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Internal anomalies in thalidomide embryopathy: results of imaging screening by CT and MRI

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AIM: To examine the prevalence and detailed radiological findings of internal anomalies in thalidomide embryopathy (TE).

MATERIALS AND METHODS: Whole-body image screening for internal anomalies using unenhanced whole-body computed tomography (CT) and head magnetic resonance imaging (MRI) was performed in 22 patients (13 women and nine men; mean age, 49 years; range, 47–51 years) with TE.

RESULTS: Among the 22 patients with TE, internal anomalies were detected in 19 (86.4%): anomalies of the auditory organ in 10 (45.5%), anomalies of the vascular system in six (27.3%), agenesis of the gallbladder in six (27.3%), hypoplasia or aplasia of the 7th or 8th cranial nerves in five (22.7%), block vertebrae in five (22.7%), fusion of the left lobe and quadrate lobe of the liver in three (9.1%), and others in five (22.7%), respectively.

CONCLUSION: In addition to limb defects or hypoplasia, various internal anomalies can be detected at a high incidence in TE using CT and MRI. Understanding these characteristic radiological findings may help radiologists detect a wide range of radiological findings of internal anomalies associated with TE.

Introduction

Thalidomide was developed in 1954 by the German pharmaceutical company Grünenthal GmbH. It was first marketed in 1957 in West Germany under the label of “Contergan” and was subsequently licensed in 46 other countries. In 1961, the German paediatrician, Widukind Lenz, and the Australian obstetrician and gynaecologist, William McBride, demonstrated that thalidomide had teratogenic effects, and it was then withdrawn from the market.[1] It was estimated that there were more than 10,000 thalidomide babies all over the world.[2] Although thalidomide had been banned from the market once, subsequent studies revealed immunomodulatory, anti-inflammatory, and anti-angiogenic effects of thalidomide, and many clinical trials demonstrated the efficacy of thalidomide treatment for several medical conditions.[3,4] Today, it is known that thalidomide is an effective drug for multiple myeloma, erythema nodosum leprosum, and several other diseases.

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Recently several new cases of thalidomide embryopathy (TE) were reported in areas in Brazil that have a high prevalence of leprosy.[4]

It is well known that thalidomide causes severe limb defects including the well-publicised phocomelia, but it also causes various internal anomalies (IAs) such as IAs of the cardiovascular system and gastrointestinal tract, some of which are fatal. Unfortunately, there are a lack of studies on the prevalence and detailed radiological findings of IAs among individuals with TE. In Japan, there are numerous individuals with TE, and many of them have been examined at National Center for Global Health and Medicine, Tokyo. Their life conditions, psychophysiological problems, and functional problems were examined. Radiologists were assigned to examine their internal anomalies using computed tomography (CT) and magnetic resonance imaging (MRI). In Japan, although many patients with TE are registered for the national database, most patients have not had a medical examination since birth.

The purpose of the present study was to examine detailed radiological findings of IAs among individuals with TE in Japan using CT and MRI, and to clarify the prevalence of IAs in this patient group.

Materials and methods

Patients

In Japan, a total of 309 individuals are registered in the national database as patients with TE. Among them, 22 patients with TE were selected who wanted to undergo a thorough medical examination at the National Center for Global Health and Medicine supported by Ishizue, a foundation for the welfare of thalidomide victims in Japan. This study involved 13 women and nine men; with the mean age of 49 years (range, 47–51 years). Two identical twins were included. Upper-limb defects were found in 19 patients, while the other patients had no external anomaly.

This study was approved by the research ethics committee of the institution, and written informed consent was obtained from each patient.

CT and MRI

Whole-body CT examinations were performed with one of two multidetector CT (MDCT) systems: a 320-MDCT system (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) and a 128-dual-source MDCT system (SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany). The section thickness was 5 mm. In addition, 1-mm section images were obtained of the cervical spine and temporal bone. The tube voltage was 120 kV. High-resolution temporal bone CT images in both the axial and coronal planes and sagittal images of the cervical spine were also obtained in all of these patients. Helical scanning was used for either site in this study. The mean dosages of head CT (including the temporal bone), CT dose index (DI) and dose–length product (DLP) were 60.91 mGy and 984.7 mGy·cm, respectively. The mean dosages of body CT (including cervical vertebrae), CTDI, and DLP were 10.64 mGy and 784.5 mGy·cm, respectively. The mean effective doses for head CT and body CT were 4 and 28 mSv, respectively.

