■ Original article

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Burden of seizures and comorbidities in patients with epilepsy: a survey based on the tertiary hospital-based Epilepsy Syndrome Registry in Japan

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ABSTRACT

Objective. To examine the current medical and psychosocial status of patients with epilepsy, aiming to facilitate appropriate application of the Intractable/Rare Diseases Act of Japan.

Methods. By analysing the cross-sectional data of patients registered in the tertiary hospital-based Epilepsy Syndrome Registry of Japan, we investigated the proportion of patients who met the severity criteria as defined by the Act (seizure frequency of at least once a month, or presence of intellectual/neurological/psychiatric symptoms, or both) and whether there are candidate syndrome/diseases to be added to the existing list in the Act.

Results. In total, 2,209 patients were registered. After excluding self-limited/idiopathic epilepsies, 1,851 of 2,110 patients (87.7%) met the severity criteria. The patients were classified into eight main epilepsy syndromes (594 patients), 20 groups based on aetiology (1,078 patients), and three groups without known aetiology (427 patients). Most of the groups classified by syndrome or aetiology had high proportions of patients satisfying the severity criteria (>90%), but some groups had relatively low proportions (<80%) resulting from favourable outcome of surgical therapy. Several small groups with known syndrome/aetiology await detailed analysis based on a sufficiently large enough number of patients registered, some of whom may potentially be added to the list of the Act.

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Significance. The registry provides data to examine the usefulness of the severity criteria and list of diseases that are operationally defined by the Act. Most epilepsy patients with various syndromes/diseases and aetiology groups are covered by the Act but some are not, and the list of designated syndromes/diseases should be complemented by further amendments, as suggested by future research.

Key words: epileptic syndrome, aetiology, comorbidity, severity, intractable/rare diseases act

In Japan, treatment and care measures had been taken to counter intractable diseases since 1972 [1]. These measures were expanded, and the Act on Medical Care and Social Supports for Patients with Intractable/Rare Diseases (the Intractable/Rare Diseases Act) was enacted in 2014 and came into effect in 2015, aiming to establish a fairer and more stable system to subsidize medical expenses and implement measures such as development of basic policy, promotion of research on medical care for intractable/rare diseases, and implementation of community-based health/medical care and welfare services [2]. Designation of intractable/rare diseases requires fulfilment of the following criteria: (1) rarity (affecting less than 0.1% of the population in Japan), (2) unknown aetiology or pathogenesis, (3) lack of effective treatment, (4) necessity of long-term care, and (5) existence of objective diagnostic criteria. The accreditation criteria for medical cost subsidy are stipulated as "patients with a certain level of severity, as defined by the disease severity classification, and who have difficulty in their daily or social lives".

As of 2020, the Intractable/Rare Diseases Act covers more than 20 syndromes/diseases (in the neuromuscular category) in which epileptic seizure is a main symptom or one of the main symptoms (Japan Intractable Disease Information Centre) (*table 1*). Some other syndromes/diseases with epileptic seizure as one of the accompanying symptoms during the course of disease may be covered by the Act under other categories, such as Glut-1 deficiency syndrome in the metabolic category. The severity criteria for eligibility of receiving care and welfare for epileptic syndromes/diseases were set as follows: when seizure with falling (including that caused by major motor seizure) or automatism with inappropriate behaviour occurs at least once a month, or when intellectual and/or neurological/psychiatric impairment is severe enough to affect daily and social activities, or both.

For proper application of this Act, it is essential to clearly define each epilepsy syndrome/disease, allowing physicians to diagnose and provide all possible and appropriate treatment strategies, but also to assess the severity and burden of epilepsy symptoms and accompanying developmental, neurological and psychosocial conditions in everyday and social life. However, there is still room for consideration of whether the severity criteria are appropriate to cover all the patients in need of care, and also whether there are other intractable/rare conditions with epilepsy that should be covered by the Act.

We have established the Epilepsy Syndrome Registry (ESR) in November 2014, with the aim to comprehend to what degree the epilepsy syndrome/diseases underlying conditions and comorbidities (defined according to Feinstein [3] as conditions occurring in the same individual irrespective of temporal or causal relation to epilepsy) affect the cognitive, physical and social conditions of the patients; whether the current treatment is successful; and what types of care and support are needed by the patients. In the ESR, we collect a wide range of cross-sectional clinical data of consecutive patients with epilepsy syndromes/diseases, from seizure type to

▼ **Table 1.** The syndromes/diseases related to epilepsy covered by the Intractable/Rare Diseases Act of Japan as of 2020.

