL scores compared with members of the general public of the same age group (50s). The QOL of thalidomide victims was comparable to members of the general public in their 80s, which suggests that aging more strongly affects this group. Kruse et al. added that as they age, thalidomide victims suffer secondary sequelae and pain as well as subsequent difficulty remaining mobile and performing physical labor, which reduces what they can do. The above findings indicate that thalidomide victims have a markedly lower QOL than healthy people and that the pain and decline in physical function they experience may threaten their lifestyle. The psychiatric effects of age-related decline in QOL must be followed.

2 Tips for Caring for Patients with Thalidomide Embryopathy

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 easily carry out daily and social activities, while others are not. Caregivers engaging with the patient with TE must work flexibly in consideration of affected areas, disease severity, and patient lifestyle and personality. Horton (2015) 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[5]. Victims felt less pain when they deliberately and independently acted on their problems by, for example, listening to what their bodies were telling them, living within their limits, and seeking care when they felt it necessary. Thalidomide victims that handle life in this way will probably be more accepting of the changes associated with the difficulties that aging brings.

Many thalidomide victims are able to live life day-by-day despite their physical disabilities and social handicaps. Healthcare professionals should interact with their TE patients with a constant respect of 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 TE patient 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 their patient has to say, proceeding at his or her own pace. It is important not to fixate exclusively on mental issues because pain and other somatic symptoms must also be considered.

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XI Problems Encountered in Clinical Settings

1. Blood Collection

- 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 malformations 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 thalidomiders 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 TE patients who can lip read.

2 Technical Challenges of and Procedures 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 a medical assistant should remain with the patient for 5 or so minutes to help stop the bleeding.

3 Blood Sampling Kits

The Safe-touch PSV Set with Luer Adapter by Nipro Corporation is 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.

Blood collection, being prepared, blood sampling kit

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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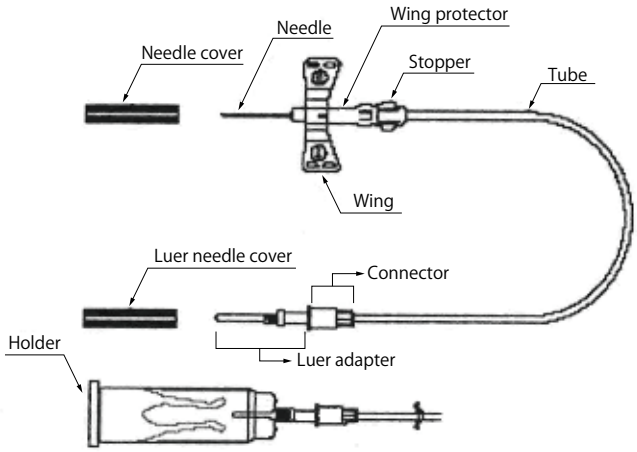

Figure 1 Names of the components in the Safe-touch PSV Set with Luer Adapter

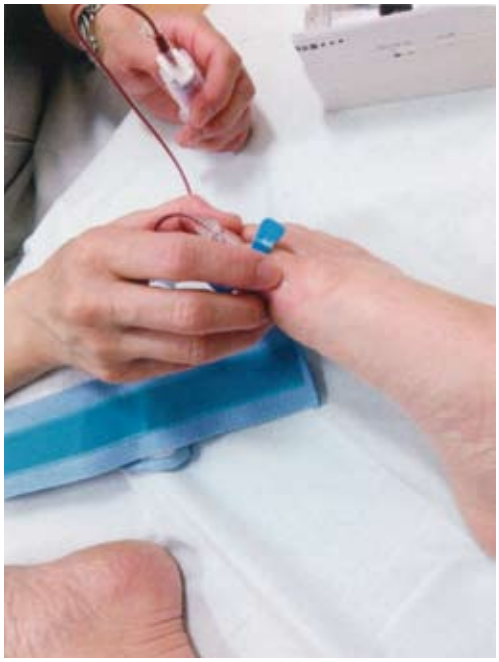

Figure 2 Patient from whom blood can be collected only from the inside of the first right toe (24 gauge)

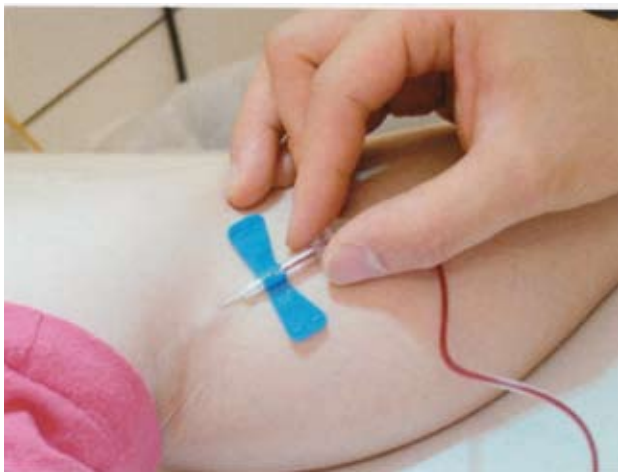

Figure 3 Patient from whom blood can be collected only from behind the left knee (24 gauge)