Head MRI examinations were performed with one of three MRI systems: a 3-T MRI system (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) and two 1.5-T MRI systems (MAGNETOM Avant, Siemens Healthcare, Erlangen, Germany; EXCELART Vantage Powered by Atlas, Toshiba Medical Systems, Otawara, Japan). In all patients, axial magnetic resonance (MR) images of T2-weighted, T1-weighted, T2*-weighted and fluid-attenuated inversion recovery (FLAIR) were obtained. To screen for cerebrovascular diseases, three-dimensional (3D) time-of-flight MR angiography (MRA) of the head and neck were also obtained. In addition, heavily T2-weighted MR images with 1-mm section thickness of the posterior fossa were obtained in 20 of the 22 patients using MR sequences of 3D- fast imaging employing steady state precession (CISS; Siemens) or steady-state free-procession (SSFP; Toshiba).

Image analysis

The CT and MR images were prospectively interpreted by five reviewers: four experienced board-certified radiologists (neuro-, thoracic, abdominal, and general radiologists) and a radiology resident. The auditory organ was examined using high-resolution temporal bone CT imaging in both the axial and coronal planes, the vascular system on the head-and-neck MRA, and whole-body CT images; the cranial nerves and facial nuclei on the head MRI including heavily T2-weighted axial MR images with 1-mm section thickness of the posterior fossa; the cervical spine on thin-slice CT images in both axial and sagittal planes; and the thoracic and abdominal organs on the CT images.

The prevalences of the abnormal findings were then calculated based on the observers' evaluations, and if there was discrepancy among observers, the matter was decided by consensus.

Statistical analysis

For categorical variables, Fisher's exact and chi-squared tests were applied. For comparison of the two parameters, an unpaired *t*-test was used. For statistical analyses, analysis software (JMP version 9.0.2, SAS Institute Japan, Tokyo, Japan) was used. For all studies, *p*-values of <0.05 were taken to indicate a statistically significant difference.

Results

Relationship between limb defects and IAs

Patient profiles are shown in Table 1. There were no patients who had lower-limb defects. Various types of IAs were detected using CT and MRI as shown in Table 2 including: anomalies of the auditory organ in 10 of 22 patients (45.5%; Fig 1); anomalies of the vascular system in six of 23 patients (27.3%); agenesis of the gallbladder in six of 23 patients (27.3%); hypoplasia or aplasia of the 7th/8th

Table 1
Patient profiles: the results of limb defects and internal anomalies.

Case no./ age/ gender	Limb defects	Anomalies of the AO	Anomalies of the VS	Agenesis of the GB	Hypoplasia or aplasia of the 7th/8th CN	Block vertebrae	Abnormal lobulation of the liver	Other internal anomalies
1/49/M	+							
2/50/M		b			b7th/8th			
3/51/F	+		+	+		+		
4/49/M	+					+		
5/49/M	+	b		+		+		
6/49/F	+		+					
7/51/F	+	b						
8/49/M		b		+				
9/50/M	+	b			r7th			
10/47/F	+		+			+	+	Hypoplasia of unilateral thorax, AA
11/48/M		b		+	r7th		+	
12/49/F	+							
13/51/F	+			+		+		
14/49/M		b			l7th			
15/50/M	+							
16/49/F	+		+					
17/48/F	+						+	Right-sided LTH
18/49/F	+	l	+					
19/50/F	+		+					
20/49/F	+	b						Congenital hip dislocation
21/48/F	+							Transection of the pituitary stalk
22/49/F	+	b			r7th/8th			Vaginal atresia

AO, auditory organ; VS, vascular system; GB, gallbladder; AA, anal atresia; LTH, ligamentum teres hepatis; b, bilateral; r, right; l, left; CN, cranial nerves.

cranial nerves in five of 22 patients (22.7%; Fig 2); block vertebrae in five of 22 patients (22.7%; Fig 3); fusion of the left lobe and quadrate lobe of the liver in two of 22 patients (9.1%; Fig 2); and other IAs in five of 22 patients (22.7%), including transection of the pituitary stalk, hypoplasia of the hemithorax, right-sided ligamentum teres hepatis, vaginal atresia, and unilateral congenital hip dislocation in one case each (Table 2).