Aicardi syndrome
Angelman syndrome
Dravet syndrome
Early myoclonic encephalopathy
Epilepsy associated with focal cortical dysplasia
Epilepsy associated with hemimegalencephaly
Epilepsy associated with neuronal migration disorders
Epilepsy of infancy with migrating focal seizures
Epilepsy with myoclonic absences
Epilepsy with myoclonic atonic seizures
Epileptic encephalopathy with continuous spike-waves during sleep (CSWS)
Hemiconvulsion-hemiplegia-epilepsy syndrome
Landau-Kleffner syndrome
Lennox-Gastaut syndrome
Mesial temporal lobe epilepsy with hippocampal sclerosis (bilateral type)
Ohtahara syndrome
PCDH19-related syndrome
Progressive myoclonus epilepsy
Rasmussen encephalitis
Rett syndrome
Ring 20 chromosome-epilepsy syndrome
Sturge-Weber syndrome
Tuberous sclerosis complex
West syndrome

physio-psycho-social status. Using these data, we examined the proportions of patients with various intractable/rare syndromes/diseases who met the severity criteria. We also investigated potential candidate syndromes/diseases for inclusion in the Act, as an interim report.

Subjects and methods

The ESR registered patients with epilepsy using a web-based electronic data capture system [4, 5]. The input items include age, gender, epilepsy syndrome, underlying disease/aetiology, seizure type, frequency of seizure, examination results (EEG, CT/MRI and others), therapies (except details of the drugs used), concurrent developmental or physical disorder, severity of intellectual disability, current social status, and use of health and medical services. There are 88 input fields, and registration is completed only after all fields are checked. The data is cleaned up regularly to ensure that the individual data is free of missing values. Registration is conducted by or under the supervision of certified clinical epileptologists (by the Japan Epilepsy Society), in order to maintain the quality of diagnosis of epilepsy syndrome/disease and comorbidities. Twenty-three tertiary hospitals from all over Japan participated. The system had an interruption between 2015 and 2017, and was restarted thereafter. A total of 2,209 cases were registered during the 37 months until November 2019.

The registry should eventually contribute to practical use of the current Intractable/Rare Diseases Act and possible expansion in the future. Therefore, we listed the syndromes/diseases currently covered by the Act, and also some other well-known epilepsy syndromes or diseases with epilepsy [6, 7] as well as some general categories such as "other focal epilepsy", "other generalized epilepsy", and "unclassified epilepsy" for epilepsies that could not be classified into any specific syndrome or disease, in order to cover as many patients with epilepsy as possible.

This database allows grouping of patients based on specific clinical features, such as aetiology. We first identified the patients with known epileptic syndromes/diseases and analysed the severity of their clinical features. We then grouped the patients without a diagnosis of syndrome/disease according to aetiology, using the classification based on the ILAE diagnostic manual [7], and examined their clinical characteristics, especially with regard to the burden of seizures and comorbid conditions, but regardless of whether each group constitutes a clinically meaningful entity. "Rarity" as defined in the Act was not taken into consideration in this report.

The indicator for severity of epilepsy was a frequency of main seizure type of at least once a month, and the indicator for comorbid condition was the presence of apparent intellectual and/or neurological/psychiatric symptom. Standard intellectual/neuropsychological/psychiatric tests were used to determine the presence and severity of comorbidities, if necessary.

The registry was approved by the Ethics Review Board of each participating hospital as well as the Japan Epilepsy Society. Informed consent was obtained from the participants or their guardians in written form or in the form of opt-out based on

▼ **Table 2.** Demographics and clinical features of 2,110 cases registered in the Epilepsy Syndrome Registry.

