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Regular Article

Psychological and mental health problems in patients with thalidomide embryopathy in Japan

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Aim: The aim of the study was to examine the presence of psychological and mental health problems in patients with thalidomide embryopathy in Japan in order to develop and build future support systems.

Methods: The present study examined the presence/absence of electroencephalographic abnormalities, intellectual/cognitive functions, and mental health problems in 22 participants (nine men, 13 women) with thalidomide embryopathy. Participants completed the electroencephalograph instrument. Participants were also assessed using the Wechsler Adult Intelligence Scale-III; the Autism-Spectrum Quotient; the General Health Questionnaire-28, and the Mini-International Neuropsychiatric Interview.

Results: The results suggest the following: (i) electroencephalographic abnormality observed in several thalidomide embryopathy participants is unlikely to be the direct result of thalidomide; (ii) the cognitive functions of working memory and processing speed are lower in thalidomide embryopathy patients than in healthy individuals; and (iii) 40.9% of the thalidomide embryopathy participants have possible mental disorders, with more mental problems observed than in healthy individuals.

Conclusions: Deterioration of mental health in patients with thalidomide embryopathy is indicated. Anxiety, insomnia, and physical symptoms were especially remarkable and may have resulted in restriction of social activities. Therefore, careful examination and active support of patients' psychological and mental problems is essential.

Key words: cognitive performance, electroencephalography, Mini-International Neuropsychiatric Interview, psychological tests, thalidomide embryopathy.

PATHOLOGICAL CHARACTERISTICS OF thalidomide embryopathy (TE) include not only mesodermal system abnormalities, such as limb hypoplasia, but also various degrees of ectoblast abnormality, including nervous system effects. Because the prevalence of epilepsy is higher in TE patients than in the general population, Kanno suggested that thalidomide elicits not only morphologic abnormality but also functional cacogenesis.[1]

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In a study of 100 thalidomide victims in Sweden, Strömland *et al*. reported that 4% were diagnosed with autism.[2] Previous studies of TE patients have also indicated that those with hearing impairment scored more poorly on the Wechsler Adult Intelligence Scale than did healthy individuals.[3,4] These studies also suggested that age-related decline of physical functions and flexibility in TE patients with limb deformities can cause accompanying decline in their mental status.

Based on the results of previous studies, the present study examined TE patients in Japan with the following aims: to evaluate the existence of functional abnormalities, represented by epilepsy, by means of electroencephalography; to assess intellectual and cognitive functions; to examine the presence/absence

of mental health problems as well as mental disorders; and to assess the presence of autism. Assessment of the actual psychological and mental status of TE patients in Japan is important because the study of autism in TE patients has been reported in other countries, but never in Japan, and because time has passed since the last research on patients with TE in Japan was conducted by Saito and Sekine.[4]

METHODS

Participants

Participants were 22 patients with TE who were admitted to a hospital for medical examination during the period from September 2011 to February 2012. There were nine male and 13 female patients aged 47–51 years. Among the 22 patients, 16 had limb deformities (four men, 12 women), two had hearing impairment (both male), and four had both limb deformities and hearing impairment (three men, one woman).

Procedure

Each patient first had an individual interview with a medical staff member regarding their background information, including age, marital and educational status, and work experiences. After the interview, an electroencephalograph was administered. Experienced psychotherapists administered psychological tests, and the Mini-International Neuropsychiatric Interview (MINI). Communication with the six patients having hearing impairments was conducted by writing. Written instructions were also given when administering the interviews and the psychological tests. Two patients with limb deformities used their feet to complete the psychological tests.