Upper limb defects and IAs were seen in 18 (81.8%) and 19 (86.4%) of the 22 patients, respectively. The association between the two categories was not statistically significant (chi square test, $p=0.9416$; Fisher's exact, $p=1.00$). Patients who had both limb defects and one or more IAs comprised 15 of the 22 patients (68.2%).

Table 2
Prevalence of internal anomalies by various imaging techniques.

Types of internal anomalies	Imaging technique	Number of patients	Percentages (%)
Anomalies of the auditory organ	CT	10	45.5
Anomalies of the vascular system	CT/MRI	6	27.3
Agenesis of the gallbladder	CT	6	27.3
Hypoplasia or aplasia of the 7th/8th cranial nerves	MRI	5	22.7
Block vertebrae	CT	5	22.7
Fusion of the left lobe and quadrate lobe of the liver	CT	2	9.1
Others	CT/MRI	5	22.7

Others includes transection of the pituitary stalk, hypoplasia of unilateral thorax, right-sided ligamentum teres hepatis, vaginal atresia and unilateral congenital hip dislocation.
CT, computed tomography; MRI, magnetic resonance imaging.

Anomalies of the auditory organ

Anomalies of the auditory organ were seen in 10 of the 22 patients (45%; Fig 1): hypoplasia of the semicircular canals in eight patients (80%); hypoplasia of the auditory ossicles in five (50%); hypoplasia of the vestibule in five (50%); hypoplasia of the cochlea in four (40%); internal auditory meatus abnormality in four (40%); bilateral narrow internal auditory meatus in three (30%), bilateral absence of internal auditory meatus in one (10%); external auditory meatus abnormality in three (30%); unilateral narrow external auditory meatus in two (20%), bilateral narrow external auditory meatus in one (10%). Of the 10 patients with anomalies of the auditory organ, six (60%) patients had hearing loss.

Anomalies of the vascular system

Anomalies of the vascular system were seen in six patients: double superior vena cava (SVC) in three patients (50%); laterality of the height of the carotid sinus in two (33%); duplicated middle cerebral artery in one (16.7%); a middle meningeal artery arising from the internal carotid artery in one (16.7%); aberrant right subclavian artery in one (16.7%); and azygos vein flowing into the superior vena cava from the highest intercostal vein without forming the arch of azygos vein in one (16.7%).

Anomalies of the cranial nerves

Hypoplasia or aplasia of the 7th/8th cranial nerves was seen in five of 22 patients (23%): hypoplasia of unilateral 7th

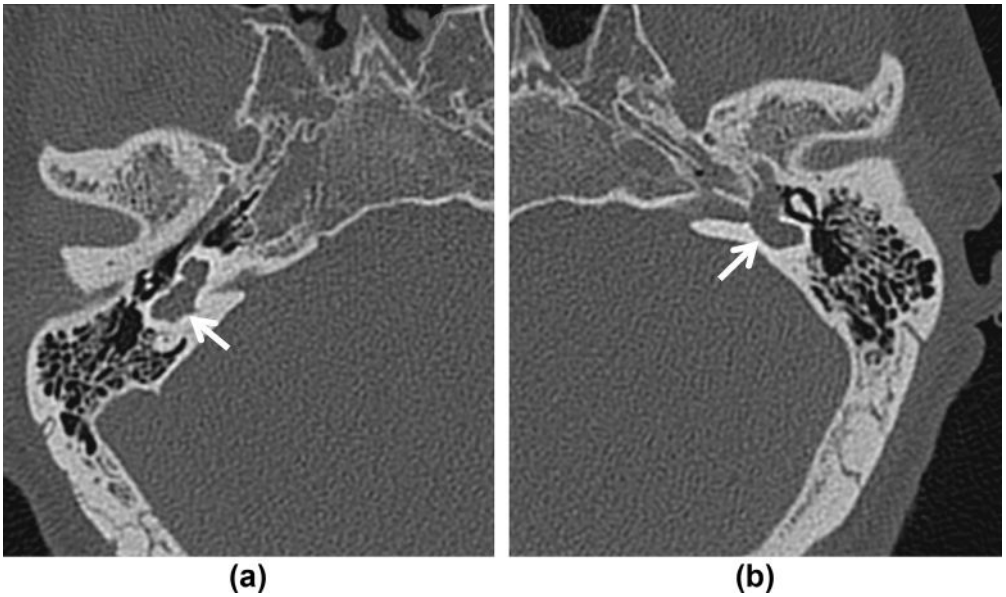

Figure 1 A 48-year-old man with anomalies of the bilateral auditory organs resulting in bilateral hearing impairment. High-resolution CT images of the temporal bone in the axial plane showed hypoplasia of bilateral semicircular canals, cochlea, vestibule, and right malleus. Lateral semicircular canal, cochlea, and vestibule formed cavities (arrows) on both sides.

