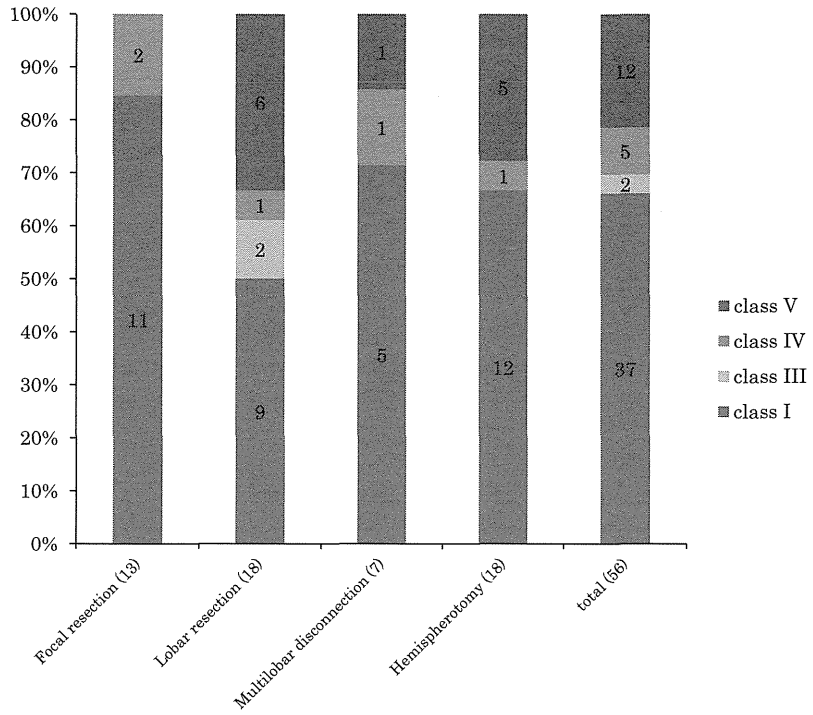

Fig. 7. Surgical procedure and seizure outcome (ILAE classification). Parentheses indicate the number of patients.

Table 1
Histopathology, surgical procedures and seizure outcome of 56 patients. Parentheses indicate number of seizure free (class I) patients.

Surgery CD type	Focal resection	Lobar resection	Multilobar disconnection	Hemispherotomy	Total	Class I (%)
HMC				16 (11)	16 (11)	69%
PMG		2 (0)	2 (1)	1 (0)	5 (1)	20%*
FCD type I	2 (2)	4 (1)			6 (3)	50%
FCD type IIA	6 (4)	7 (5)	5 (4)	1 (1)	19 (14)	74%
FCD type IIB	5 (5)	5 (3)			10 (8)	80%
Total	13 (11)	18 (9)	7 (5)	18 (12)	56 (37)	66%
Class I (%)	85%	50%	71%	67%		

HMC: hemimegalencephaly, PMG: polymicrogyria, FCD: focal cortical dysplasia.
* $P < 0.05$.

surgical procedure, and seizure outcome of the patients are listed in Table 1. Class 1 outcome was obtained in 69% of patients with HMC, 20% of patients with PMG, 50% of patients with FCD type I, 74% of patients with FCD type IIA, and 80% of patients with FCD type IIB. There were no statistical differences in seizure outcome among CD histological subtypes except PMG ($P < 0.05$), in which 4 children remained in class 5 even though 2 underwent repeated surgery and 1 patient underwent hemispherotomy.

3.4. Repeated surgery

Because of recurrent seizures, repeated surgery was indicated in 9 cases (1 patient received 3 surgeries) at 1–20 months (mean: 9 months) after the initial surgery. The repeated surgeries included 2 focal, 6 lobar, and 1 multilobar procedures. Seizure freedom was finally obtained in 5 children (56%; all class 1a). In all cases but 1, additional resection at the insular and periventricular structures was indicated.

