

Multicenter Investigation of Lifestyle-Related Diseases and Visceral Disorders in Thalidomide Embryopathy at around 50 years of age

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Background: In utero exposure to thalidomide causes a wide range of birth defects, including phocomelia, hearing loss and visceral disorders, known as thalidomide embryopathy (TE). Fifty years after the first report of TE, we conducted the first cross-sectional multicenter study to investigate the development of lifestyle-related diseases and identify risk factors for visceral disorders in subjects with TE. **Methods:** Seventy-six cases with TE (31 men, 45 women) underwent medical examinations between 2011 and 2014 to determine the types of TE-related anomalies (limbs, auditory organs, or visceral organs) and lifestyle-related diseases present. Logistic multiple regression analyses, adjusted for gender and age, were conducted between TE and lifestyle-related diseases and to evaluate association between block vertebra and gallbladder aplasia. **Results:** Fatty liver (FL), nonalcoholic FL disease and dyslipidemia were detected in 52.6%, 35.0%, and 23.7% of subjects, respectively, with higher incidences among men. Dyslipidemia was detected in 40.0% of subjects with FL and was significantly associated with

FL (odds ratio = 8.86; $p = 0.008$). Block vertebrae were detected in 44.4% of subjects with gallbladder aplasia, and this association was significant (odds ratio = 9.96; $p = 0.006$). **Conclusion:** Subjects with TE have also a risk for lifestyle-related disease as well as the general Japanese population. In addition, cervical spine radiography and magnetic resonance imaging are recommended to assess block vertebrae in subjects with TE with gallbladder aplasia who develop shoulder pain.

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Key words: thalidomide embryopathy; lifestyle-related disease; visceral disorders; gallbladder aplasia; block vertebra

Introduction

Thalidomide (α -[*N*-phthalimido]-glutarimide) was first marketed in 1957 as a sedative in Germany, where it was promoted to alleviate nausea and morning sickness in pregnant and nursing women due to its rapid onset of effects and apparent safety. Thalidomide was then made available in over 46 countries (Friedman and Kimmel, 1999; Miller and Strömland, 1999; Yasui et al., 2005). In Japan, thalidomide was first marketed in 1958 under the trade name Isomin as a sleep-inducing agent. Afterward, Pro-ban M, containing a small amount of thalidomide, entered the market in 1960

for the treatment of digestive ulcers (Kayamori, 2014). Although thalidomide was initially considered extremely safe, the occurrence of phocomelia in newborns of women who took thalidomide during early pregnancy (36–56 days after the last menstrual period; Kayamori, 2013a) was first recognized in 1961 (Friedman and Kimmel, 1999). In Japan, thalidomide embryopathy (TE) was first reported in 1959, and the number of cases peaked in 1962. A total of 309 cases of TE have been recognized in Japan (Kayamori, 2014) and, of these, 294 individuals survive as of January 2015. Globally, there are an estimated 5850 cases of TE (Kayamori, 2014). Shortly thereafter, thalidomide was withdrawn from the market worldwide (Friedman and Kimmel, 1999).

In the late 1990s, the immunomodulating effects of thalidomide were described. Five decades after its introduction, thalidomide was found to be useful for the treatment of erythema nodosum leprosum, aphthous ulceration in HIV infection, inflammatory bowel disease, and multiple myeloma. Thalidomide inhibits the expression of tumor necrosis factor- α and proliferation of infiltrating lymphocytes and vascular endothelial cells in relation to tumor angiogenesis (Yasui et al., 2005). In addition, thalidomide interferes with angiogenesis and causes a variety of birth defects (Stephens et al., 2000; Kayamori, 2013b). Most cases of TE are characterized by developmental abnormalities of the limbs and/or auditory organs (Kayamori, 2013a). In Japan, 75% of TE cases exhibit abnormalities of the limbs (Kayamori, 2014), although visceral disorders, including cardiac anomalies, gallbladder aplasia, and anal atresia, have also been reported. Among limb abnormalities, deformities range from amelia (lacking upper and/or lower limbs) to hypoplasia of the thumb. The severity

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of auditory abnormalities is determined by the degree of deafness. These abnormalities are often accompanied by aplasia of the abducens and facial nuclei (Kayamori, 2013a).