Gender; n	Female 1021, male 1089
Ages (range, median); years	Age at registration, 0-85, 17; age at seizure onset, 0-83, 3
Main seizure	Focal impaired awareness seizure 723 (34.3%), spasm 323 (15.3%), bilateral tonic-clonic seizure 310 (14.7%), focal aware seizure 292 (13.8%), tonic 198 (9.4%), gelastic 76 (3.6%), myoclonus 55 (2.6%), clonic 35 (1.7%), absence 27 (1.3%), atonic 12 (0.6%), nonconvulsive status 19 (0.9%), convulsive status 14 (0.5%), others 16
Seizure type	Single 954 (45.2%), multiple 1156 (54.8%)
Frequency of main seizure	Daily 578 (27.4%), weekly 356 (16.9%), monthly 395 (18.7%), yearly 266 (12.6%), less than yearly or disappeared 515 (24.4%)
Neurological findings	No neurological findings 1391 (65.9%); hemiparesis 146 (6.9%), diplegia 21 (1.0%), quadriplegia 176 (8.3%), ataxia 121 (5.7%), involuntary movement 66 (3.1%), dysphagia 86 (4.1%), others 105 (overlapping) (5.0%), bedridden 205 (9.7%), no head control 84 (4.0%), artificial respiration 12 (0.6%), unknown 20
Intellectual impairment*	Not impaired 843 (40.0%); mild 334 (15.8%), moderate 248 (11.8%), severe 633 (30.0%), unknown 52
Neuropsychiatric findings	ASD 355 (16.8%), ADHD 39 (1.8%), memory disturbance 104 (4.9%), aphasia 17 (0.8%), executive dysfunction 46 (2.2%), other cognitive dysfunctions 28 (1.3%); delusion-hallucination 45 (2.1%), affective disorder 53 (2.5%), personality disorder 76 (3.6%), sleep disturbance 49 (2.3%), other psychiatric symptoms 38 (1.8%)
Laboratory testing	Gene mutation 228/301 (75.7%); *SCN1A* (71 cases), *PCDH19* (9), *CDKL5* (8), *KCNT1* (6), *STXBP1* (6) and others Cytogenetic abnormality 104/332 (31.3%): chromosomes 21 (23 cases), 15 (23), 20 (16), 1 (6) and others
EEG	Normal 159 (7.5%); suppression-burst 22 (1.0%), hypsarrhythmia 148 (7.0%), generalized spike-waves 292 (13.8%), CSWS 19 (0.9%), focal spikes 892 (42.3%), multifocal spikes 360 (17.1%), other paroxysms 88 (4.2%), rapid/fast rhythm 67 (3.2%), abnormal background activity 308 (14.6%); information not available 32
CT/MRI	Abnormal 1290 (61.1%) (bilateral 363); information not available 43
Aetiology	Malformation of cortical development 264 (12.5%), tumour 176 (8.3%), neurocutaneous syndrome 117 (5.5%), infection 76 (3.6%), hypoxic-ischemic encephalopathy 69 (3.3%), cerebrovascular disorder 50 (2.4%), trauma 34 (1.6%), immune-mediated disorder 32 (1.5%), metabolic 25 (1.2%), degenerative disorder 18 (0.9%), others 486 (23.0%), unknown 767 (36.4%)
Therapy	Drug 2031 (96.3%), hormone (ACTH, steroid) 349 (16.5%), diet 65 (3.1%), surgery 547 (25.9%) (resection 327, hemisherotomy/-rectomy 37, callosotomy 102, stereotactic surgery 69, vagus nerve stimulation 68, other 12: multiple surgery 60); no previous treatment 39
Social status	Preschool 476 (22.6%), school 642 (30.4%) (school for disabled 420), employed 428 (20.3%) (employment for disabled 105), housekeeping 126 (6.0%), job training 44 (2.1%), job seeking 187 (8.9%), in need of life care 167 (7.9%) [150/956 (15.7%) of those aged $\geq$ 20 years]

ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; CSWS: continuous spike waves during sleep; diet: ketogenic diet therapy.
*Intellectual impairment: mild=IQ/DQ between 50-69; moderate=IQ/DQ between 35-49; severe=IQ/DQ less than 35. Assessed using the test results from 969 cases, otherwise from the information provided by caregivers.

announcement on the bulletin board or web site of each hospital.

Results

Of the 2,209 registered patients, we excluded those (99 patients) with a diagnosis of self-limited or idiopathic epilepsy syndrome that is known to have a benign course with few comorbidities [8]. For the remaining 2,110 patients, the clinical features are summarized in *table 2*. Frequency of the main seizure type was at least once a month in 1,329 patients (63.0%), and any intellectual or neurological/psychiatric symptoms were present in 1,500 patients (71.1%). There were 1,851 patients (87.7%) who had at least monthly seizures, or any intellectual/neurological/psychiatric symptom, or both.

Based on both the clinical data and examination results, we were able to diagnose the epileptic syndrome in 594 patients as shown in *table 3,* although we excluded those syndromes with a very small number of registered patients (less than 10): early myoclonic encephalopathy (one patient), epilepsy with myoclonic absence (six patients), Landau-Kleffner syndrome (one patient) and myoclonic encephalopathy in non-progressive disorders (three patients), because detailed analysis was not possible. We then grouped the remaining patients according to aetiology or relevant past history (1,078 cases) as shown in *table4*. The categories designated as other structural, other genetic and metabolic included heterogeneous groups of patients with known aetiology, but the number of registered patients in each group was less than 10, such as PCDH19-related epilepsy (nine patients) in the other genetic group and mitochondrial disease (six patients) in the metabolic group. The remaining 427 patients had no diagnosis of known syndrome or aetiology, including 342 patients with other focal epilepsy, 58 with other generalized epilepsy and 27 with unclassified epilepsy.

Epileptic syndromes

We identified eight epileptic syndromes (*table 3*). Age at seizure onset was generally young, mostly during early childhood, except progressive myoclonus epilepsy (PME). PME included heterogeneous types with late childhood and adult onset, such as dentatorubropallidoluysian atrophy (six patients) and benign adult familial myoclonus epilepsy (four patients). As the age of registration was not uniform and generally several years after seizure onset, the main seizure types may be variously mixed representing different age-related features.

The frequency of the main seizure was high in Dravet syndrome, epilepsy of infancy with migrating focal seizures (EIMFS), Lennox-Gastaut syndrome (LGS), Ohtahara syndrome and West syndrome, with more than 70% of the patients having at least monthly seizures. The seizure frequency was relatively low in epileptic encephalopathy with continuous spike-waves during slow wave sleep (ECSWS). Many syndromes manifested multiple seizure types.