3.5. Surgical complications

Surgical complications were experienced in 5 cases (9%); these included 1 post-operative hydrocephalus, 1 chronic subdural hematoma, 2 intracranial cyst formation at resected cavity, and 1 transient meningitis that were successfully managed without sequel by ventricular peritoneal shunt, burr hole irrigation, cyst wall resection, and antibiotics administration, respectively. No mortality or severe morbidity occurred.

4. Discussion

The present report demonstrates that early surgical intervention in children with CD and intractable seizures in infancy and early childhood can yield favorable seizure outcome without mortality or severe morbidities. Post-operatively, ILAE class 1 (seizure free) outcome was obtained in 66% of the cases, and class 1a (completely seizure free since the surgery) outcome was observed in 55% of the cases in a mean follow-up of 4 years.

Half of the children underwent surgery were during infancy at an age less than 10 months, and the majority (80%) of these infants needed extensive surgical procedures, such as hemispherotomy and multi-lobar disconnection. Post-operative seizure outcome did not differ significantly with the type of surgery although it was slightly better for focal resection: 85% with focal resection, 50% with lobar resection, 71% with multilobar disconnection, and 67% with hemispherotomy. These data may indicate that careful and meticulous pre-surgical evaluations are valuable to localize epileptogenicity and to pursue minimum tissue removal in infants.

However, pre-surgical evaluations for infants with intractable seizures are challenging, particularly when epileptic encephalopathy is associated [23]. This is because interictal scalp EEG frequently shows bilateral abnormalities, the localizing value of ictal semiology in infant is limited, and MRI only demonstrates tissues with severe histological abnormalities. Therefore, to define a focal epileptogenicity, the role of additional diagnostic modalities, such as FDG-PET, ictal SPECT, MEG, and intra-cranial EEG monitoring have been stressed [24–29].

Our strategy for resective epilepsy surgery in infancy was principally based on multimodal neuroimaging, that is, co-registering all the imaging data obtained and checking congruency of MRI findings to FDG-PET abnormalities, ictal hyper-perfusion, and MEG dipole clustering. The resection plan basically included all MRI-visible and non-visible pathologies congruent to such diagnostic modalities, which often included not only cortical but also subcortical structures [30,31].

We recently reported a series of 8 children with extensive frontal lobe CD, in which pre-surgical functional neuroimaging studies showed ictal hyper-perfusion, reduced iomazenil uptake, and/or spike dipole clustering in subcortical structures surrounding the anterior horn of the lateral ventricle [32]. In all patients, seizure freedom was obtained after resection of the peri-ventricular white matter and part of the striatum, where histological evaluation revealed dysplastic neurons in some cases.

Epileptogenicity in subcortical brain structures has not been well elucidated. However, the data indicate that hemispherotomy, either by a horizontal or vertical approach, achieves complete disconnection of all cortical and subcortical structures surrounding the striatum and thalamus, which includes the insular cortex, the limen insulae, and the subcallosal area [15–17,33]. Incomplete removal of these structures is reported to cause surgical failure [34,35]. Moreover, some authors had even mentioned the role of resection of a part of the basal ganglia and thalamus to prevent recurrent seizures [33].

It is considered rational, therefore, to remove the CD located at the structures covering the striatum and thalamus in order to obtain favorable seizure outcome. Anatomically, these structures include not only the insular cortex but also the bottom of deep cortical sulci surrounding the striatum and thalamus, such as the vertical ramus of the Sylvian fissure and the circular insular sulcus, which locate close to the periventricular white matter. In our series, periventricular and insular regions, which were continuous to the cortical pathologies, were also removed in 23% of focal resection and 61% of lobar resection, which may have yielded our comparatively good seizure outcome.

Histological subtypes of CD may influence seizure outcome. CD, in general, is extremely variable and usually treatable by surgery when it is focal or within one hemisphere [4,36–38]. Although FCD is commonly confined to a single hemisphere, PMG, lissencephaly, and pachygyria often involve both cerebral hemispheres [4,36], in which the pathophysiological bases are heterogeneous and include genetic causes [39]. HMC is also known to associate with dysplastic contralateral abnormalities [6], which have been reported as a negative factor for post-surgical seizure and developmental outcome [38,40,41].