New cases of TE continue to be reported in countries with less strict regulations, such as Brazil (Castilla et al., 1996; Lary et al., 1999; Schuler-Faccini et al., 2007), where women still take thalidomide during pregnancy and, subsequently, babies are born with deformities, including phocomelia. Furthermore, the first infants diagnosed with TE are currently approximately 50 years old, although the current health status of this population remains poorly understood, leading to inefficient treatments. Therefore, a multicenter survey was conducted in Japan from 2011 to 2014 to investigate the manifestations of TE in individuals aged around 50 years. Generally, the incidence of metabolic syndrome (MS) increases with age among the Japanese population (Ministry of Health, Labour and Welfare, Japan, 2013). Therefore, we investigated the frequency of lifestyle-related diseases, such as MS and visceral disorders, in adults with TE.

Materials and Methods

STUDY POPULATION

A multicenter survey was conducted in Japan from 2011 to 2014 by the National Center for Global Health and Medicine, Teikyo University School of Medicine and National Hospital Organization, Kyoto Medical Center. Seventy-six adults with TE who agreed to receive medical examinations were included in this study: 40 subjects (18 men and 22 women) who visited the National Center for Global Health and Medicine, 18 subjects (9 men and 9 women) who visited Teikyo University School of Medicine and 18 subjects (4 men and 14 women) who visited the National Hospital Organization, Kyoto Medical Center. There were no exclusion criteria. This study was performed in along with the public service corporation, ISHIZUE foundation, which is a foundation for the welfare of thalidomide victims in Japan. The ISHIZUE foundation chose the participants from 286 subjects who belong to the foundation. The participants were chosen as “healthier” subjects, i.e., they were healthy or outpatients. During the study and after its completion, there were no deaths to report. The study protocol was approved by the Ethics Committee of The National Center for Global Health and Medicine (NCGM-G-001031-04), and all participants provided written informed consent.

STUDY DESIGN

This cross-sectional study was conducted to analyze associations between TE and lifestyle-related diseases, including MS.

CRITERIA FOR CLASSIFICATION OF IMPAIRMENTS

The subjects with TE were divided into three groups the limb group, the auditory organ group, and the mixed

group. The limb group contained participants with abnormalities of the limbs, the auditory organ group contained those with hearing loss (mainly sensorineural deafness or mixed hearing loss) and the mixed group contained those with both limb and auditory abnormalities. Other cranial nerve abnormalities were not classified in this study.

DEFINITION OF RISK FACTORS

The health check-up examinations included the following: physical assessment, somatometry (height, body weight, and abdominal circumference), blood pressure, complete blood count, blood biochemistry, urinalysis, pulmonary function, electrocardiography, abdominal ultrasonography, chest radiography, upper gastrointestinal endoscopy, visual acuity, tonometry, ocular fundus assessment (retinal photography), audiometry (hearing test), bone mineral density examinations (only for half of the subjects), whole body computed tomography, and craniocervical X-ray. In addition, women underwent gynecological examinations (internal examination, endovaginal ultrasonography, and cervical cytology) as well as breast cancer screening (clinical breast examination, mammography, and mammary ultrasonography).