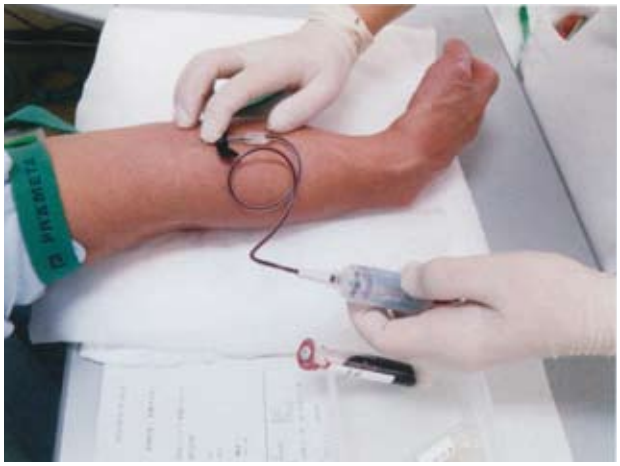

Figure 4 Patient from whom blood was successfully collected from a vein of the upper right limb (22 gauge)

Figures 1 to 4 were adopted from "Q&A on Thalidomide-Impaired People" by the previous research team[1].

XI Problems Encountered in Clinical Settings

2. Measuring Blood Pressure

- Properly prepare the environment prior to measurement.
- Carefully decide which of the limbs of the thalidomide embryopathy patient 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 PAD.

1 Before Measuring Blood Pressure

Have the patient remain still for 2 to 3 minutes in a supine position 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. Blood pressure can normally be measured at the left or right upper arm of healthy people, but may have to be measured at different sites, including those in the lower limbs, in thalidomide embryopathy (TE) patients with upper-limb defects. In health screenings at 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 mean 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 mark 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.

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. Currently, we usually use a medium cuff to measure blood pressure at four locations. 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. And a small cuff should be used at all measurement sites.

There is disagreement about cuff sizes and measurement sites. The recommendations of a Swiss expert are informative[URL1)].

5 Evaluating Lower Limb Systolic Blood Pressure

To determine if upper-limb blood pressure could be estimated from lower-limb measurements, the previous research team 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 team derived the following formula for medium cuffs: Upper-limb systolic blood pressure = 0.88 × (lower-limb systolic blood pressure + 8). The team 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.

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

This formula is now recommended for estimating upper-limb blood pressure. Further examination with a larger sample size is needed to better evaluate the validity of the formula.

6 Evaluation When Peripheral Artery 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. Since measuring blood pressure in those with TE is inherently challenging, preventing arteriosclerosis in this population is all the more important. 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 pressure index (ABI) 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 measure systolic blood pressure in the dorsalis pedis and posterior tibial arteries via a Doppler blood flow monitor. 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 monitor is available. This, however, may not work if the patient has PAD, so PAD cannot be ruled out with an auscultation approach[2].

7 Recommendations of a Swiss Expert for Blood Pressure Measurement

The German-born Swiss physician, Dr. Schulte-Hillen, also published recommendations for blood pressure measurement on the Internet[URL1].

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XI Problems Encountered in Clinical Settings

3. Considerations for Anesthesia and Surgery

- Know the condition of the patient well 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 deformities.
- Thoroughly prepare for waking the patient and extubation, checking for neurological changes after the patient wakes.

Patients with thalidomide embryopathy (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. Caregivers must identify the severity and sites of congenital anomalies (e.g., upper limbs, lower limbs, face [eyes, ears, lacrimal glands], organs [heart, kidney/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 obviously want to try to perform routine preoperative tests when possible. Blood sampling, however, may be difficult because of difficult-to-locate peripheral blood vessels associated with the above congenital anomalies. Problems may also face 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).

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, 1,2]. 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. Intraoperative management based on lower-limb blood pressure is possible when no lower-limb anomaly is present, but it must be remembered that lower-limb readings are generally somewhat higher (approximately 10–20 mmHg higher) than upper-limb readings (see section XI.2 Measuring Blood Pressure). Shiga and colleagues 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[3]. Another publication discusses the usefulness of recently developed devices that measure blood pressure with a finger cuff[4]. Relevant to all measurement techniques is not only whether a cuff can be fitted, but also the degree of blood flow at the measurement site. Preoperative ultrasonography and Doppler imaging are needed to evaluate blood vessel distribution and blood flow at candidate sites.

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

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 cannulization is possible.