Subtypes of FCD may also affect surgical outcome [10,42]. It is reported that the seizure outcome of resective surgery in young children with FCD type I was not as good as that in children with to FCD type II [5,43]. On average, post-operative seizure freedom (Engel class I) was reported in 47% (range 21–67%) of patients with FCD type I and 76% (range 60–100%) of patients with FCD type IIB [4,5,44–48]. However, FCD type IIA is less well characterized and only a few studies have addressed it thus far [4,46,49]. Although our sample size was small, we did not obtain statistically different seizure outcomes (class 1) among CD subtypes except in PMG (HMC 69%, PMG 20%, FCD type I 50%, FCD type IIA 74%, and FCD type IIB 80%). More studies are needed to clarify the difference in the nature of epileptogenicity among histological subtypes of FCD.

5. Conclusions

Early surgical intervention in children with CD and intractable seizures in infancy and early childhood can yield favorable seizure outcome without mortality or severe morbidities although younger children often need extensive surgical procedures.

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None of the authors has any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with their guidelines.

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Original article

Clinical analysis of catastrophic epilepsy in infancy and early childhood: Results of the Far-East Asia Catastrophic Epilepsy (FACE) study group ☆

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Abstract

Purpose: We studied children younger than 6 years old who developed catastrophic epilepsy and were registered in the FACE study group to clarify their clinical characteristics and prevalence of seizure as well as epilepsy types. Subjects: Subjects were prospectively recruited from children with epilepsy who satisfied the following criteria and underwent intensive examination between 2009 and 2012 in 14 collaborative centers: (1) younger than 6 years old and (2) more than 10 seizures/month refractory to all available medical treatments including ACTH therapy, leading to significant psychosocial morbidity. Methods: We analyzed epilepsy onset age, predominant seizure type, etiology, neuropsychological findings, and syndromic classification according to

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the pre-determined registration format. Results: A total of 314 children were enrolled in this study. Epilepsy onset age in 239 cases (80%) was younger than 12 months. The most frequent seizure type was epileptic spasms (ES), followed by generalized tonic seizures (GTS), which accounted for 42% and 20%, respectively. West syndrome (WS) was the most frequent epileptic syndrome and accounted for 37%, followed by unclassified epilepsy at 21%, neocortical epilepsy at 19%, Lennox–Gastaut syndrome at 12%, Dravet syndrome at 4%, Rasmussen syndrome at 2%, and others. The two most frequent causes of epilepsy were cortical dysplasia and chromosomal anomalies, as shown in 16% and 6%, respectively. However, the etiology of nearly one half of all patients remained unknown. Psychomotor development was already worse than a moderate degree in 62% of subjects at the first examination. Conclusion: The highest proportion of catastrophic epilepsy was WS and its related syndromes featuring ES and GTS, followed by neocortical epilepsy, whose psychomotor development was significantly retarded at examinations.

Keywords: Catastrophic epilepsy; Young children; West syndrome; Etiology; Epilepsy surgery; Classification