The potential risk factors for lifestyle diseases were defined as follows: (1) diabetes mellitus (DM): fasting plasma glucose ≥ 126 mg/dl and hemoglobin A1c (National Glycohemoglobin Standardization Program value) $\geq 6.5\%$ and/or taking medications for DM; (2) hyperuricemia: uric acid > 7 mg/dl and/or taking medications for hyperuricemia; (3) MS was diagnosed using the 2005 guidelines defined by the Evaluation Committee on Diagnostic Criteria for Metabolic Syndrome of Japan (Matsuzawa, 2005), including central obesity (waist circumference: ≥ 85 cm for men; ≥ 90 cm for women) and at least 2 of the following conditions: elevated blood pressure (systolic blood pressure ≥ 130 mmHg), previous treatment for hypertension and dyslipidemia (hypertriglyceridemia [serum triglyceride levels ≥ 150 mg/dl] and/or high-density lipoprotein cholesterol [HDL-C] < 40 mg/dl), previous treatment for dyslipidemia and impaired fasting glucose (IFG) ≥ 110 mg/dl or previous treatment for DM and (4) left ventricular hypertrophy (LVH): $SV1 + RV5 \geq 3.5$ mV and $RV5 \geq 2.6$ mV on electrocardiography (Sokolow and Lyon, 1949) or (5) nonalcoholic fatty liver disease (NAFLD) defined as fatty liver (FL) without hepatitis B or C virus infection or a history of alcohol abuse (> 20 g of ethanol per day). FL was diagnosed using abdominal ultrasonography with findings of high hepatorenal echo contrast, liver brightness and/or deep attenuation.

Of note, blood pressure is very difficult to measure in the affected limbs of subjects with TE. Therefore, systolic blood pressure was measured in a recumbent position using this equation: prediction of upper limb = $0.88 \times$ (blood pressure in lower limb measured by an S-size cuff [average blood pressure in both sides]) (Shimbo et al.,

TABLE 1. *Impact of Gender on Lifestyle-Related Diseases and Metabolic Syndrome in Subjects with Thalidomide Embryopathy*

Factors	Total	Males	Females
Hypertension	35/75 (46.7%)	19/31 (61.3%)	16/44 (36.4%)
Fatty liver	40/76 (52.6%)	22/31 (70.9%)	18/45 (40.0%)
NAFLD	14/40 (35.0%)	11/18 (61.1%)	3/22 (13.6%)
Central obesity	16/66 (24.2%)	10/23 (43.5%)	6/43 (14.0%)
Dyslipidemia	18/76 (23.7%)	11/31 (35.5%)	7/45 (15.6%)
IFG	14/76 (18.4%)	11/31 (35.5%)	3/45 (6.7%)
Diabetes mellitus	2/40 (5.0%)	1/18 (5.6%)	1/22(4.5%)
LVH	13/76 (17.1%)	6/31 (19.4%)	7/45 (15.6%)
Hyperuricemia	16/76 (21.1%)	13/31 (41.9%)	3/45(6.7%)
Central obesity + hypertension	4/66 (6.1%)	1/23 (4.3%)	3/43 (7.0%)
Central obesity + dyslipidemia	3/66 (4.5%)	3/23 (13.0%)	0/43 (0.0%)
Central obesity + IFG	2/66 (3.0%)	1/23 (4.3%)	1/43 (2.3%)
MS (hypertension + IFG + dyslipidemia, hypertension + IFG, hypertension + dyslipidemia, dyslipidemia + IFG)	5/66 (7.6%)	5/23 (21.7%)	0/43 (0.0%)
MS (hypertension + IFG)	1/66 (1.5%)	1/23 (4.3%)	0/43 (0.0%)
MS (hypertension + dyslipidemia)	3/66 (4.5%)	3/23 (13.0%)	0/43 (0.0%)
MS (dyslipidemia + IFG)	0/66 (0.0%)	0/23 (0.0%)	0/43 (0.0%)

NAFLD, nonalcoholic fatty liver disease; IFG, impaired fasting glucose; LVH, left ventricular hypertrophy; MS, metabolic syndrome

2014). Diastolic blood pressure was not measured because there is currently no standardized protocol for TE-affected limbs.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS statistical software (version 21; IBM SPSS, Inc., Armonk, NY). We investigated the frequency of lifestyle-related diseases among subjects with TE. The association between FL and risk factors was examined by multivariate logistic regression analysis. We also examined the association between visceral disorders by multivariate logistic regression analysis. A *p* value of <0.05 was considered statistically significant.