Surgery was performed most actively for LGS (callosotomy in 29 of 37 patients and vagus nerve stimulation (VNS) in 15) and Ohtahara syndrome (hemispherectomy/-rotomy in seven of 10 patients). In West syndrome, 36 patients underwent callosotomy and seven patients VNS.

Ataxia was commonly seen in Dravet syndrome and PME, and more than a half of the patients with EIMFS and Ohtahara syndrome were bedridden. Mechanical ventilation was necessary in three patients with West syndrome, one with Ohtahara syndrome and one with EIMFS. More than 90% of the patients with EIMFS, LGS and Ohtahara syndrome had intellectual disability. In adult life, more than a half of the patients with Dravet syndrome (13/16), LGS (21/38) and West syndrome (3/4) required life care, although there was no information for EIMFS, epilepsy with myoclonic atonic seizures (EMAS), ECSWS and Ohtahara syndrome, because all the patients were aged under 20 years at registration.

Autism spectrum disorder (ASD) was a frequent comorbidity in Dravet syndrome, EMAS and ECSWS.

More than 90% of the patients with the above syndromes except EMAS had at least monthly seizures, or any intellectual/neurological/psychiatric symptom, or both.

Epilepsies grouped according to aetiology

We extracted 20 groups according to aetiology (*table 4*). The ages at epilepsy onset ranged widely from infantile onset, childhood onset to adult onset depending on the aetiology. The frequency of the main seizure was high in epilepsy due to neuronal migration disorders (NMD), hypoxic-ischaemic encephalopathy (HIE), tuberous sclerosis complex (TSC), other structural aetiology, ring chromosome 20-epilepsy syndrome (R20), infectious disease, Rasmussen encephalitis (RE) and other autoimmune disorders (AI), with more than 70% of the patients having at least monthly seizures. Surgery was performed in more than a half of the patients with hypothalamic hamartoma (HH), dysplastic tumour (DT) (such as dysembryoplastic neuroepithelial tumour and gangliolioma), mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE) and Sturge-Weber syndrome (SWS).

All the patients with Angelman syndrome and Rett syndrome, as well as most of the patients with other genetic aetiology and HIE, had intellectual impairment.

▼ **Table 3.** Seizure characteristics and associated symptoms of patients with various epileptic syndromes.

	n	Gender (female/male)	Age at registration (range, median)	Age at seizure onset (range, median)	Type of main seizure: *n* (%)	A: Frequency of main seizure: ≥ monthly *n* (%)	Multiple seizure type: *n* (%)	Therapy other than ASM: *n* (%)	B: Intellectual impairment*: *n* (%)	C: Prominent neurological/psychiatric symptoms: *n* (%)	Either A or B/C or both: n (%)
Dravet syndrome	89	47/42	0-38 (10)	0	GTC 51 (57.3), Focal 18 (20.2)	67 (75.3)	71 (79.8)	Diet 8 (9.0)	75 (84.3)	Ataxia 43 (48.3), ASD 45 (50.6)	86 (96.6)
Epilepsy of infancy with migrating focal seizures	15	10/5	0-15 (3)	0-2 (0)	Focal 7 (46.7), Tonic 6 (40)	13 (86.7)	13 (86.7)	Surgery 2 (13.3)	15 (100)	Bedridden 10 (66.7)	15 (100)
Epilepsy with myoclonic atonic seizures	11	3/8	3-15 (6)	0-5 (3)	Myoclonic atonic 11 (100)	7 (63.6)	9 (81.8)	Diet 4 (36.4)	6 (54.5)	ASD 4 (36.4)	9 (81.8)
Epileptic encephalopathy with CSWS	36	11/25	4-19 (9)	0-7 (3)	Focal 21 (58.3), Absence 8 (22.2)	12 (33.3)	28 (77.8)	Surgery 6 (16.7)	26 (72.2)	ASD 16 (44.4), Paresis 10 (27.8)	33 (91.7)
Lennox-Gastaut syndrome	85	50/35	5-50 (17)	0-11 (2)	Tonic 58 (68.2),	75 (88.2)	80 (94.1)	Hormone 29 (34.1) Surgery 37 (43.5)	84 (98.8)	ASD 22 (25.6), Paresis 17 (20.0)	85 (100)
Ohtahara syndrome	24	8/16	0-19 (4)	0	Tonic 11 (45.8), Spasm 8 (33.3)	17 (70.8)	11 (45.8)	Surgery 10 (41.7)	22 (91.7)	Bedridden 14 (58.3)	24 (100)
Progressive myoclonus epilepsy	31	17/14	4-80 (33)	1-52 (12)	Myoclonus 16 (51.6), GTC 11 (35.5)	20 (64.5)	20 (64.5)	0thers 2 (6.5)	17 (54.8)	Involuntary movement 17 (54.8) Ataxia 11 (35.5),	29 (93.5)
West syndrome including Aicardi syndrome	303	147/156	0-51 (3)	0-2 (0)	Spasm 263 (86.8),	226 (74.6)	137 (45.2)	Hormone 217 (71.6) Surgery 48 (16.0)	259 (85.5)	Bedridden 108 (35.6), ASD 40 (13.2)	289 (95.4)

ASM: antiseizure medication; ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; CSWS: continuous spike waves during sleep; Diet: ketogenic diet therapy; GTC: generalized tonic-clonic seizure; Hormone: ACTH or steroid therapy.
*Surgical therapy includes vagus nerve stimulation. ** Impairment: IQ/DQ less than 70.