1. Introduction

The term "catastrophic childhood epilepsy" was first introduced by North American pioneers who began performing epilepsy surgery on children whose seizures begin early in life and were so frequent and intense that their psychomotor development and daily life were significantly impaired [1–4]. Because of the impact that catastrophic seizure disorders have on a child's life and the lack of effective antiepileptic drugs, new therapies are especially needed for this group of patients [5]. However, the earlier that epilepsy develops, the more severe and malignant the nature of that epilepsy, the etiology of which is serious and diverse from neurometabolic disorders such as mitochondrial encephalopathy to acquired structural brain abnormalities such perinatal hypoxic–ischemic encephalopathy [6–8]. Therefore, it is true that the outcome of catastrophic epilepsy largely depends on the etiology of patients rather than the treatment strategy. However, it is still also true that the control of epileptic seizures or epileptic encephalopathy may contribute to better developmental outcomes irrespective of the etiology. Although the most recent ILAE proposal has not recommended using the term "catastrophic" because it sounds hopeless for families, we have tried new treatment strategies to release these groups of patients from catastrophes [9]. However, no systematic survey has been globally undertaken so far on the epidemiology and treatment prognoses of these patients. Since patients with catastrophic epilepsy are relatively rare and are referred to specialized pediatric epilepsy centers, an international multicenter study among these major pediatric epilepsy centers is needed. Therefore, we conducted a multi-institutional study including 14 collaborative Asian centers to reveal the clinical characteristics of this patient group.

2. Subjects

Subjects were children with highly refractory epilepsy who satisfied the following criteria and underwent an extensive examination at one of the 14 collaborative hospitals or institutions participating in the Far-East Asia Catastrophic Epilepsy (FACE) study group.

(1) Age younger than 6 years old at the first seizure, (2) more than 10 seizures/month refractory to more than two antiepileptic drugs and ACTH therapy, resulting in the stagnation/deterioration of psychomotor development, (3) extensive examinations including ictal and interictal EEG, brain MRI, brain SPECT/PET, developmental assessments, and cytogenetic studies if required during admission, and (4) patients with nonepileptic conditions, atypical forms of benign epilepsy, and severe non-cerebral physical co-morbidities were excluded. Patients were prospectively collected during the registration period between 2009 and 2012, according to the predetermined registration format (Table 1S).

3. Methods

All data including brain MRI, EEG, seizure, and epileptic syndrome classifications, as well as psychomotor development at the time of investigation, were evaluated in each hospital according to the registration format and were used for this analysis. We analyzed ages at the onset of epilepsy, etiology, main seizure type classification based on the 1981 International Classification of Epileptic Seizures [10], and syndrome classifications based on the 1989 International Classification of Epilepsy [11] and Epileptic syndromes and psychomotor development at the time of first examination. Seizure type classification was made either based on the ictal video-EEG examinations or clinical grounds if it was difficult to apply because of infrequent seizures.

Psychomotor development was assessed according to the Tsumori/Inage, Enjoji, and Vineland and KIDS test for those in other countries. All results were categorized to normal ($\geqslant 80$), borderline to mild delay (<80, $\geqslant 70$), moderate delay (<60, $\geqslant 50$), severe delay (<49, $\geqslant 35$), most severe delay (<34, $\geqslant 20$), and extremely severe disabling (<20) according to the developmental quotient. Tanaka-Binet Japan-made IQ tests were applied for Japanese patients who were able to respond to this test.

The proposed protocol was approved by the Ethics Review Board of each hospital participating in the

FACE study group prior to the start of the study. Written informed consent was obtained from the participants in each hospital or institution before the registration.

4. Results

A total of 314 children (boys: 185, girls: 129) who fulfilled the criteria were enrolled in this study. The onset age of epilepsy was between 0 and 6 months in 185 patients or 58.9%, between 7 and 12 months old in 60 patients or 19.1%, and older than 12 months in the remaining 69 patients or 22.0%. Thus, in a total of 245 cases or 78% of all patients, epilepsy developed at or younger than 12 months old (Fig. 1).

4.1. Etiology

The etiology of epilepsy was estimated from past histories, and brain MRI, CT, and cytogenetic findings. It consisted of cortical dysplasia, which accounted for 16%, hypoxic–ischemic encephalopathy of a largely perinatal origin (the period from 28th week of gestation through the 7th day after birth) for 11%, tuberous sclerosis for 7%, other cytogenetic abnormalities for 5%, central nervous system infection for 5%, vascular lesions for 4%, and others (Table 1). Thus, 28.5% of all patients had prenatal origins, and another 29% had postnatal origins. However, the etiology was still unknown in the remaining 42% of patients.