Results

A total of 76 subjects with TE (31 men and 45 women) aged 47 to 54 years (mean age: 50.2 ± 1.2 years) were included in this study. The frequency of lifestyle-related diseases among male and female subjects is shown in Table 1. Hypertension (46.7%), FL (52.6%), and NAFLD (35.0%) were the most common health issues encountered in these subjects. Approximately 25% of subjects had central obesity, dyslipidemia and IFG, although only 5.0% were diagnosed with DM. In addition, LVH and hyperuricemia were also major concerns for subjects with TE, with

frequencies of 17.1% and 21.1%, respectively. Overall, men were more susceptible than women to lifestyle-related diseases, with the exception of LVH and DM.

Combinations of central obesity and hypertension, dyslipidemia or IFG were reported in 3.0% to 6.1% of subjects with TE (Table 1). In contrast, MS combined with central obesity and 2 of these conditions affected 1.5% to 4.5% of subjects, except for MS (dyslipidemia + IFG). There were no gender-specific differences in the incidence of lifestyle-related diseases, except for central obesity with dyslipidemia, which was not detected in female subjects. In this study, only men developed MS. Taken together, these data demonstrated that men were at a higher risk than women for the development of lifestyle-related diseases, including MS.

Dyslipidemia was detected in 40.0% of subjects with FL and 71.4% of subjects with NAFLD (data not shown). Therefore, multivariate logistic regression analysis was conducted to identify the risk factors for FL in subjects with TE. As shown in Table 2, age and gender were not identified as risk factors for FL. Regression model analysis adjusted for age and gender revealed that dyslipidemia was significantly associated with FL (odds ratio = 8.86; *p* = 0.008). Hypertension was not significantly associated with LVH, although hypertension was detected in 58.3% of subjects with LVH.

TABLE 2. Multivariate Logistic Analysis of Risk Factors of Fatty Liver in Subjects with Thalidomide Embryopathy

Factors	Subjects with FL	Subjects without FL	Adjusted OR(95% CI)	p value
	Number (%)			
Age			0.97 (0.59–1.61)	0.91
Male	22/40 (55.0%)	9/36 (25.0%)	2.16 (0.64–7.29)	0.22
Female	18/40 (45.0%)	27/36 (75.0%)		
Dyslipidemia	16/40 (40.0%)	2/36 (5.6%)	8.86 (1.75–44.95)	0.008
Hypertension	22/39 (56.4%)	13/36 (36.1%)	1.66 (0.53–5.20)	0.38
Impaired fasting glucose	10/40 (25.0%)	4/36 (11.1%)	2.00 (0.45–8.92)	0.36

OR, odds ratio; CI, confidence interval; FL, fatty liver.

Gallbladder aplasia was diagnosed in 10 (13.2%) of 76 subjects with TE (5 men and 5 women), and all belonged to the limb group or mixed group (Table 3). Block vertebra was detected in 4 (44.4%) subjects (2 men and 2 women) with gallbladder aplasia (Table 4). Multivariate logistic regression analysis identified block vertebra as a significant risk factor for gallbladder aplasia in subjects with TE (odds ratio = 9.96; $p = 0.006$). Overall, 87.5% of subjects with block vertebrae were in the limb group or mixed group. No subject with gallbladder aplasia developed auditory complications.

Discussion

Decades ago, thalidomide was banned for the treatment of nausea in pregnant women due to the high risk of severe birth defects. Nonetheless, the survivors are now adults and require special treatment to cope with their unique challenges. Therefore, the aim of the present multicenter study was to document the types of deformities and lifestyle-related diseases that developed in subjects due to the physical limitations of TE. This survey identified aspects of lifestyle-related diseases among subjects with TE that should be targeted to improve health and quality of life.