(2) Airway management and intubation

Particular caution is required when administering general anesthesia in a patient with facial deformities 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, laryngoscope, 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 as much as possible since thalidomiders with limb defects 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 seldom 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 thalidomiders with limb defects also have sensorineural defects at the affected areas[URL1)], patients must be carefully monitored for prolonged muscle relaxant effects and unintended neurological changes. In addition, since TE patients with any of the above-mentioned facial deformities 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 for extubation under close observation. Once awake, the patient should be closely monitored for sensory disturbances and paralysis and the range of conduction/local anesthesia.

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XI Problems Encountered in Clinical Settings

4. Considerations for Transnasal Endoscopy of the Gastrointestinal Tract

- Routine transnasal endoscopy is suitable for patients with thalidomide embryopathy.
- General considerations for transnasal endoscopy apply to this population.
- Patients with an auditory defect should be fully informed about the endoscopy procedure and their understanding should be obtained in advance.
- *Helicobacter pylori* prevalence and the degree of gastric mucosal atrophy in thalidomide embryopathy patients are comparable to those in the general population.
- 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 thalidomide embryopathy.

1 Introduction

Nine of the 10 patients with thalidomide embryopathy (TE) examined in FY2012, all eight TE patients examined in FY2013, all eight TE patients examined in FY2014, and six of the seven TE patients examined in FY2015 (31 of 33 patients in all) underwent endoscopy of the upper gastrointestinal tract at Center for Health Examination, National Health Organization Kyoto Medical Center. The patients were informed about the transnasal and transoral approaches before the procedure. The transnasal approach was used for 15, and the transoral approach for 16 (one patient with narrow nasal cavities was switched from a transnasal to transoral approach, but the narrowing was not associated with TE). Patients with an auditory defect in particular should be fully informed about the endoscopy procedure in advance because they may not be able to read signs during the procedure. Physical contact by a nurse will help reassure the patient. 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. No other anatomical anomalies were identified. Of the 31 patients, 17 had a gastric mucosal atrophy classification of C0, one had a classification of C1, six had a classification of C2, two had a classification of O1, and five had a classification of O2. We have classified patients into gastric cancer risk categories during endoscopy since FY2014, also evaluating *H. pylori* infection status.

Eight of 14 patients were not infected, three had a current infection, two were previously infected and had not undergone eradication, and one was previously infected and had undergone eradication. The infection rate did not differ from similarly aged members of the general population. None of these patients were on a proton pump inhibitor, had renal dysfunction, or had undergone a gastrectomy.

2 Transnasal Endoscopists

Endoscopists well trained in the transoral approach should be technically capable of performing transnasal endoscopy provided they understand the idiosyncrasies of transnasal endoscopy and have reviewed their knowledge of otolaryngological anatomy or pathology. They must, however, be even more committed to minimizing overlooking issues than when taking a transoral approach.

3 Contraindications for Transnasal Endoscopy

- Transnasal endoscopy is contraindicated in patients with a lidocaine allergy because of the risk of anaphylactic shock. The procedure is also contraindicated with patients with aspirin-induced asthma because the paraben preservative in lidocaine jellies and lubricants can trigger aspirin-induced asthma.
- Bilateral obstructive disease of the nasal cavities or upper pharynx
- Severe bleeding tendency due to underlying disease
- The procedure is contraindicated in patients on a monoamine oxidase inhibitor because these drugs,

Transnasal endoscopy, contraindication, accidental symptom, *H. pylori* infection

when used with 0.05% naphazoline nitrate, can cause a sudden increase in blood pressure.

4 Advantages and Disadvantages of Transnasal Endoscopy

- Advantages include the fact that this approach may be more comfortable because 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 autonomic nervous system is not stimulated as much as with a transoral approach.
- Disadvantages include the fact that this approach can cause nasal pain and bleeding. In addition, some scopes are inferior in resolution, operability, and performance to most transoral scopes. Because of poorer picture quality, air/water channels, and suction, the procedure may take 20–30% longer. Scopes also have poorer biopsy capabilities when inverted in the cardiac part of the stomach or lesser curvature of the upper body.

5 Preparation

(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.
(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 air flow.
(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% lidocaine 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 after 90 seconds. The patient is asked to swallow lidocaine 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. If the patient complains of pain following insertion, apply lidocaine jelly (or viscous lidocaine solution) to the scope to enhance anesthesia, keeping the total lidocaine dose below 200 mg. Switch to a transoral approach (with the patient's consent) if the scope cannot be inserted into either side.

6 Scope Route

Insert via the wider of the middle or inferior concha routes. The opening of the eustachian tube will appear on the left if the scope is inserted on the left side or on the right if the scope is inserted on the right side. After locating the upper pharynx, guide the scope to the middle pharynx. After the middle pharynx, the route is the same as that with the transoral approach.