cranial nerve in three (60%); hypoplasia of unilateral 7th and 8th cranial nerves in one (20%; Fig 3); and aplasia of bilateral 7th and 8th cranial nerves in one (20%). All but one of the patients with unilateral hypoplasia of the 7th cranial nerve also had a narrow internal auditory meatus. The patient with aplasia of bilateral 7th and 8th cranial nerves had bilateral defects of the internal auditory meatus.

In five patients with abnormalities of the 7th cranial nerve, four (80%) patients had crocodile tears syndrome and one (20%) patient had facial palsy. In the six patients with crocodile tears syndrome, four had hypoplasia or aplasia of the ipsilateral 7th cranial nerve. One patient with facial palsy had hypoplasia of the ipsilateral 7th cranial nerve.

Two patients with hypoplasia or aplasia of the 8th cranial nerve had hearing loss. In eight patients with hearing loss, six (75%) patients had anomalies of the auditory organ, and one (12.5%) patient had a cholesteatoma.

Abducens palsy was seen in three patients, but abnormalities of the 6th cranial nerve could not be detected by MRI in any patient.

Block vertebrae

Block vertebrae were seen in five of 22 patients (23%): fusion of vertebral bodies and arches of C2–C3 in one (20%); fusion of vertebral bodies and arches of C2–C3 and C6–T1 in one (20%); fusion of vertebral bodies and arches of C3–C5 and C6–T2 in one (20%; Fig 4); and fusion of vertebral bodies and arches of C7–T1 in two (40%).

Other IAs

Other IAs were seen in five patients as follows (Table 2): transection of the pituitary stalk in one; hypoplasia of the

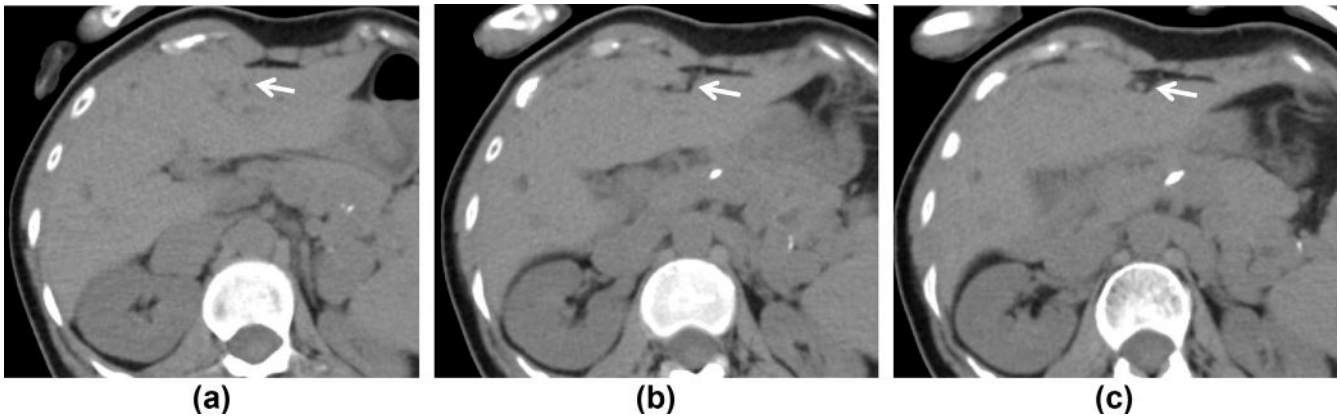

Figure 2 A 47-year-old woman with fusion of the left lobe and quadrate lobe of the liver. Unenhanced axial CT images of the abdomen show the hypoplasia of the fissure for ligamentum teres (arrows). In this case, the function and size of the liver was normal, and anomaly in the biliary system is not seen.

