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Current medico-psycho-social conditions of patients with West syndrome in Japan

Shinsaku Yoshitomi[1], Shin-ichiro Hamano[2], Masaharu Hayashi[3], Hiroshi Sakuma[3], Shinichi Hirose[4], Atsushi Ishii[4], Ryoko Honda[5], Akio Ikeda[6], Katsumi Imai[1], Kazutaka Jin[7], Akiko Kada[8], Akiyoshi Kakita[9], Mitsuhiro Kato[10], Kensuke Kawai[11], Tamihiro Kawakami[12], Katsuhiro Kobayashi[13], Toyojiro Matsuishi[14], Takeshi Matsuo[15], Shin Nabatame[16], Nobuhiko Okamoto[17], Susumu Ito[18], Akihisa Okumura[19], Akiko Saito[8], Hideaki Shiraishi[20], Hiroshi Shirozu[21], Takashi Saito[22], Hidenori Sugano[23], Yukitoshi Takahashi[1], Hitoshi Yamamoto[24], Tetsuhiro Fukuyama[25], Ichiro Kuki[26], Yushi Inoue[1], (Japan Rare Epilepsy Syndrome Registry Group: JRESG)

[1]NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan
[2]Division of Neurology, Saitama Children's Medical Center, Saitama, Japan
[3]Department of Brain Development and Neural Regeneration, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[4]Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan
[5]Department of Pediatrics, NHO Nagasaki Medical Center, Nagasaki, Japan
[6]Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[7]Department of Epileptology, Tohoku University Graduate School of Medicine, Sendai, Japan
[8]Clinical Research Center, NHO Nagoya Medical Center, Nagoya, Japan
[9]Department of Pathology, Brain Research Institute, Niigata University, Niigata, Japan
[10]Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan
[11]Department of Neurosurgery, Jichi Medical University, Tochigi, Japan
[12]Department of Dermatology, Tohoku Medical and Pharmaceutical University, Sendai, Japan
[13]Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[14]Research Centre for Children and Research Centre for Rett Syndrome, St Mary's Hospital, Kurume, Japan
[15]Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan
[16]Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan
[17]Department of Medical Genetics, Osaka Women's and Children's Hospital, Osaka, Japan
[18]Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan
[19]Department of Pediatrics, Aichi Medical University, Aichi, Japan
[20]Department of Pediatrics, Hokkaido University Hospital, Sapporo, Japan
[21]Department of Functional Neurosurgery, NHO Nishiniigata Chuo Hospital, Niigata, Japan
[22]Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan
[23]Department of Neurosurgery, Epilepsy Center, Juntendo University, Tokyo, Japan
[24]Department of Pediatrics, St. Marianna University School of Medicine, Kanagawa, Japan
[25]Department of Pediatrics, School of Medicine, Shinshu University, Matsumoto, Japan
[26]Department of Pediatric Neurology, Children's Medical Center, Osaka City General Hospital, Osaka, Japan

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• **Correspondence:**
Yushi Inoue
NHO Shizuoka Institute of Epilepsy and Neurological Disorders,
Urushiyama 886,
Aoi-ku, Shizuoka 420-8688, Japan
<yshinoue@gmail.com>

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ABSTRACT

Objective. To unveil current medical and psychosocial conditions of patients with West syndrome in Japan.

Methods. A cross-sectional analysis was performed in patients with West syndrome registered in the Rare Epilepsy Syndrome Registry (RES-R) of Japan. Furthermore, new-onset patients registered in the RES-R were observed prospectively and their outcomes after one and two years of follow-up were compared with data at onset.