Instruments/measures

1 The electroencephalographic instrument (Neurofax EEG-1524, Nihon Kohden, Tokyo, Japan) measured and graphically recorded electrical activities of the brain. It was used to examine the presence or absence of electroencephalogram abnormality in TE patients.
2 Psychological tests
   - The Wechsler Adult Intelligence Scale-III (WAIS-III; Japanese Version) is an intelligence test administered individually to adults aged 16–89 years. The mean score is 100 (SD 15).[5]
   - The Autism-Spectrum Quotient (AQ) is a self-administered questionnaire measuring the degree to which an adult with normal intelligence has traits on the autistic spectrum. The cut-off point of the test is 32 out of 33.[6]
   - The General Health Questionnaire-28 (GHQ-28) is a self-administered screening instrument designed to measure psychological distress and minor psychiatric disorders. The total possible score ranges from 0 to 84. It is a shortened version of the GHQ and its cut-off point is 5 out of 6.[7]
3 MINI is a short structured psychiatric diagnostic interview instrument used to make diagnoses of psychiatric disorders.[8]

Analyses

The purpose of administering the electroencephalograph and the structured psychiatric diagnostic interview was to assess the actual situations/conditions of TE patients at present. The psychological tests were used to examine the long-term effects of thalidomide on intellectual and cognitive functions as well as mental status by comparing the results of the present study with results of standardized data of healthy individuals. The procedures for each test are indicated below. Data analysis was performed using IBM SPSS 19 (IBM, Armonk, NY, USA).

Electroencephalograph test

Waking brain waves, including light stimulation and over-breathing load, were measured for 20 min for all patients. No drug was administrated to patients for sleep induction. According to Kanno, the following five criteria define normal brain waves: (i) basic rhythm is 9 Hz or higher; (ii) basic rhythm has occipital dominance; (iii) frequency of appearance of θ waves is 9% or less; (iv) left–right asymmetry and focus are not observed; and (v) spike is not observed. A single assessor performed all assessments.[1]

WAIS-III

Differences in the mean scores of full-scale IQ (FIQ), verbal IQ (VIQ), performance IQ (PIQ), index score

values, and mean subtest scores between the two groups (TE patients group and healthy subjects group) were evaluated by *t*-test. For the healthy subjects group, standardization data of 120 subjects aged 45–54 years old were used.[5] Scores of the WAIS-III subtests and the electroencephalograph results (presence/absence of abnormality) were compared.

AQ

Differences of the means of the total AQ score and each of the five subscales (communication, social skills, imagination, attention to detail, and attention switching) were analyzed by *t*-test. Standardized data of 194 healthy subjects were used to represent the data of the healthy subjects group.[6] Moreover, each of the subscale scores was compared with the electroencephalograph results (presence/absence of abnormality).

GHQ-28

The global total and mean scores on the subscales (somatic symptoms, anxiety/insomnia, social dysfunction and severe depression) of two groups (TE patients group and healthy subjects group) were compared using *t*-tests.

For the global total, the standardization data of 50 healthy individuals were used as data for the healthy subjects group.[7] For the subscale scores, data collected from 257 university students and 50 adults were used as standardization data.[7] The GHQ-28 global total score and the differences in mean scores of the four subscales were analyzed according to the presence/absence of a spouse, employment status, and locus of physical disability.

MINI

An interview was carried based on the method of Otsubo *et al*.[8] The TE patients who fell under a certain diagnostic module were classified according to their disorder.

The ethics committee of The National Center for Global Health and Medicine approved the study (NCGM-G-001031-03) and all participants provided written informed consent. To protect personal information, all identifying information about the participants was coded for the data analysis.