▼ **Table 4.** Seizure characteristics and associated symptoms of patients with epilepsy grouped according to aetiology.

Aetiology		n	Gender (female/male)	Age at registration (range, median)	Age at seizure onset (range, median)	Type of main seizure: *n* (%)	A: Frequency of main seizure: ≥ monthly *n* (%)	Multiple seizure types: *n* (%)	Therapy other than ASM: *n* (%)	B: Intellectual impairment: *n* (%)	C: Prominent neurological/psychiatric symptoms: *n* (%)	Either A or B/C or both: *n* (%)
Structural	Focal cortical dysplasia	108	63/45	0-67 (17)	0-42 (3)	Focal 91 (84.3)	69 (63.9)	49 (45.4)	Surgery 53 (49.1)	54 (50.0)	ASD 21 (19.4) Paresis 15 (13.9)	96 (88.9)
	Neuronal migration disorders	37	21/16	0-48 (18)	0-28 (5)	Focal 29 (78.4)	26 (70.3)	22 (59.5)	Surgery 5 (13.5)	22 (59.5)	Paresis 6 (16.2)	36 (97.3))
	Hypothalamic hamartoma	72	33/39	2-53 (10)	0-10 (0)	Gelastic 72 (100), Focal 24 (33.3)	20 (27.8)	48 (66.7)	Surgery 70 (97.2)	25 (34.7)	ADHD 7 (9.7)	42 (58.3)
	Cavernous hemangioma	25	14/11	2-76 (40)	1-73 (24)	Focal 23 (92.0)	15 (60.0)	15 (60.0)	Surgery 9 (36.0)	3 (12.0)	Memory disturbance 3 (12.0)	16 (64.0)
	Dysplastic tumour*	24	11/13	2-52 (20)	0-36 (4)	Focal 24 (100)	9 (37.5)	13 (54.2)	Surgery 19 (79.2)	10 (41.7)	ASD 6 (25.0) Memory disturbance 3 (12.5)	17 (70.8)
	Trauma	32	5/27	5-77 (43)	0-73 (18)	Focal 28 (87.5)	12 (37.5)	19 (59.4)	Surgery 7 (21.9)	15 (46.9)	Paresis 12 (37.5) Executive dysfunction 5 (15.6)	27 (84.4)
	Hypoxic-ischaemic encephalopathy	29	9/20	1-53 (20)	0-20 (2)	Focal 22 (75.9)	22 (75.9)	16 (55.2)	Surgery 2 (6.9)	25 (86.2)	Paresis 14 (48.3), Bedridden 5 (17.2)	29 (100)
	Vascular disorder	41	11/30	6-69 (37)	0-66 (24)	Focal 35 (85.4)	17 (41.5)	18 (43.9)	Surgery 7 (17.1)	13 (31.7)	Paresis 14 (34.1) Memory disturbance 7 (17.1)	32 (78.0)
		197	109/88	4-77 (41)	0-75 (11)		122 (61.9)			38 (19.3)		

▼ **Table 4.** Seizure characteristics and associated symptoms of patients with epilepsy grouped according to aetiology (*Continued*)