Results. For the cross-sectional study, 303 patients with West syndrome were included. Seizures (such as spasms, tonic seizures and focal seizures) occurred daily in 69.3% of the patients at registration. Seizure frequency of less than one per year was observed in cases of unknown etiology (22.6%), genetic etiology (23.8%) and malformation of cortical development (MCD; 19.1%). Neurological findings were absent in 37.0%, but a high rate of abnormality was seen in patients with Aicardi syndrome, hypoxic-ischemic encephalopathy (HIE), genetic etiology and MCD other than focal cortical dysplasia, accompanied by a >50% rate of bedridden patients. Abnormal EEG was found in 96.7%, and CT/MRI was abnormal in 62.7%. Treatments included antiepileptic drug therapy (94.3%), hormonal therapy (72.6%), diet therapy (8.3%) and surgery (15.8%). Intellectual/developmental delay was present in 88.4%, and was more severe in patients with Aicardi syndrome, genetic etiology and HIE. Autism spectrum disorder was found in 13.5%. For the longitudinal study, 27 new-onset West syndrome patients were included. The follow-up study revealed improved seizure status after two years in 66.7%, but worsened developmental status in 55.6%, with overall improvement in 51.9%.

Significance. The study reveals the challenging neurological, physical and developmental aspects, as well as intractable seizures, in patients with West syndrome. More than a half of the children showed developmental delay after onset, even though seizures were reduced during the course of the disease.

Key words: West syndrome; epileptic spasms; infantile spasms; rare epilepsy syndrome registry; cross-sectional study; longitudinal study; outcomes

West syndrome, synonymous with infantile spasms in this report, is one of the most common types of epileptic encephalopathy [1]. This intractable epilepsy syndrome is characterized by epileptic spasms occurring in clusters, hypsarrhythmia on EEG, and psychomotor delay or regression. West syndrome has many challenging issues including difficulties in achieving seizure freedom, deciding on optimal treatment, detecting an underlying disease or disorder, and predicting prognosis [2]. Moreover, limited social resources, as well as health and medical services, are also serious issues to be solved, since patients with West syndrome and their parents/caregivers are compelled to bear the heavy financial and psychosocial burden for medical care and support, which continues long-term.

Although several epidemiological and clinical studies on West syndrome have been published [3,4,5,6,7,8,9], the sample size and issues investigated are still insufficient to address the above-mentioned problems.

To understand the present situation of intractable/rare epilepsy syndromes/diseases, the "Rare Epilepsy Syndrome Registry (RES-R)" was initiated in 2014 in Japan. RES-R covers a wide variety of items about epilepsy, from seizure type to psychosocial status. With the collaboration of physicians engaged in epilepsy practice from all over Japan, RES-R accumulates and follows epilepsy cases nationwide to gain epidemiological evidence on intractable/rare epilepsy syndromes/diseases. In this study, we focused on West syndrome and analyzed the current medical and psychosocial conditions of patients suffering from this syndrome in Japan.

Subjects and methods

Twenty-three hospitals from all over Japan participated in RES-R, providing input of individual patient information in a WEB-based registry system. For the cross-sectional study, patients with the following data were included: age, gender, epilepsy syndrome, underlying disease/etiology, seizure type, seizure frequency, examination results (EEG, CT/MRI and others), therapy (apart from details of drugs used), intellectual disability, comorbid developmental or physical disorders, current social status, and use of health and medical services. We extracted the information of the patients with West syndrome, registered from November 2014 to November 2019 with an interruption between December 2015 and November 2017 due to the rescheduling of the study; hence over a total period of 37 months. One year after registration, a check was made to ascertain whether the patient was alive.

A total of 2,209 patients were registered during this period. Complete data were obtained from 303 patients with West syndrome including nine patients with Aicardi syndrome. These subjects constituted the study population for the cross-sectional study.

We also collected new-onset cases between November 2014 and November 2015 and prospectively followed their clinical course for two years. There were 32 new cases of West syndrome, but only 27 were followed for two years. The other five cases were excluded from the study due to a change in residence or a change in physician. These 27 cases are the subject of longitudinal observational study.

The causative disorders (etiologies) were divided into six categories according to ILAE classification [10]: structural (including acquired and congenital), genetic, metabolic, infectious, immune and unknown etiologies.

The registry system, including the cross-sectional and longitudinal observational studies, was approved by the ethics review board of each participating hospital. Informed consent was obtained from the participants or their guardians in written form or in the form of opt-out based on an announcement for the studies on the bulletin board or website of each hospital.