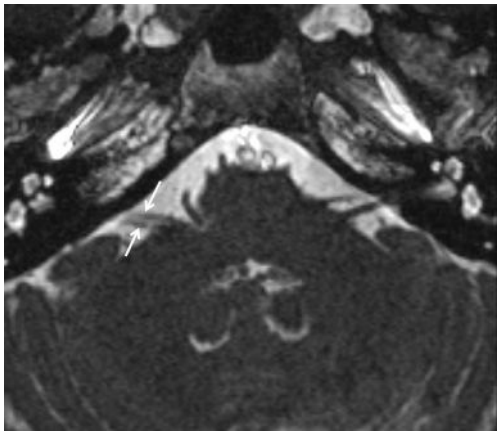

Figure 3 A 49-year-old woman with hypoplasia of the right 7th/8th cranial nerves. Heavily T2-weighted MRI image with 1-mm section thickness of the posterior fossa shows the narrow right 7th/8th cranial nerves (arrows). See the normal 7th/8th cranial nerves on the contralateral side. There was no abnormality in the 6th cranial nerve.

hemithorax in one; right-sided ligamentum teres hepatis in one; vaginal atresia in one; and unilateral congenital hip dislocation in one.

Discussion

It has been reported that TE can occur when a mother takes thalidomide from her last menstrual period to 34–50 days into the pregnancy.[1] In the late 1950s and early 1960s, thalidomide was sold as a hypnotic drug, it was advertised as safe for use during pregnancy and was even used to alleviate nausea and emesis during pregnancy; as a result there is a generation of affected individuals. Over 30 hypotheses have been proposed regarding the teratogenic mechanisms of thalidomide; however, current research is concerned mostly with the following: oxidative stress/damage, DNA intercalation, inhibition of angiogenesis, and cereblon binding.[5] Cereblon is a protein that forms an E3 ubiquitin ligase complex. Recently, cereblon has been identified as a primary target of thalidomide teratogenicity.[7,8] There are a few case reports demonstrating IAs and their prevalence in TE. In previous reports, common IAs were anomalies of cranial nerves, eyes (anophthalmia and microphthalmia), auditory organ (anomalies of inner, middle, and external ear), cardiovascular system (pulmonary stenosis, ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA)) hepatobiliary system (agenesis of the gallbladder), alimentary tract (duodenal atresia, anal atresia, pyloric stenosis, and inguinal hernia), urinary tract (absent, horseshoe, ectopic, hypoplastic, or rotated kidney and ectopic ureter), and genital tract (undescended, small, or absent testis, vaginal atresia hypospadias and bicornuate uterus).[1,2,6,9–12] These previous reports were sporadic, and can be classified into reports based on either clinical diagnosis or image diagnosis, such as radiographs, echocardiography, and pyeloureterography. In the present study, various IAs in the whole body were detected using CT and MRI: there were upper-limb defects in 18 of the 22 participants with TE (81.8%), anomalies of internal organs in 19 of 22 (86.4%), and both in 15 of 22 (68.2%). The concurrence of both anomalies was frequently observed, but significant correlation was not found for malformation of the arms and IAs.

There have been studies investigating anomalies of the auditory organ, but almost all of these evaluated the auditory organ by radiographs,[13] and to the authors' knowledge, no previous study has evaluated them using high-resolution temporal bone CT. The prevalence rate in TE of anomalies of the auditory organs was estimated by radiographs at approximately 20%,[14] whereas in the present study the prevalence rate by high-resolution temporal bone CT images was 45%. It seems that this difference may be related to the detection ability of each of these imaging