Aetiology		n	Gender (female/male)	Age at registration (range, median)	Age at seizure onset (range, median)	Type of main seizure: *n* (%)	A: Frequency of main seizure: ≥ monthly *n* (%)	Multiple seizure types: *n* (%)	Therapy other than ASM: *n* (%)	B: Intellectual impairment: *n* (%)	C: Prominent neurological/psychiatric symptoms: *n* (%)	Either A or B/C or both: *n* (%)
	Mesial temporal lobe epilepsy with hippocampal sclerosis					Focal 197 (100)		116 (58.9)	Surgery 117 (59.4)		Memory disturbance 26 (13.2)	153 (77.7)
	Sturge-Weber syndrome	35	18/17	0-60 (5)	0-27 (0)	Focal 22 (62.9)	17 (48.6)	22 (62.9)	Surgery 25 (71.4)	21 (60.0)	Paresis 13 (37.1)	32 (91.4)
	Tuberous sclerosis complex	51	24/27	0-48 (11)	0-16 (0)	Focal 32 (62.7) Tonic 9 (17.6)	37 (72.5)	31 (60.8)	Surgery 15 (29.4)	40 (78.4)	ASD 15 (29.4)	48 (94.1)
	Other structural	161	80/81	0-85 (28)	0-83 (9)	Focal 125 (77.6), Tonic 18 (11.2)	113 (70.2)	80 (49.7)	Surgery 40 (24.8)	75 (46.6)	Paresis 30 (18.6) Bedridden 14 (8.7)	105 (65.2)
Genetic	Angelman syndrome	26	11/15	1-41 (10)	0-31 (1)	Tonic 5 (19.2), Myoclonus 5 (19.2)	16 (61.5)	12 (46.2)	0	26 (100)	Ataxia 8 (30.8) Sleep disturbance 10 (38.5)	26 (100)
	Ring 20 epilepsy syndrome	16	11/5	6-65 (20)	1-14 (7)	Focal 10 (62.5) NCSE 4 (25.0)	16 (100)	11 (68.8)	Surgery 2 (12.5)	10 (62.5)	0	16 (100)
	Rett syndrome	37	37/0	5-44 (14)	0-17 (4)	Focal 12 (32.4), Tonic 10 (27.0)	16 (43.2)	10 (27.0)	0	37 (100)	ASD 25 (67.6) Sleep disturbance 14 (37.8) Bedridden 10 (27.0)	37 (100)
	Other genetic	62	36/26	1-36 (9.5)	0-25 (0)	Focal 28 (45.2), GTC 11 (17.7)	34 (54.8)	33 (53.2)	Hormone 6 (9.7)	57 (91.9)	ASD 22 (35.5) Bedridden 12 (19.4)	60 (96.8)

▼ **Table 4.** Seizure characteristics and associated symptoms of patients with epilepsy grouped according to aetiology (*Continued*)

Aetiology		n	Gender (female/male)	Age at registration (range, median)	Age at seizure onset (range, median)	Type of main seizure: *n* (%)	A: Frequency of main seizure: ≥ monthly *n* (%)	Multiple seizure types: *n* (%)	Therapy other than ASM: *n* (%)	B: Intellectual impairment: *n* (%)	C: Prominent neurological/psychiatric symptoms: *n* (%)	Either A or B/C or both: *n* (%)
Metabolic	Metabolic disorder	17	5/12	1-47 (7)	0-42 (1)	Focal 8 (47.1), Tonic 4 (23.5)	10 (58.8)	7 (41.2)	Diet 4 (23.5)	14 (82.3)	Paresis 7 (41.2) Bedridden 5 (29.4)	15 (88.2)
Infectious	Infectious disease	60	24/36	1-55 (26)	0-38 (7)	Focal 54 (90.0)	45 (75.0)	38 (63.3)	Surgery 12 (20.0)	42 (70.0)	Paresis 13 (21.7)	57 (95.0)
Immune	Rasmussen encephalitis	20	9/11	10-48 (19)	0-25 (4)	Focal 20 (100)	19 (95.0)	2 (10.0)	Hormone 11 (55.0) Surgery 9 (45.0)	14 (70.0)	Paresis 15 (75.0)	20 (100)
	Other autoimmune disorder	28	18/10	6-75 (41)	1-74 (22)	Focal 26 (92.9)	23(82.1)	16 (57.1)	Immune 9 (32.1) Surgery 4 (14.3)	5 (17.9)	Memory disturbance 8 (28.6)	26 (92.9)
Unknown	Other focal epilepsy without known aetiology	342	155/187	0-85 (27)	0-83 (10)	Focal 333 (97.4)	198 (57.9)	157 (45.9)	Surgery 35 (10.2), hormone 12 (3.5)	128 (37.4)	ASD 68 (19.9) Memory disturbance 24 (7.0) Paresis 16 (4.7)	267 (78.1)
	Other generalized epilepsy without known aetiology	58	26/32	1-63 (20.5)	0-42 (6.5)	GTC 26 (44.8), Absence 10 (17.2)	30 (51.7)	28 (48.3)	Hormone 3 (5.5)	27 (46.6)	ASD 10 (17.2)	45 (77.6)
	Unclassified epilepsy without known aetiology	27	9/18	0-63 (25)	0-49 (9)	GTC 13 (48.1), Focal 6 (22.2)	10 (37.0)	13 (48.1)	Others 2 (7.4)	13 (48.1)	Ataxia 3 (11.1) Involuntary movement 3 (11.1)	19 (70.4)

NCSE: non-convulsive status epilepticus.
*Dysplastic tumour includes dysembryoplastic neuroepithelial tumour and ganglioglioma.

Neurological/psychiatric impairments were diverse, and more than a quarter of the patients with Rett syndrome and metabolic aetiology were bedridden. More than a half or nearly a half of adult patients with Rett syndrome (8/9), TSC (9/15), Angelman (3/6) and HIE (9/19) required life care in our series. ASD was most frequently found in Rett syndrome, followed by other genetic, TSC and DT patients.