Results

Cross-sectional study

- ***Demographics and etiology***

The demographic and clinical features of 303 patients with West syndrome registered in RES-R are summarized in *table 1*. The mean age at registration was 4.5 years (median: 3 years; range: 0-51 years). Three of the four patients who were adults at registration had been seizure-free for long periods. There were 147 females and 156 males. The age at seizure onset was below 12 months in 263 patients, while onset occurred after 12 months in 40 patients. Two patients died within one year after registration. Regarding causative disorders or etiology, structural etiology constituted 40.3%, followed by genetic etiology (13.9%), but etiology was unknown in 43.9% of the patients.

▼ **Table 1.** Demographic and clinical data of patients with West syndrome in the cross-sectional study.

	Total (*n*=303)	
	n	%
Gender (female)	147/303	48.5
Seizures other than spasms		
Tonic	73	24.1
Clonic	8	2.6
Absence	4	1.3
Myoclonic	12	4.0
Atonic	5	1.7
Focal aware	32	10.6
Focal unaware	32	10.6
Bilateral tonic-clonic	11	3.6
Status epilepticus	3	1.0
Others	4	1.3
Seizure frequency		
Daily	210	69.3
Weekly	14	4.6
Monthly	12	4.0
Yearly	10	3.3
Less than yearly or seizure-free	57	18.8
Etiology		
Structural	122	40.3
Aicardi syndrome	9	3.0
Malformation of cortical development	47	15.5
Focal cortical dysplasia	24	7.9
Heterotopia	2	0.7
Hemimegalencephaly	3	1.0
Polymicrogyria and related anomalies	6	2.0
Others	12	4.0
Neurocutaneous syndrome	21	6.9
Tuberous sclerosis	18	5.9
Hypoxic ischemic encephalopathy	36	11.9
Cerebrovascular disorders	6	2.0
Others	3	1.0
Genetic	42	13.9
Metabolic	2	0.7
Infectious	3	1.0
Immune	1	0.3
Unknown	133	43.9

▼ **Table 1.** Demographic and clinical data of patients with West syndrome in the cross-sectional study (*continued*).

Neurological findings		
Normal	112	37.0
Hemiplegia/hemiparesis	16	5.3
Diplegia	4	1.3
Quadriplegia	72	23.8
Dysphagia	32	10.6
Ataxia	6	2.0
Involuntary movement	6	2.0
Physical condition		
No head control	58	19.1
Sitting position only	33	10.9
Bedridden	108	35.6
Others	15	5.0
Examinations		
Abnormality on gene testing	24/51	47.1
Abnormality on chromosome testing	30/108	27.8
Abnormal findings on EEG	293	96.7
Hypsarrhythmia	145	47.9
Focal spikes	117	38.6
Generalized spike-waves	36	11.9
Fast rhythm	4	1.3
Abnormal background activity	56	18.5
Abnormal findings on neuroimaging (CT/MRI)	190	62.7
Unilateral abnormality	70	23.1
Bilateral abnormality +/- unilateral lesion	120	39.6
Treatment		
Antiepileptic drugs	286	94.4
ACTH	216	71.3
Steroids	4	1.3
Diet therapy	25	8.3
Surgery	48	15.8
Callosotomy	36	11.9
Hemispherotomy/rectomy	7	2.3
Focal resection	15	5.0
Vagus nerve stimulation	7	2.3
Others	16	5.3

▼ **Table 1.** Demographic and clinical data of patients with West syndrome in the cross-sectional study (*continued*).

Cognitive/developmental status		
Intellectual/developmental disability*		
Most severe	118	38.9
Severe	57	18.8
Moderate	40	13.2
Mild	44	14.5
None	35	11.6
Unknown	9	3.0
Autism spectrum disorder	41	13.5
Social status		
Preschool	218	71.9
Special class or school for disabled children	77	25.4
Regular school or class	4	1.3
Life support (aged ≥ 20 year)	4/4	100
Using medical/welfare benefits	253	83.5

* Intellectual/developmental disability: none: IQ/DQ above 70; mild: IQ/DQ between 50-69; moderate: IQ/DQ between 35-49; severe: IQ/DQ between 34-20; most severe: IQ/DQ less than 20.