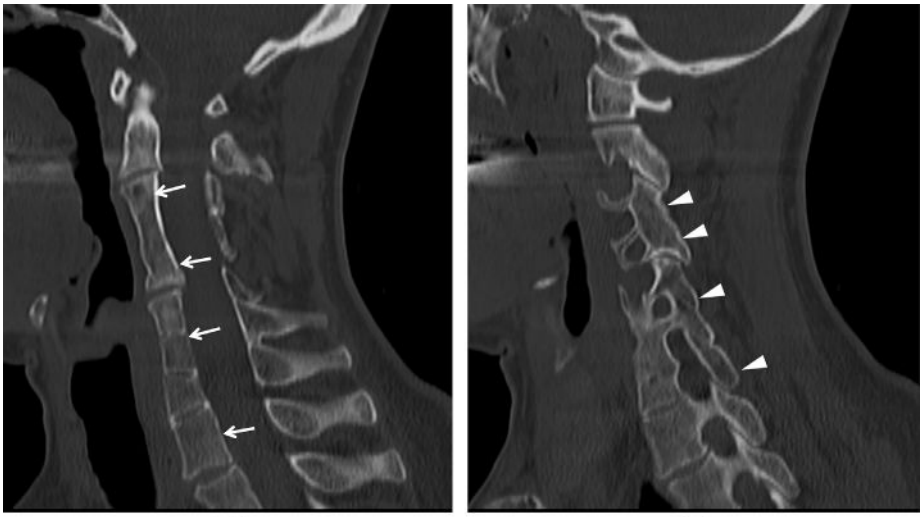

Figure 4 A 47-year-old woman with block vertebrae. Unenhanced CT images of the cervical spine in the sagittal plane showed fusion of the (a) vertebral bodies (arrows) and (b) arches (arrowheads) of C3–C5 and C6–T2.

techniques. In this study, five out of the 10 patients with anomalies of the auditory organ had hearing impairment, and four of the 10 patients had severe anomalies of the auditory organ, which included overlapping defects in the semicircular canals, auditory ossicles, and vestibules. In contrast, four of five patients with normal hearing ability had relatively mild anomalies, such as anomalies of the semicircular canals, ossicles, and internal auditory meatus, which did not overlap with other anomalies. The degrees of anomalies of the auditory organ due to thalidomide show a spectrum from mild to severe, which may be associated with their clinical symptoms. High-resolution temporal bone CT is the most useful imaging method to evaluate the cause of hearing impairment. In addition, in the present study, six of 10 patients (60%) with anomalies of the auditory organs also had upper-limb defects. Kida *et al.*[15] reported that 47 of 82 patients (57.3%) with hearing impairment had upper-limb defects. Their findings generally corresponded to the present results.

Among anomalies of the vascular system, double superior vena cava was seen in three of 22 patients (13.6%) using unenhanced CT; this prevalence rate was 23 times higher than that in the Japanese adult population, which is at 0.6%. The association with thalidomide exposure is strongly suggested.[16] No other anomalies of the vascular system were detected. Other anomalies of the vascular system in the branch vessels of the aorta or the inferior vena cava might have been detected if contrast-enhanced CT or angiography had been used; however, invasive examination was not performed in the present study unless it was clinically necessary.

Anomalies of the cranial nerve were seen in five of 22 patients (23%) in the present study. There have been several reported cases of abducens nerve palsy or facial nerve palsy in TE. In a report on 18 patients with TE,[19] abducens nerve palsy, facial nerve palsy, and crocodile tears syndrome were seen in 67% (12/18), 33% (6/18), and 39% (7/18), respectively. The cause of facial nerve palsy suggested hypoplasia of the facial nucleus.[20–22] Kayamori and Mikami[23] reported hypoplasia of the facial nucleus on MRI in patients with facial nerve palsy in TE. In the present study, left facial nerve palsy was seen in one patient, whose left facial nerve was hypoplastic, but the left facial nucleus was not hypoplastic. These results agree with the report of Kayamori and Mikami. It seems that further studies evaluating the facial nerve nucleus in TE will be necessary in the future.

Of the six patients with crocodile tears syndrome, four had hypoplasia of the facial nerves on MRI. Abducens nerve palsy was seen in three patients, but no abnormality of the abducens nerve was detected in any of the present cohort. Limitations of the resolution of MRI may be associated with this discrepancy.

Block vertebrae were seen in 23% of patients with TE in the present study. To the authors' knowledge, there have been no focused reports regarding the complication of block vertebrae in patients with TE. Generally, block vertebrae can lead to spondylosis of the adjacent vertebrae and result in neurosis, so it often becomes a clinical problem.[25] The causes of block vertebrae can be congenital or acquired. Injuries and infectious diseases, such as tuberculosis, have been cited as causes of acquired block vertebrae, but there was no such medical history in any of the present patients with block vertebrae. What was profoundly interesting was the fact that the two patients with block vertebrae were identical twins and they shared similar patterns of block vertebral fusion. This suggests a correlation between thalidomide and block vertebrae. A decrease in local blood flow during weeks 3–7 in pregnancy has been considered the cause of block vertebrae[24]; in patients with block vertebra, exposure to thalidomide during pregnancy should be considered a possibility.[25] Moreover, all patients with block vertebrae had upper-limb defects; this finding showed a significant correlation.