The rates of patients who had at least monthly seizures, or any intellectual/neurological/psychiatric symptom, or both, were: 100% in HIE, Angelman, R20, Rett and RE; more than 90% in NMD, SWS, TSC, other genetic, infectious, and AI; and less than 80% in HH, cavernous hemangioma (CA), DT, vascular, mTLE and other structural aetiology.

Epilepsies without a known aetiology

The group of other focal epilepsy without known aetiology consisted of patients with widely varied age at epilepsy onset (*table 4*). Around a half of the patients with other focal and other generalized epilepsy had at least monthly seizures. Intellectual impairment was seen in around a half of patients with generalized and unclassified epilepsy. Surgery was performed in 10% of patients with other focal epilepsy, including resection surgery in 23 and VNS in 13. A fifth (7/33) of the patients with other generalized epilepsy needed life care in adult life.

The rate of patients who had at least monthly seizures, or any intellectual/neurological/psychiatric symptom, or both, was less than 80%.

Epilepsy patients without comorbidities

When we looked at seizure frequency in patients without any intellectual/neurological/psychiatric co-morbid condition, 94 patients (4.5% of 2,110 patients) had yearly seizures (at least once a year but less than monthly) and 161 patients (7.6%) had less than yearly (once in several years) or no seizure (*table 5*). The unemployment rate of patients aged between 18 and 65 was similar in both groups (10.3% and 8.9%, respectively). More than 20% of patients with CA, DT, HH and other focal/unclassified epilepsy without known aetiology had less than monthly seizures and no comorbidities.

Discussion

Under the universal health coverage system in Japan, 70% of all medical expenses are covered by health insurance. In addition, all epilepsy patients are exempt from outpatient care co-payment to some extent. However, hospitalization co-payment is exempted only under the Intractable/Rare Disease Act. There is a disability certificate system for welfare, education and employment, and also a pension system for living assistance. Therefore, the benefits of using the Intractable/Rare Disease Act are not so great. However, as the Act is expected to be further enhanced, it is important to properly incorporate the relevant epilepsy syndromes/diseases into the Act and to ensure that application of the Act is more relevant to the real situations of people with epilepsy.

We conducted an analysis of the clinical data accumulated in our registry to examine the proportion of patients with epilepsy covered for provision of services by the Act, and whether there are missing syndromes/diseases in the list of target diseases. We found that the patients in various epilepsy syndromes/diseases or aetiology groups are mostly covered by the Act but some are not, and the list of designated syndrome/disease should be complemented.

First of all, among our study patients with epilepsy, more than 70% had one or more accompanying conditions, suggesting the important impact of co-morbid conditions on daily and social life of these patients. Similar figures have been reported by Ho *et al*. [9] who conducted a web-based questionnaire survey on the prevalence and characteristics of comorbidities in 795 persons with rare epilepsies, and found that nearly all were medically complex, with a high prevalence of multiple comorbidities including learning/developmental disability (71%), mental health issues (71%), and sleep disorders (60%), especially those who were diagnosed with epilepsy in the first year of life. In our series, when the burden of seizures was included, the severity criteria (at least monthly seizures and/or presence of comorbid conditions) designated by the Act were met in 87.7% of the patients.

We identified eight epileptic syndromes with more than 10 registered patients each. All syndromes except ECSWS tended to have a high seizure frequency. Despite the low seizure frequency, ECSWS had high comorbidity, thus more than 90% of the patients met the severity criteria, similar to the other syndromes. Only EMAS had a relatively low seizure frequency and comorbidity rate compared to others, with 81% meeting the severity criteria.

Among the aetiology groups, Angelman syndrome, NMD, AI, infectious, HIE, RE, Rett syndrome, R20, SWS and TSC, more than 90% of patients met the severity criteria, whereas for HH, CA, DT, vascular disorder and mTLE, this was less than 80%, and for focal cortical dysplasia (FCD) and trauma, the figure was between the two. AI, infectious and HIE appeared to be equally severe as other syndromes/aetiology groups already included in the Act. For HH, DT and mTLE, surgery was

▼ **Table 5.** Number of patients with seizures occurring less than monthly and without comorbidities.