RESULTS

Electroencephalograph test

Of the 22 patients, 18 were determined to be normal and four to be abnormal. Characteristics of the four patients who were determined to be abnormal were: (i) frequent slow wave and appearance of polyspike and wave; (ii) frequent slow wave and single-shot of positive sharp wave; (iii) multiple occurrences of slow wave swarms; and (iv) appearance of slow wave in median and left hemisphere followed by single-shot of phase-2 slow wave. In Case 1, sodium valproate was taken orally, with a diagnosis of epilepsy. History of epileptic stroke was not recognized in cases 2, 3 and 4. Abnormality in the cerebral parenchyma was observed by head magnetic resonance imaging (MRI) for four patients, with electroencephalogram abnormality recognized. Their characteristics were: (i) residual lobar hemorrhage; (ii) atrophy of brainstem and cerebellum, mainly in pons, and positive cross sign in pons (diagnosed at another hospital as spinocerebellar degeneration); (iii) T1 high signal in bilateral globus pallidus (considered to be affected by a history of hepatic function disorder); and (iv) pituitary stalk transection. It is unknown if all of these abnormalities in head MRI were directly cause by thalidomide. It is also unclear whether the electroencephalographic abnormalities had any correlation with those in cerebral parenchyma recognized by head MRI. Only one patient was recognized with an abnormality in cerebral parenchyma with mild cerebellar atrophy, in spite of determination of normal brain wave.

WAIS-III

Descriptive classification of FIQ

The mean average of FIQ for the TE patients group was 92.3 (SD 20.4). The mean average of VIQ and PIQ for the TE patients group was 91.8 (SD 20.6) and 94.4 (SD 21.4). The descriptive classifications of FIQ for the 22 TE patients were superior ($n = 1$), high average ($n = 5$), average ($n = 7$), low average ($n = 4$), borderline ($n = 2$), and extremely low/mental retardation ($n = 3$). Two of the three TE patients classified as extremely low had either a history of spinocerebellar degeneration or a possibility of mental disorder according to MINI. These disorders may have had an influence on higher brain function of the patients, which resulted in their classification on the FIQ. The

Table 1. Comparison of average scores (SD) for Wechsler Adult Intelligence Scale-III subtests

	Patient group ($n = 22$)		Healthy group ($n = 120$)		*t*-test		
	Average score	SD	Average score	SD	*t* value	d.f.	*P*-value
Verbal scale							
Vocabulary	8.68	3.60	9.80	3.40	**2.26**	**52.79**	**0.03**
Similarities	9.68	4.11	9.90	2.90	0.24	24.97	0.81
Arithmetic	7.59	3.70	10.00	3.00	**3.36**	**140.00**	**0.00**
Digit span	8.45	3.10	10.10	2.90	**2.42**	**140.00**	**0.02**
Information	8.45	3.42	10.00	3.10	**2.12**	**140.00**	**0.04**
Comprehension	9.64	4.69	9.90	3.10	0.25	24.48	0.80
Letter–number sequencing	9.64	3.43	10.20	2.90	0.81	140.00	0.42
Performance scale							
Picture completion	8.68	3.43	10.10	2.80	**2.11**	**140.00**	**0.04**
Digit symbol coding	8.27	3.68	10.00	3.00	**2.39**	**140.00**	**0.02**
Block design	9.41	4.20	9.90	3.20	0.52	25.65	0.61
Matrix reasoning	9.68	4.64	9.90	3.10	0.21	24.54	0.83
Picture arrangement	9.41	4.18	10.10	3.10	0.74	25.40	0.47
Symbol search	7.55	3.32	10.00	3.00	**3.47**	**140.00**	**0.00**
Verbal†	52.50	19.15	59.70	14.20	1.68	25.40	0.11
Performance†	45.45	16.30	50.00	10.40	1.26	24.23	0.22
Full†	97.95	32.31	109.70	22.90	1.63	25.01	0.12
Verbal comprehension	26.82	10.05	29.70	8.40	1.43	140.00	0.15
Perceptual organization	28.50	11.34	29.90	7.00	0.56	24.01	0.58
Working memory‡	25.68	8.71	30.30	7.00	**2.74**	**140.00**	**0.01**
Processing speed‡	15.82	6.51	20.00	5.40	**3.23**	**140.00**	**0.00**

†For comparison of Verbal-, Performance-, and Full-scale IQ, Symbol Search and Letter–Number Sequencing are excluded.
‡The subtests for Working Memory are Arithmetic, Digit Span, and Letter–Number Sequencing. The subtests for Processing Speed are Digit Symbol and Symbol Search.
Bold and underline, significant difference.

other TE patient classified as extremely low was diagnosed with intellectual impairment prior to the test; therefore, the test result ratified the diagnosis.