7 Accidental Symptoms and Interventions

(1) Epistaxis

Keep the tip of the endoscope away from Kiesselbach's area during insertion. When the route is narrow and resistance is encountered, gently guide the scope forward while twisting it back and forth. When insertion is very difficult, switch to the other side rather than forcing the scope in. 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. 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. If blood flows from the nose, insert a cotton roll soaked in 0.1% topical adrenaline diluted by a factor of 1 to 10 into the nasal cavity and pinch the nasal wing. This will often stop the bleeding.

(2) Nose pain

The patient may experience pain if the scope presses against the nasal concha or septum. Guide the scope in while asking the patient if he or she is in pain. Different people experience different levels of pain. Extra anesthetic can be applied if the patient reports some pain, but the scope should be inserted on the other side if pain is intense.

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XI Problems Encountered in Clinical Settings

5. Nursing

- It is important to approach patients with thalidomide embryopathy with awareness of their disease, understanding of their social circumstances, and a considerate attitude.
- Considerate nursing practice and care that factors in the disorders of the individual patient are necessary to ensure that testing proceeds smoothly.
- Carefully decide how to communicate with patients with an auditory defect (e.g., sign language, written communication, lip reading, use of assistive forms) on an individual basis.
- Care requires a multidisciplinary approach with healthcare professionals from other disciplines, who should be closely partnered with.

The following considerations for testing and examinations are based on the experiences of the authors in detailed medical examinations.

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. Assist patients who have difficulty transferring their urine to the Spitz tube or on 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 gel remaining 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.

4 Computed Tomography

Assist the patient with securing the upper limbs with a belt if necessary.

5 Hearing Tests and Otolaryngology Examinations

Before the patient is examined, remove any excess earwax that the patient cannot because of upper-limb defects. Make sure that the hair does not cover the ears.

6 Gynecological Examinations

Adjust the gown so that the top does not cover the midriff when the patient sits on the exam table.

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 gel remaining 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. Thalidomide embryopathy patients with upper-limb defects tend to strain more than others and may therefore have difficulty breathing. Provide emotional support during the

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

procedure by, for example, gently rubbing the patient's back. Assist patients who are unable to maintain a side-lying position. When an 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 an auditory defect, inform testing personnel in advance about how the patient should be communicated with (e.g., sign language, written communication, lip reading) 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 will 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 and explain the test as necessary to ease the patient's tension.
(4) Ask patients with an auditory defect the way they usually communicate (e.g., sign language, written communication, lip reading) and communicate on an individual basis.
(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 to patients who are anxious or resistant to undergo examination because of previous bad experiences in healthcare situations.
(11) Be considerate when informing the patient about the test as some thalidomide victims are uneasy around others.
(12) It is important to approach patients with awareness of their disease, understanding of their social circumstances, and a considerate attitude.

Erika Samukawa and Yukiko Nagata
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XII Related Information

1. Network of Healthcare Providers Serving Thalidomide Survivors

The network of healthcare providers serving Japanese thalidomide survivors was established in 2015. This network consists of about 60 members who are physicians, nurses, physiotherapists, researchers, pharmacists and other healthcare providers.

2. Website of the Thalidomide Embryopathy Research Group

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

3. Information on the Ishizue Foundation

The Public Interest Incorporated Foundation, Ishizue Foundation, was founded in 1974 for thalidomide victims living in Japan. The URL is: http://www008.upp.so-net.ne.jp/ ishizue/index.html.

4. Notable Sites for Information on Thalidomide Embryopathy Outside Japan

- Conterganstiftung für behinderte Menschen (Germany)
  http://www.gruenenthal-opfer.de/Kurzvorstellung
- Wiederholt durchzuführende Befragungen zu Problemen, speziellen Bedarfen und Versorgungsdefiziten von contergangeschädigten Menschen
  https://www.contergan-infoportal.de/fileadmin/downloads/NEU-DOWNLOADS/Dokumentation/Zwischenbericht_Studie_Contergan.pdf#search=%27Contergan+Greiner+Christina%27
- Damage to Health, Psychosocial Disorders and Care Requirements of Thalidomide Victims 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#search=%27Damage+to+Health%2C+Psychosocial+Disorders+and+Care+Requirements+of+Thalidomide%27
- The Thalidomide Trust (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#search=%27UK+thalidomide+firefly%27
- Falls and Balance Problems Briefing Paper (Final–May 2017)
  https://www.thalidomidetrust.org/wp-content/uploads/2016/10/Falls-and-Balance-Problems-Briefing-Paper-FINAL.pdf#search=%27falls+problems+thalidomide+ and+ballance%27
- EX-Center (Sweden)
  http://www.ex-center.org/web/home/

* This information mentioned above was obtained in 2017.