Most of the deformities in surviving Japanese cases with TE were of the upper and/or lower limbs, followed by the auditory organs and visceral organs. Japanese cases with TE were divided into three groups based on the type of disorders they had limb, auditory and mixed. In several

auditory organ cases, there is an absence or underdevelopment of the abducens and facial nerve nuclei or their peripheral nerves. The oculomotor nerve compensates for the aplasia of the abducens nucleus or nerve, resulting in Duane's syndrome. Facial nerve paralysis and Bogorad's syndrome also are common complications (Kayamori, 2014). The most common lifestyle-related disease diagnosed in Japanese subjects with TE was hypertension, which affected nearly half of the study participants. In contrast, central obesity was observed in 24.2%. Although the lack of exercise is a known cause of central obesity, it may be difficult for cases with both limb deformities and auditory problems to exercise. It is important to consider the limitations of blood pressure and central obesity measurements in cases with TE with limb deformities. Hypertension measurements in subjects with TE are biased because there is no definite estimate for diastolic blood pressure in deformed lower extremities. Hypertension can only be estimated through predictions for upper limb systolic pressure from corrected lower limb blood pressure measured with an S-size cuff. If the perimeter of the upper limbs is too small because of the handicap, blood pressure may be underestimated. Moreover, it is difficult to measure blood pressure of subjects with TE with limb deformities, thus it is difficult to clinically control hypertension.

Furthermore, the definition of obesity in subjects with TE using body mass index may not be accurate without consideration of the missing weight of the affected limbs. Although subjects with a body mass index ≥ 25 are

TABLE 3. Proportions of Disorder Type and Gallbladder Aplasia

Factors	The limb group	The auditory organ group	The mixed group
	Number (%)		
Male	17/31 (54.8%)	8/31 (25.8%)	6/31 (19.4%)
Female	27/45 (60.0%)	7/45 (15.6%)	11/45 (24.4%)
Gallbladder aplasia	6 (2 males, 4 females)/76 (7.9%)	0/76 (0.0%)	4 (3 males, 1 female)/76 (5.3%)

TABLE 4. Multivariate Logistic Regression Analysis of Risk Factors of Gallbladder Aplasia in Subjects with Thalidomide Embryopathy

Factors	Gallbladder aplasia	No gallbladder aplasia	Adjusted OR(95% CI)	p-value
	Number (%)			
Age			0.93 (0.41–1.81)	0.831
Male	5/10 (55.6%)	26/66 (60.6%)	1.09 (0.25–4.73)	0.910
Female	5/10 (44.4%)	40/66 (39.4%)		
Block vertebrae	4/9 (44.4%)	4/65 (6.2%)	9.96 (1.91–51.93)	0.006

OR, odds ratio; CI, confidence interval.

considered obese, certain subjects with a body mass index < 25 may also be considered obese. Therefore, the definition of obesity herein was limited to waist circumference, which is considerably less reliable. Nonetheless, these measurements can be valid to determine differences between genders. Our data demonstrated that men were approximately 1.5- to threefold more likely to develop hypertension and obesity than women. This gender ratio was similar to the general Japanese population (Ministry of Health, Labour, and Welfare of Japan, 2013).

Lifestyle-related diseases in subjects with TE can be accurately diagnosed by measurements of dyslipidemia, hyperglycemia and hyperuricemia, which are known markers of arteriosclerosis. In our study, these conditions affected approximately 25% of subjects with TE. Furthermore, dyslipidemia was detected in 71.4% of subjects with NAFLD and was significantly associated with FL. NAFLD is no longer considered a primary liver disease, but rather a component of MS, insulin resistance and lifestyle-related diseases, such as diabetes, dyslipidemia and hypertension (Ikai et al., 1995; Reid, 2001; Akahoshi et al., 2001; Donati et al., 2004; Hamaguchi et al., 2005; Targher et al., 2007; Fan et al., 2007; Leite et al., 2009; Fu et al., 2011; Siddiqui et al., 2013). The frequency of NAFLD is 10% to 50% worldwide and 10% to 40% among Japanese adults, as determined by annual health screenings by means of abdominal ultrasonography (Ikai et al., 1995; Akahoshi et al., 2001; Hamaguchi et al., 2005; Jimba et al., 2005; Fan et al., 2007; Williams et al., 2011; Vernon et al., 2011; Hashimoto et al., 2015). In our study, NAFLD was observed in 35.0% of subjects with TE, which was consistent with the frequency in the general Japanese population. We also demonstrated that men were four- to fivefold more likely to develop NAFLD than women. Jimba et al. (2005) and Eguchi et al. (2012) reported that men were more susceptible to NAFLD than women. The differences in age and gender observed in this study were caused by differences in the rate of obesity and lifestyle-related diseases (Hashimoto and Farrell, 2009). Kojima et al. (2003) reported that the rate of FL in men remained almost unchanged in the >30-year-old group, while the rate gradually increased with age in women and the prevalence of