Comparison of FIQ, VIQ, and PIQ with the healthy subjects group

The mean scores of FIQ, VIQ, and PIQ of the TE patients group were compared with those of the healthy subjects group. There were no significant differences (FIQ: $t(25.01) = 1.63$, *ns*; VIQ: $t(25.40) = 1.68$, *ns*; PIQ: $t(24.23) = 1.26$, *ns*; Table 1).

Comparison of the indices and the subtests with the healthy subjects group

Mean index scores of the TE patients group and the healthy subjects group was compared (*t*-tests). The results showed that the TE patients group had substantially lower Working Memory and Processing Speed scores than the healthy group ($P < 0.01$) (Table 1). In comparisons of subtest scores between the two groups, the TE group scores were lower on Arithmetic and Symbol search ($P < 0.01$) and on Vocabulary, Digit span, Information, and Picture completion ($P < 0.05$).

Comparison with electroencephalographic results

FIQ, VIQ, and PIQ were compared with the electroencephalography (EEG) results. No significant differences among those variables were found.

AQ

Comparison with healthy group

The average AQ score of the TE patients group was 18.95 (SD 5.95). When a cut-off point of 32 out of 33

Table 2. Comparison of average scores (SD) for AQ

	Patient group ($n = 22$)		Healthy group ($n = 194$)		*t*-test		
	Average score	SD	Average	SD	*t* value	d.f.	*P*-value
AQ full scale	18.95	5.95	18.5	6.21	0.32	214.00	0.75
Social Skill	3.00	2.37	3.4	2.38	0.77	23.06	0.45
Attention switching	4.18	2.38	4.3	2.06	0.37	214.00	0.71
Attention to detail	4.64	2.01	4.9	1.96	0.58	214.00	0.56
Communication	3.32	1.99	2.8	2.07	1.12	214.00	0.26
Imagination	3.82	1.68	3.2	1.67	1.35	214.00	0.10

AQ, Autism-Spectrum Quotient.

points was applied to the groups of TE patients, none met the criterion of autistic pathologic standard. No significant differences were found between the point counts of each AQ score for the TE patients group and the healthy subjects group (Table 2).

Comparison with electroencephalographic results

No significant difference was found when the presence/absence of EEG abnormality was compared with each AQ subscore.

GHQ-28

Results

When a cut-off point of 5 out of 6 points was used, 13 of 22 (59.1%) patients were judged as having some kind of mental health problem. Nine of 16 patients with limb deformities were judged as having a mental health problem (56.3%). Of the two patients with hearing impairments, one had a mental health problem. Of the four patients with both limb deformities and hearing impairment, three were judged as having some type of mental health problem.

Moreover, among the 22 patients, 14 showed mild somatic symptoms, 13 showed anxiety and insomnia, 13 showed social dysfunction, and six showed severe depressions on the GHQ subscales.

Comparison with healthy group

According to Nakagawa and Daibo, 86% of healthy individuals scored below 5 points, and 90% of individuals with neurosis scored higher than 6 points on the full GHQ.[7] In the present study, the average GHQ full score of the TE patients group was 7.36 (SD 5.48). The score of TE patients group was significantly higher than that of the healthy subjects group ($P < 0.01$).

In addition, a comparison of differences of average scores of the GHQ subscales between the TE patients group and the healthy subjects group revealed significantly higher scores for somatic symptoms, anxiety and insomnia, and social dysfunction in the TE patients group than in the healthy subjects group ($P < 0.01$; Table 3).

Effects of locus of disability, marital status, and employment status

Total GHQ-28 score and differences between average values of GHQ subscales scores were also examined for each attribute of patient group (by locus of disability, marital status, and employment status). Saito reported that severe depression was weaker in patients with spouses than in those without spouses.[9] In the present study, higher depression scores were observed in single/divorced subjects than in married subjects. Moreover, a previous study found that the mental status of unemployed individuals was worse than that of employed individuals.[3] In the present study, scores for impaired social activities were significantly higher in the group without spouses than those in the group with spouses (Table 4).