Klippel–Feil syndrome is one of the diseases complicated with block vertebra and upper-limb defects; its three main symptoms are short neck, low hairline, and limited neck movement; this syndrome is also associated with upper-limb defects, hearing impairment, and various other anomalies of the internal organs. The gene mutation of GDF6 and GDF3 has been considered the cause of this syndrome. The deformities observed in Klippel–Feil syndrome and TE have many similarities. This fact may contribute to the elucidation of the mechanism of the deformities in Klippel–Feil syndrome and TE.

Until now, few articles about the lobulation anomaly of the liver in TE have been published, and none with any degree of detail. In the present study, fusion of the left lobe and quadrate lobe of the liver were observed. As there were reports of similar abnormalities in rabbits that had been exposed to thalidomide, a correlation between lobulation anomaly of the liver and thalidomide is strongly suggested.[26] In general, patients with lobulation anomaly of the liver are reported to show intrahepatic bile duct and portal vein anomalies; however, such anomalies can be fully evaluated by unenhanced CT alone and detailed evaluation can be achieved using contrast-enhanced CT and MR cholangiopancreatography (MRCP).

Conversely, agenesis of the gallbladder was observed in 27.3%. Some cases with TE had complicated agenesis of the gallbladder.[17,18] The frequency of agenesis of the gallbladder in TE has been reported as 10%.[17] Moreover, there have also been reports that 23% of these patients have such symptoms as right upper abdominal pain, nausea, fatty food intolerance, and so on. It is necessary to pay attention to such gastrointestinal symptoms when examining patients with TE.[19]

In the present study, no anomalies of the eye or urinary system were observed, whereas such anomalies have been reported as relatively common IAs of TE. This discrepancy can be explained in three ways. First, such eye anomalies in TE in the present study would be difficult to detect by imaging; according to Miller and Strömland,[1] most TE patients (86%) had ocular abnormalities, but many of these were strabismus, dacryorrhoea, and uveal defect. Most of these issues could not be detected using MRI. In contrast, ocular abnormalities, which could be detected using MRI, such as nanophthalmia were seen in only three of 86 (3.5%) of patients with TE in that study. Second, the difference in the age of the patients may be an issue. In almost all reports regarding IAs in TE, the ages of the patients were either similar to or younger than those in the

report of Miller and Strömland (age range, 27–30 years).[1] In the present study, the patients ranged in age from 47 to 51 years, older than those of the previous studies about IAs in TE. Third, the selection bias of patients may have affected the present results. In this study, patients with TE were selected who wanted to undergo a thorough medical examination at the National Center for Global Health and Medicine supported by Ishizue. It is possible that patients with serious complications did not want to participate in the present study and vice versa.

The present study had some limitations. First, the study population was small. IAs, such as the transection of the pituitary stalk, hypoplasia of the hemithorax, right-sided ligamentum teres hepatis, vaginal atresia, and unilateral congenital hip dislocation were observed in only one patient each. In order to assert a correlation between such IAs and thalidomide, more cases are required. Second, some IAs have no criteria on CT or MR images. For example, narrowing of the internal acoustic meatus and hypoplasia of the cranial nerves are difficult to define. Third, as only unenhanced CT was used for the evaluation of the body, some IAs may have been missed. Fourth, in most individuals with TE, keeping vascular lines, drawing blood, and undergoing contrast-enhanced examinations are often difficult because of arm deficit and chronic fear of medical care. Therefore image screening was performed by unenhanced CT as an objective evaluation. Evaluations using unenhanced CT may not detect small lesions within the organs due to the lower contrast resolution; however, owing to the detailed interpretation by several specialist radiologists in the evaluation of certain morphological abnormalities of the internal organs and vascular abnormalities, such as fused lobes of the liver, aplasia of the gall bladder, and double SVC, unenhanced CT was considered to be a reliable imaging technique.

Anomalies of the limbs in patients with TE have been widely known and their presence could be easily detected at the time of their medical examination. From this study, association with limb defects and various kinds of IAs was demonstrated. These imaging findings are important in managing the health of patients with TE. In conclusion, image screening using CT and MRI is useful for identifying various IAs in individuals with TE, and such imaging findings may also help clarify the mechanism of the occurrence of IAs after intrauterine thalidomide exposure.

Acknowledgements

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