FL eventually became equal between men and women in the 60- to 69-year-old group. These results suggest an influence of female hormones on FL development. Estrogen suppresses visceral fat accumulation and increases subcutaneous fat accumulation (Yoshida et al., 1991); therefore, a decrease in estrogen activity may increase the accumulation of visceral fat, resulting in the development of FL (Kojima et al., 2003).

In contrast, the high incidence of MS cannot be entirely attributed to the lack of regular exercise because only Japanese men with TE, but not women, developed MS. Therefore, gender-specific characteristics appear to play a major role in the development of metabolic disease in the Japanese population, and there may be an association between sex hormones and MS. Tanaka et al. (2005) reported that among females aged ≥ 50 years, nearly half of those with at least moderate insulin resistance developed MS, whereas <30% of females in Okinawa prefecture aged <50 years were found to have MS. There was no similar phenomenon among males. Hence, female hormones might inhibit the development of MS.

Tanaka et al. (2005) also reported that the prevalence of abdominal obesity was lower than that of low HDL-C among females in Okinawa prefecture, which might explain the lower rate of MS among women compared with that among men. Therefore, it may be necessary to separately define criteria for abdominal obesity from visceral fat-type obesity for the diagnosis of MS among Japanese females.

Malformations in TE cause a gradual loss of muscle mass and strength leading to pain due to overuse syndrome, which includes stenosing tenosynovitis, carpal tunnel syndrome, coxarthrosis, shoulder pain, poor posture, and backache. The causes of shoulder pain include block vertebrae, which were detected in 24 (11.1%) of the 217 subjects with TE diagnosed with this anomaly of the cervical vertebrae. The range of motion in block vertebrae is limited and overload is applied on the anteroposterior surface, which causes shoulder stiffness, pain and accelerated degeneration of these vertebrae (Kayamori, 2013a). Block vertebrae also weaken the muscles of the upper limbs and induce intermittent headaches and cervical pain (Yoshizawa et al., 2012). In the present study, block vertebrae

were significantly associated with gallbladder aplasia. Therefore, if subjects with TE with gallbladder aplasia develop shoulder stiffness and/or pain, cervical spine X-ray and magnetic resonance imaging are recommended to investigate the presence of block vertebrae.

All subjects with gallbladder aplasia and 87.5% of those with block vertebrae developed hypoplasia of the upper limbs. However, there was no significant association between hypoplasia of the upper limbs and visceral disorders (i.e., aplasia of the gallbladder and block vertebrae). However, these data suggest new information on the teratology of TE. During pregnancy, corpus vertebrae development begins during gestational week 6, whereas block vertebrae are believed to be caused by blood flow obstruction from gestational week 3 to 8. In addition, hypoplasia of the upper limbs develops during gestational week 3 to 7. The fact that TE is caused by inhibition of vascularization establishes a causal effect for block vertebrae in subjects with TE and hypoplasia of the upper limbs (Yoshizawa et al., 2012). Accordingly, we detected block vertebrae in 7 (87.5%) of 8 subjects with TE and hypoplasia of the upper limbs. Therefore, clinicians should consider block vertebrae among subjects with TE, hypoplasia of the upper limbs and shoulder stiffness.

In conclusion, subjects with TE have also a risk for the development of lifestyle-related disease as well as the general Japanese population. In addition, for subjects with TE and gallbladder aplasia that develop shoulder stiffness and/or pain, it is recommended to obtain X-rays and magnetic resonance imaging of the cervical spine to determine the presence of block vertebrae.

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The authors have no conflict of interest to declare.

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