MINI

From the MINI, 19 diagnostic modules of psychiatric disorders were found to be applicable to nine of the 22 patients with TE (40.9%): eight of the 16 patients

Table 3. Comparison of average scores (SD) on GHQ-28

	Patient group ($n = 22$)		Healthy group[†,‡]		*t*-test		
	Average score	SD	Average	SD	*t* value	d.f.	*P*-value
GHQ-28	7.36	5.48	2.76	2.31	**3.79**	**24.35**	**0.00**
Somatic symptoms	2.86	2.24	1.02	1.09	**3.82**	**21.72**	**0.00**
Anxiety/insomnia	2.41	1.87	1.24	1.4	**2.87**	**22.71**	**0.01**
Social dysfunction	1.18	1.15	0.28	0.53	**3.64**	**21.64**	**0.00**
Severe depression	0.91	1.90	0.28	0.79	1.54	21.52	0.14

[†]GHQ-28 average scores and SD of healthy groups are standardized data by Nakagawa and Daibo.[7] These data were collected from 50 healthy persons.
[‡]The average scores and SD of somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression of healthy groups are data by Nakagawa and Daibo.[7] These data were collected from 50 healthy persons and 307 university students.
GHQ-28, General Health Questionnaire-28.
Bold and underline, significant difference.

with limb deformities and one of the four patients with both limb deformities and hearing impairment. The applicable diagnostic modules included major depressive episode, dysthymia, suicidality, hypomania episode, panic disorder, agoraphobia, post-traumatic stress disorder (PTSD), alcohol abuse, and psychotic disorders. Five of nine patients fell under more than one diagnostic module: one with suicidality (moderate), hypomania episode (past), and psychotic disorders (lifetime); one with hypomania episode (past), alcohol abuse (current), and psychotic disorders (lifetime); one with major depressive episode (past and current), suicidality (moderate), and PTSD; one with dysthymia (current), suicidality (high), and agoraphobia (current); and one with suicidality (low) and panic disorder (lifetime) (Table 5).

DISCUSSION

Electroencephalograph test

It was noted by Kanno that no electroencephalographic abnormalities were observed in patients with impaired hearing, or in patients with impaired intelligence.[1] Moreover, as observed by head MRI, no electroencephalographic abnormalities were recognized in patients with structural abnormalities of the ear, without any other abnormalities. Furthermore, no correlation was observed between WAIS-III score, or the AQ score and the presence, or absence of electroencephalographic abnormalities. One of the four patients with electroencephalographic abnormalities was diagnosed as epileptic with a history of epileptic stroke. Kanno reported that epileptic morbidity and

Table 4. Score differences by locus of disability, marital status, and employment status

	Marital status				Employment status				Locus of disability	
	Married	Single and divorced	Mann–Whitney U	*P*-value	Employed	Unemployed	Mann–Whitney U	*P*-value	Kruskal-Wallis	*P*-value
GHQ-28	10.09	12.91	76.00	0.31	9.82	14.44	75.50	0.12	0.47	0.79
Somatic symptoms	12.18	10.82	53.00	0.62	10.64	13.00	68.00	0.41	1.39	0.50
Anxiety/insomnia	10.82	12.18	68.00	0.62	9.82	14.44	79.35	0.10	0.34	0.84
Social dysfunction	7.55	15.45	104.00	**0.00**	10.68	12.94	67.50	0.41	0.95	0.62
Severe depression	9.00	14.00	88.00	**0.01**	10.54	13.19	69.50	0.21	1.63	0.44

GHQ-28, General Health Questionnaire-28.
Bold and underline, significant difference.