	n	Seizure frequency: yearly *n* (%)	Seizure frequency: < yearly or none *n* (%)	Total *n* (%)
Angelman syndrome	26	0	0	0
Dravet syndrome	89	3	0	3 (3.4)
Epilepsy due to autoimmune disease	28	1	1	2 (7.1)
Epilepsy due to cavernous haemangioma	25	3	6	9 (36.0)
Epilepsy due to dysplastic tumour	24	1	6	7 (29.2)
Epilepsy due to focal cortical dysplasia	108	7	6	13 (12.0)
Epilepsy due to hypothalamic hamartoma	72	0	28	28 (38.9)
Epilepsy due to hypoxic-ischaemic encephalopathy	29	0	0	0
Epilepsy due to infectious disease	60	2	1	3 (5.0)
Epilepsy due to metabolic disorders	17	0	2	2 (11.8)
Epilepsy due to neuronal migration disorders	37	1	0	1 (2.7)
Epilepsy due to other genetic disorders	62	2	0	2 (3.2)
Epilepsy due to other structural disorders	161	9	10	19 (11.8)
Epilepsy due to trauma	32	1	4	5 (15.6)
Epilepsy due to vascular disorder	41	3	5	8 (19.5)
Epilepsy of infancy with migrating focal seizures	15	0	0	0
Epilepsy with myoclonic atonic seizures	11	0	2	2 (18.2)
Epileptic encephalopathy with CSWS	36	1	2	3 (8.3)
Lennox-Gastaut syndrome	85	0	0	0
Mesial temporal lobe epilepsy with hippocampal sclerosis	197	12	27	39 (19.8)
Ohtahara syndrome	24	0	0	0
Other epileptic syndromes	11	1	0	1 (9.1)
Other focal epilepsy without known aetiology	342	39	31	70 (20.5)
Other generalized epilepsy without known aetiology	58	3	8	11 (19.0)
Progressive myoclonus epilepsy	31	0	2	2 (6.5)
Rasmussen encephalitis	20	0	0	0
Rett syndrome	37	0	0	0
Ring 20-epilepsy syndrome	16	0	0	0
Sturge-Weber syndrome	35	1	2	3 (8.6)
Tuberous sclerosis complex	51	0	3	3 (5.9)
Unclassified epilepsy without known aetiology	27	3	5	8 (29.6)
West syndrome incl Aicardi syndrome	303	1	10	11 (3.6)
Total	2110	94	161	255 (12.1)

performed in more than 50% of the cases. For CA, surgery was performed in a third of the patients, but there were originally few comorbidities. In our series, almost all HH patients with gelastic seizures underwent surgery and more than a half of them became seizure-free. This is because there is a centre specialized for HH where MRI-guided stereotactic radiofrequency thermocoagulation (SRT) is performed actively with favourable outcome [10]. Many patients with DT also underwent surgical therapy and had similar seizure status as those with HH. Thus, surgical treatment has a significant impact on seizure status. In the case of FCD, the lesions were extensive in some patients, and although surgery was performed in almost a half of the patients, comorbidities could be serious in surgically untreatable patients or cases with surgical failure. This also applies to SWS, with a large number of surgical cases.

In more than 250 patients, although the epilepsy syndrome/disease or aetiology was known, detailed clinical features could not be analysed due to the small number of registered cases. This category is composed of a variety of heterogeneous conditions and is considered to include several serious diseases as indicated by the presence of severe impairments. If a sufficient number of patients could be registered to allow clinical analysis, some well-defined epilepsy syndromes/diseases may be extracted, which may need to be included in the list of the Act.

The 427 cases with no known syndrome/aetiology were also considered to be very heterogeneous. Advances in diagnostic methods such as brain imaging and genetic research are expected to lead to elucidation of aetiology and detailed classification of epilepsy in these patients.

The effect of less than monthly seizures, even in the absence of accompanying symptoms, on the social life of patients with epilepsy should be investigated. In many countries, a driving license is not allowed when seizures occur yearly. There are also some restrictions on employment when seizures repeat yearly [11]. According to Kwan *et al*. [12], absolute seizure freedom, usually taken as at least 12 months, is the only relevant outcome consistently associated with meaningful improvement in quality of life. The proportion of patients in our series who had seizures on a yearly basis without comorbidity was 4.5%. Should the severity criteria include yearly seizure frequency, then the patients who meet the revised criteria would increase to 1949 (92.4%).

From this data analysis, it seems appropriate to consider including AI, infectious, and HIE in the list of designated conditions of the Act. Furthermore, as there are many groups with less than 10 cases, further accumulation of cases and analysis may reveal that some of them could be recommended to be added to the list of the Act.

There are limitations of this study. First, the participating hospitals were tertiary centres for epilepsy care, visited mostly by relatively difficult-to-treat patients with very few new-onset patients. The results of this study therefore cannot be generalized. Second, registration was left to the discretion of the treating physicians, resulting in active registration of some syndromes/diseases but not others, and overall, the number of cases registered was not as high as expected. The number of cases registered is estimated to represent only 0.9-40% of the cases of epilepsy syndrome/disease in Japan, as calculated from the prevalence of each syndrome/disease documented at the Japan Intractable Disease Information Centre [13]. Third, although EEG and CT/MRI examinations were performed in almost all cases, genetic or cytogenetic examinations were limited. Therefore, some recently described syndromes/diseases could have been overlooked in the registry. Nevertheless, the results of a relatively large number of cases covering a wide range of epilepsy syndromes/diseases/aetiologies in this study may provide an overview of the epilepsy conditions in order to help modify the care strategies for these patients. ■

Supplementary material.

Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) What proportion of epilepsy patients may have comorbid conditions, if self-limited epilepsy and idiopathic generalized epilepsy are excluded?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.