● ***Seizures***

The main seizure types of individual patients at registration were spasms in 263 patients (86.8%), tonic seizures in 20 (6.6%), focal impaired awareness seizures in seven (2.3%), focal aware seizures in six (2.0%), bilateral tonic-clonic seizures in four (1.3%), and clonic seizures in three (1.0%). However, since 137 patients (45.5%) had multiple seizure types, the total number of patients with tonic seizures was 73 (24.1%), followed by 32 (10.6%) for focal aware seizures and 32 (10.6%) for focal unaware seizures.

Seizure frequency (of any type) at registration was daily in 210 patients (69.3%) and less than yearly or zero in 57 patients (18.8%), the latter consisted mostly of patients with a single seizure type (45 patients). According to etiology, patients with less than yearly seizures or seizure freedom mostly had genetic etiology (23.8%), followed by unknown (22.6%) and MCD (19.1%). All patients with Aicardi syndrome had daily seizures (*table 2*).

● ***Neurological/physical findings***

Neurological findings were absent in 112 patients (37.0%) (61.9% of whom had neurocutaneous syndrome and 53.7% with unknown etiology), and were mostly present in patients with Aicardi syndrome, HIE or genetic etiology. In subcategories of MCD, neurological findings were found in 2/2 patients with heterotopia, 6/6 patients with polymicrogyria and related anomalies, 2/3 patients with hemimegalencephaly, 6/24 patients with FCD, and 9/12 patients with "others". Fifty-eight patients (19.1%) had no head control and 108 patients (35.6%) were bedridden, and the proportion of bedridden patients was 75.0% for HIE, 66.7% for Aicardi syndrome, 57.1% for genetic etiology, and 56.5% (13 patients) for MCD other than FCD (*table 2*).

● ***Examinations***

Gene testing was performed in 51 patients, and gene abnormalities were detected in 24 patients. The causative genes detected were *CDKL5* (4), *ARX* (1), *STXBP1* (4), *KCNQ* (1) and other genes (14). Cytogenetic testing was performed in 108 patients, and chromosome abnormalities were detected in 30 patients. The abnormal chromosomes (chr) identified were chr2 (3), chr7 (1), chr13 (1), chr15 (2), chr18 (2), chr21 (14), chr22 (1), chrX (1), chr1+18 (1), chr13+14 (1), chr14+21 (1) and unknown (2).

EEG was performed in all patients and 293 patients (96.7%) showed abnormal findings at the most recent

▼ **Table 2.** Clinical features of West syndrome according to etiology.