Table 5. Number of patients diagnosed with disorder by Mini-International Neuropsychiatric Interview

		Limb deformities ($n = 16$)	Hearing impairment ($n = 2$)	Both limb deformities and hearing impairment ($n = 4$)
Disorder	Timeframe			
Major depressive disorder	Past 2 weeks	1 (1)	0	0
	Lifetime	1 (1)	0	0
Dysthymic disorder	Past 2 years	2 (1)	0	0
Suicidality	Current	5 (4)	0	0
Mania	Lifetime	0	0	0
	Current	0	0	0
Panic Disorder	Lifetime	1 (1)	0	0
	Current	0	0	0
Agoraphobia	Current	1 (1)	0	0
Social phobia	Current	0	0	0
Specific phobia	Current	0	0	0
Obsessive–compulsive disorder	Current	0	0	0
Generalized anxiety disorder	Current	1 (0)	0	0
Alcohol dependence	Current	0	0	0
Alcohol abuse	Current	1 (1)	0	0
Drug dependence (non-alcohol)	Current	0	0	0
Psychotic disorder	Lifetime	2 (2)	0	1 (0)
	Current	0	0	0
Anorexia nervosa	Past 3 mos	0	0	0
Bulimia	Past 3 mos	0	0	0
Post-traumatic stress disorder	Current	1 (1)	0	0
Antisocial personality disorder	Lifetime	0	0	0

Note ()overlapping number.

electroencephalographic abnormalities were higher in thalidomide patients than in the general population and suggested that not only morphological, but also functionally generated abnormalities were possibly induced by thalidomide. However, in the present study, because of the small number of patients, comparison with general morbidity (0.5–1%) was considered inappropriate.

Comparison of WAIS-III results of patients and healthy subjects

The present results did not support the findings of Saito and Asaka[3] that FIQ, VIQ, and PIQ scores of TE patients were significantly lower than those of healthy individuals. Previous studies have reported that the hearing impairment group scored significantly lower than any other group. One potential reason for this discrepancy could be the differences in the number of patients with hearing impairments between this and previous studies.

The results of comparing the indices and subtests of patients and healthy subjects have three main implications. First, TE patients showed slowness in Processing Speed. However, this could be because most patients in the TE group had limb deformities, producing functional limitations that made it difficult for them to solve these problems. Second, the TE group showed a reduced ability to process information effectively, while maintaining attention to visual and auditory information. Finally, it is possible that differences in participants' educational backgrounds may have affected the results. Many TE patients graduated from special schools for children with disabilities, and thus their learning environments and experiences were more limited than those of healthy individuals.

Mental health problems

The GHQ-28 results implied that the mental status of the TE patients was poorer than that of healthy

subjects. Specifically, TE patients showed evidence of suffering from somatic symptoms, anxiety, and insomnia, as well as social dysfunctions. The results of the MINI suggested that 40.9% of the TE patients had some psychiatric disorder. This is a percentage that is comparatively high. A study by Strömland *et al*. of 100 TE patients conducted in Sweden reported that 4% of the participants were diagnosed with autism. Data of the 22 TE patients in the present study differed from this result.

The present results are important from academic, social, and international perspectives. As noted earlier, few previous studies have examined the psychological and mental health problems of TE patients, either in Japan or in other countries.[1–4,9] The present study has therefore contributed to the general understanding of the actual situations of patients with TE. Although the results of the present study have significant implications for patients with TE, the number of the patients was small. Future studies will require a larger number of patients to investigate more thoroughly the psychological and mental problems of TE patients.

Future research should consider three additional points:

1 Electroencephalographic abnormality
The present results did not reveal a direct impact of thalidomide on electroencephalographic abnormality. Therefore, future studies should examine if thalidomide induces functional cacogenesis, as suggested in previous studies.
2 Intellectual/cognitive function
Because the present study suggested that patients with TE show a decrease in Working Memory capability, Working Memory should be further assessed by means of psychological tests of other cognitive functions.
3 Support system
Many of the patients with TE faced difficulties in their everyday lives because of their mental health and organic problems. Therefore, reconsideration of their existing support systems is important.

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