	Malformation of cortical development	Neuro-cutaneous syndrome	Hypoxic ischemic encephalopathy	Aicardi syndrome	Genetic	Unknown
N, %	47 (15.5)	21 (6.9)	36 (11.9)	9 (3.0)	42 (13.9)	133 (43.9)
Gender (female: *n*, %)	20 (42.6)	11 (52.4)	13 (36.1)	9 (100)	18 (42.9)	73 (54.9)
Seizure type: single (*n*, %)	22 (46.8)	8 (38.1)	18 (50.0)	4 (44.4)	26 (61.9)	83 (62.4)
Seizure frequency (*n*, %)						
Daily to weekly	36 (76.6)	16 (76.2)	28 (77.8)	9 (100)	30 (71.4)	94 (70.7)
Less than yearly or free	9 (19.1)	3 (14.3)	3 (8.3)	0	10 (23.8)	30 (22.6)
Neurological/physical condition (n, %)						
No findings	22 (46.8)	13 (61.9)	2 (5.6)	0	4 (9.5)	68 (51.1)
Hemiplegia/hemiparesis	7 (14.9)	0	0	1 (11.1)	0	3 (2.3)
Quadriplegia	7 (14.9)	0	26 (72.2)	1 (11.1)	15 (35.7)	20 (15.0)
Dysphagia	7 (14.9)	0	11 (30.6)	1 (11.1)	6 (14.3)	6 (4.5)
Ataxia	0	3 (14.3)	0	0	2 (4.8)	0
Physical condition (n, %)						
No head control	10 (21.3)	1 (4.8)	16 (44.4)	1 (11.1)	12 (28.6)	12 (9.0)
Sitting position only	0	4 (19.0)	3 (8.3)	2 (22.2)	7 (16.7)	16 (12.0)
Bedridden	14 (29.8)	0	27 (75.0)	6 (66.7)	24 (57.1)	33 (24.8)
Abnormal findings on neuroimaging (CT/MRI)	47 (100%)	20 (95.2%)	36 (100%)	9 (100%)	16 (38.1%)	46 (34.6%)
Treatment (*n*, %)						
Surgery	14 (29.8)	3(14.3)	0	1 (11.1)	4 (9.5)	24 (18.0)
Callosotomy	7	3	0	1	3	22
Hemisphrotomy/rectomy	4	0	0	1	1	1
Focal resection	7	1	0	0	0	6
Vagus nerve stimulation	1	0	0	1	2	3
ACTH	34 (72.3)	18 (85.7)	19 (52.8)	9 (100)	31 (73.8)	97 (72.9)
Steroids	1 (2.1)	1 (4.8)	1 (2.8)	0	0	0
Diet therapy	3 (6.4)	0	1 (2.8)	2 (22.2)	4 (9.5)	12 (9.0)
Cognitive/developmental status (*n*, %)						
Intellectual disability/delay	6 (12.8)	4 (19.0)	1 (2.8)	0	0	24 (18.0)
None	7 (14.9)	8 (38.1)	0	0	4 (9.5)	22 (16.5)
Mild	13 (27.7)	0	3 (8.3)	2 (22.2)	5 (11.9)	14 (10.5)
Moderate	7 (14.9)	3 (14.3)	6 (16.7)	1 (11.1)	10 (23.8)	27 (20.3)
Severe	14 (29.8)	5 (23.8)	24 (66.7)	6 (66.7)	22 (52.4)	42 (31.6)
Most severe	1	1 (4.8)	2 (5.6)	0	1 (2.4)	4 (3.0)
Unknown	9 (19.1)	5 (23.8)	2 (5.6)	0	2 (4.8)	23 (17.3)
Autism spectrum disorder						
Social status						
Preschool	36 (76.6)	17 (81.0)	23 (63.9)	4 (44.4)	34 (80.6)	91 (68.4)
Special class or school for disabled children	10 (21.3)	4 (19.0)	11 (30.6)	5 (55.6)	7 (16.7)	37 (27.8)
Regular school or class	0	0	0	0	0	4 (3.0)
Life support (aged ≥ 20 year)	1/1	0/0	2/2	0/0	0/0	1/1

examination before registration. Hypsarrhythmia (145 patients) and focal spikes (117 patients) were frequently reported.
Neuroimaging (CT and/or MRI) findings were available in all patients, and 190 patients (62.7%) showed a variety of abnormalities. Abnormal neuroimaging was less common in patients with unknown and genetic etiology (34.6% and 38.1%, respectively) (*table 2*).

- ***Treatment***

All but six patients were under treatment at registration, in particular, antiepileptic drugs (AEDs) in 286 patients. ACTH or corticosteroid was used in 220 patients (72.6%), and was more frequently used for Aicardi (100%) and neurocutaneous syndrome (85.7%), and less for HIE (52.8%) (*table 2*). Diet therapy was initiated in 25 patients. In addition to medication, 48 patients (15.8%) underwent surgical treatment. Callosotomy was the most frequent option in this series (36/48; 75%), followed by focal resection (15/48; 31.3%). Among MCD, nine patients with FCD (9/24; 37.5%), three patients with hemimegalencephaly (3/3; 100%) and two patients with heterotopia (2/2; 100%) underwent surgery. On the other hand, surgery was an exception for HIE, genetic etiology and Aicardi syndrome.

- ***Cognitive and developmental status***

Intellectual ability was assessed by performing tests in 129 patients, otherwise based on information from caregivers. Intellectual ability was not reported in nine cases. Intellectual/developmental ability was within normal range in 35 cases (11.6%), but impaired to various degrees, as shown in *table 1*. The most severe intellectual impairment was seen in cases of HIE, Aicardi syndrome and genetic etiology, compared to other etiologies (*table 2*).
As a comorbidity, autism spectrum disorder (ASD) was found in 41 (13.5%) cases, including nine (19.1%) patients with MCD (eight patients with FCD; 33.3%), five (23.8%) patients with neurocutaneous syndrome (four patients with TSC; 22.2%), and 23 (19.0%) patients with unknown etiology (*table 2*). Sleep disturbance was reported in six (2.0%) cases.

- ***Social status***

Seventy-seven (95.1%) of 81 school-aged children were attending special classes or school for children with disabilities. All four adult patients required life care.

- ***Medical/welfare benefits***

At the time of study, 245 patients (80.9%) were utilizing medical/welfare benefits, in addition to health insurance that covers all people in Japan. The most frequently used medical or health benefits were Medical Aid for Chronic Pediatric Diseases of Specified Categories (203 patients; 67%), followed by Physical Disability Certificate (78 patients; 25.7%), Child Rearing Allowance (61 patients; 20.1%) and Intellectual Disability Certificate (52 patients; 17.2%).

Longitudinal observational study

The clinical details of 27 patients with West syndrome, observed over two years from the first year of onset, are shown in *table 3*. Thirteen female and 14 male patients were studied. All but two patients had their first seizure within the first year of life. All patients had spasms at registration. Multiple seizure types were reported in eight patients. Twenty-six patients had daily seizures, while one patient was already seizure-free at registration. Gene mutation was found in three out of four patients tested (one in *CDKL5*), and a chromosomal abnormality was found in one out of nine patients examined (chr21). EEG was abnormal in all patients, particularly hypsarrhythmia in 23 patients, and 19 patients showed abnormalities on CT/MRI. Two patients had a past history of brain surgery. Etiology was MCD in five patients (18.5%), HIE in four (14.8%), tuberous sclerosis complex (TSC) in four (14.8%), others in four (14.8%), genetic in two (7.4%), and unknown in eight (29.6%). The distribution of etiology was roughly the same as that in the cohort of 303 patients in the cross-sectional study, although neurocutaneous syndrome was twice as frequent, and genetic and unknown etiology less frequent. There was no case of Aicardi syndrome. ACTH was given to 19 patients and was the only treatment in two patients. Developmental status was normal in seven patients and was already severely or most severely delayed in 10 patients. Six patients had paralysis, 11 patients had no head control, and 10 patients were bedridden. Neurological status was normal in only five patients at registration. Of the eight patients with unknown etiology, four patients were developmentally within normal limits, three patients were neurologically normal and eight patients were neuroradiologically normal.
During follow-up of two years, tonic seizures increased and seizure frequency decreased with more patients achieving seizure freedom. The number of patients with EEG abnormalities decreased. Developmental delay was found in more patients and became more severe during follow-up, and only two patients had normal development after two years (unknown etiology). The number of patients with physical problems was almost unchanged, except for head control, and the number of patients with ASD increased (two patients with TSC and three with unknown etiology). The three patients who were treated with ACTH alone became spasm-free, and had normalized EEG. These patients had no known etiology nor neuroradiological

▼ **Table 3.** West syndrome: changes in clinical features after one year and two years of follow-up in 27 patients.

		At registration	After 1 year	After 2 years
Seizure type	Spasms	27	24	23
	Tonic	4	7	9
	Focal	4	0	2
	Others	1	0	1
Seizure frequency	Daily	26	9	8
	Weekly	0	2	4
	Monthly	0	1	0
	Yearly	0	0	1
	free	1	15	14
EEG abnormality		27	20	19
CT/MRI abnormality		19	19	20
Treatment	Antiepileptic drugs	22	23	23
	ACTH	19	10	5
	Diet	0	1	1
Developmental delay	None	7	3	2
	Mild	5	3	3
	Moderate	1	8	5
	Severe	4	5	7
	Most severe	6	7	9
	Unknown	4	1	1
Neurological findings	No neurological findings	5	9	9
	Diplegia	1	0	0
	Quadriplegia	5	7	7
	Dysphagia	3	2	1
Physical condition	No head control	11	8	5
	Sitting position only	1	3	5
	Bedridden	10	13	10
	Other physical problems	2	1	1
Other comorbidities	Autism spectrum disorder	1	1	5
	Sleep disturbance	0	1	0

abnormalities, but one patient showed delayed development during the course.

Overall, seizure status was assessed as improved or markedly improved after two years in 18 of 27 patients (66.7%), but developmental status had worsened in 15 patients (55.6%), as shown in *table 4*. Overall assessment showed improvement or marked improvement in 14 patients (51.9%). Among 14 patients who showed an improvement or marked improvement in overall assessment after two years, 10 patients were seizure-free at two years. In the two patients with worse overall assessment, developmental status deteriorated although seizure frequency was unchanged in one and decreased in the other; etiology was HIE and unknown, respectively.

Discussion

In the cohort of the cross-sectional study, the etiology was confirmed in 182 of 303 patients (60.1%). This result is roughly the same as that in recent reports: 50/80 (63%) patients [4]; 61/207 (61%) patients [6]; 40/80 (50%) patients [8] and 219/377 (58%) patients [9]. When compared with the percentage of 40-50% reported

▼ **Table 4.** West syndrome: assessment after one year and two years of follow-up in 27 patients.

	Seizure status		Intellectual status		Overall	
	After 1 year	After 2 years	After 1 year	After 2 years	After 1 year	After 2 years
Markedly improved	13	14	0	0	8	3
Improved	4	4	3	3	6	11
No change	9	8	12	8	12	11
Worsened	0	1	11	15	0	2
Unknown	1	0	1	1	1	0

in 1991 [3], the recent figures reflect the advance in our understanding of the underlying etiology of West syndrome. The rates of individual etiologies in our cohort, such as MCD (15.5%), HIE (11.9%), neurocutaneous syndrome (6.9%), and Aicardi syndrome (3.0%), were also close to those of recent reports [1,6]. Wirrell *et al*. [11] reported that clinical evaluation and MRI provided a specific diagnosis in 55% of 250 children presenting with West syndrome, and further genetic and metabolic studies revealed the cause in another 23 cases, making a total of 64.4%. In our cohort, gene testing revealed the etiology in 24 of 51 patients (47.1%) and chromosomal testing in 30 of 108 patients (27.8%). Genetic testing, however, was unfortunately not systematic, as it was left to the discretion of the treating physician in the different institutions. A systematic and advanced genetic analysis might uncover genetic etiology in a substantial number of patients in the unknown category.

The main seizure type of West syndrome was spasms and the seizure frequency was high; 86.8% of patients had spasms as a main seizure type and 69.3% experienced daily seizures even at registration. Lower seizure frequency tended to be observed in patients with genetic, unknown etiology or FCD (subcategory of MCD) as well as a single seizure type. In the literature, seizure outcome is often reported to be better in patients with unknown causes [5,12].

Neurological findings were also frequent (63.0%), especially in patients with Aicardi syndrome, HIE, genetic etiologies and MCD other than FCD (19/23; 82.6%), corresponding to high rates of bedridden patients of over 50%. On the contrary, patients with FCD (6/24; 25%), neurocutaneous syndrome (38.1%) and unknown etiology (46.3%) had lower rates of positive neurological findings.

Concerning treatment, in addition to AEDs, ACTH or steroids were used in 220 patients (72.6%), which is almost in line with the current treatment recommendations [13]. Diet therapy was conducted in 25 patients (8.3%). Although some authors recommended ketogenic diet therapy when hormonal treatment failed [14,15,16], its use was limited in our cohort as this treatment has not been covered by the health insurance system until recently in Japan.

Surgery is another option and was performed in 48 patients (15.8%). Cases of MCD or TSC may be good candidates for resective surgery [17,18], but not cases of HIE or Aicardi syndrome; palliative surgery could be a choice for the latter, especially corpus callosotomy in patients without resectable MRI lesions [19].

As for intellectual development, only 11.6% of the patients were free of disabilities. In particular, in cases with Aicardi syndrome, genetic etiology and HIE, intellectual/developmental delay was severe, consistent with previous reports [12,20].

As a comorbidity, ASD was found in 41 cases (13.5%), and the prevalence was especially high in cases of FCD, TSC and unknown etiology. An association between ASD and TSC is well known [21,22], while FCD is also suggested to be associated with ASD [23].

The majority of patients in our cohort were preschool children or children in special classes or schools for children with disabilities at registration. Judging from our data, it would be exceedingly difficult for these preschool children to subsequently attend a regular school or enter normal employment. This trend applied to all the etiology categories.

Patients with West syndrome in Japan can apply for various types of health and medical benefits. Patients who are diagnosed with West syndrome can obtain Medical Aid for Chronic Pediatric Diseases of Specified Categories (MACPDAC, Shouni-Mansei-Tokutei-Shippei) for those under 18 years of age or Medical Aid for Designated Intractable Diseases for all ages, which subsidize, in part, the medical expenses and provide various support for living and welfare. Patients may also be eligible for Disability Certificate and Rearing Allowance (Tokubetsu-Jidou-Huyou-Teate) depending on the degree of intellectual or physical disability. Some patients were not receiving these benefits at registration. The reason could be that they were going to apply after registration or that they were not informed about these benefits. As the treatment and care for persons with West syndrome pose a serious financial and care burden mostly on the families and/

or caregivers, it is essential that they are well informed of these resources.

The analyses of our longitudinal study indicate an increase in patients with lower seizure frequency or even seizure freedom during the course of disease, and seizure status was improved in two thirds of patients. A similar observation was reported by Gupta *et al*. [24] who observed seizure freedom (over > six months) in 29/61 patients (47.5%).

However, developmental status was worse in more than a half of patients. In fact, there were only two patients with normal intellectual development after two years. Gupta *et al*. [24] reported moderate to severe developmental delay in 55/61 children (91.8%). Guzzetta *et al*. [25] also indicated progressive worsening of neurosensory and developmental impairments, although the epileptic evolution was generally better. Lagae *et al*. [5] indicated that 75% of children had delay in psychomotor development, even when spasms were controlled early during the course of the disease. The overall improvement in only half of our patients may be due to these comorbidities, although seizure frequency decreased.

There are limitations to this study. First, the participating hospitals were mostly tertiary centers for epilepsy care. Consequently, many patients who visited were relatively difficult to treat and very few were new-onset patients. The results of this study therefore cannot be generalized to the general patient population for West syndrome. This also accounts for the small number of new-onset patients recruited in the prospective observational study. Second, registration was left to the discretion of the treating physicians; some of whom were active in registration while others were not. Overall, the registration number was not as high as expected. The number of cases registered may represent approximately 8% of West syndrome cases in Japan, as estimated based on a prevalence study [26]. Third, although EEG and CT/MRI examinations were performed in all cases, genetic examinations were limited. Despite these limitations, these cross-sectional and longitudinal studies may contribute to how we modify care strategies for patients with West syndrome.

Conclusion

Our cross-sectional and longitudinal studies from the RES-R in Japan, despite a limited number of registered cases, reveal the challenging conditions of patients with West syndrome regarding seizure control, neurological/physical and cognitive function as well as social status, and their effect on families/caregivers. Further development of general and etiology-oriented intensive treatment and management of seizures and comorbidities in patients with West syndrome is desirable, in addition to a comprehensive strategy to support their education and social lives. ■

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