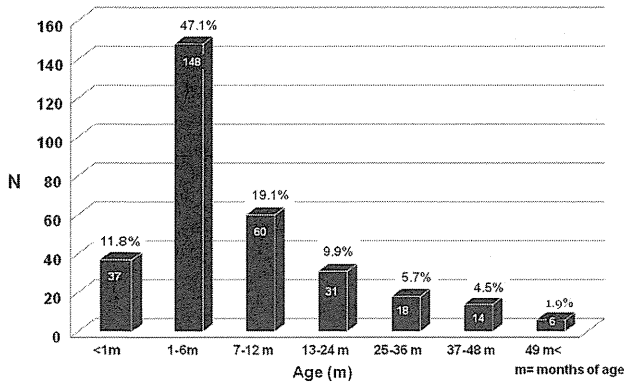

Fig. 1. Age at the onset of epilepsy ($n = 314$). Age at the onset of epilepsy in 185 patients or 58.9% was between 0 and 6 months old, and that in 60 patients or 19.1% was between 7 and 12 months old. Thus, in a total of 245 cases or 78% of all patients, epilepsy developed at or younger than 12 months.

Table 1
Etiology ($n = 314$).

	N	%
Cortical dysplasia	49	16
Hypoxic encephalopathy	33	11
Tuberous sclerosis	23	7
Genetic/chromosomal abnormalities	17	5
Infection	14	5
Vascular lesions	13	4
Tumors	3	1
Head trauma	3	1
Hemimegalencephaly	2	0.5
Other miscellaneous	23	7
Unknown	132	42
Not described	2	0.5
Total	314	100

4.2. Seizure type classification

A total of 73% of all patients had generalized seizures and the remaining 22% had focal seizures. The most frequent seizure type was epileptic spasms (ES), which comprised 37%, followed by generalized tonic seizures (GTS) in 20%, and partial complex motor seizures in 15%. Thus, ES and GTS were the main seizure types in at least 57% of all patients (Fig. 2).

4.3. Epileptic syndrome classification

At the time of investigation, the most frequent epileptic syndrome was West syndrome, which accounted for 36%, followed by unclassified epilepsy at 21%, neocortical epilepsy at 19%, Lennox–Gastaut syndrome (LGS) at 11%, Dravet syndrome at 4%, Rasmussen syndrome at 2%, and Ohtahara syndrome (OS), myoclonic-astatic epilepsy (Doose syndrome), and Sturge–Weber syndrome at 1% each (Fig. 3). Patients with neocortical epilepsy, unclassified epilepsy, and LGS included a total of 36 cases (11%) with a history of WS. Thus, a total of 47% of patients were classified into West syndrome and its related syndromes.

The unclassified epilepsy group ($n = 66$) formed the second largest group, accounting for 21% of all patients. Forty-four of these cases (67%) developed their first seizure at the age of 12 months or younger. Eight cases had a history of WS. The most disabling seizure type was GTS in 25 cases, followed by ES and head nodding attacks in 7, complex motor seizures in 6, and partial simple in 5. Interictal EEG showed generalized or multifocal epileptic abnormalities in 49 cases. Thus, more than half of the patients with unclassified epilepsy were categorized into some form of diffuse epileptic encephalopathy featuring ES or GTS and generalized or multifocal epileptic EEG abnormalities unclassifiable for either WS or LGS.

The third largest group was neocortical epilepsy ($n = 60$), accounting for 19% of all patients. Seventy-three percent of these cases developed their first seizure at an age of less than 12 months. Focal and generalized seizures accounted for 63% and 37%, respectively. The most disabling seizure types consisted of partial complex motor seizures in 31 cases, followed by hypomotor seizures in 6, and partial simple motor seizures in one. The etiology of epilepsy comprised focal cortical dysplasia, which accounted for 13%, generalized cortical dysplasia for 5%, hypoxic–ischemic encephalopathy for

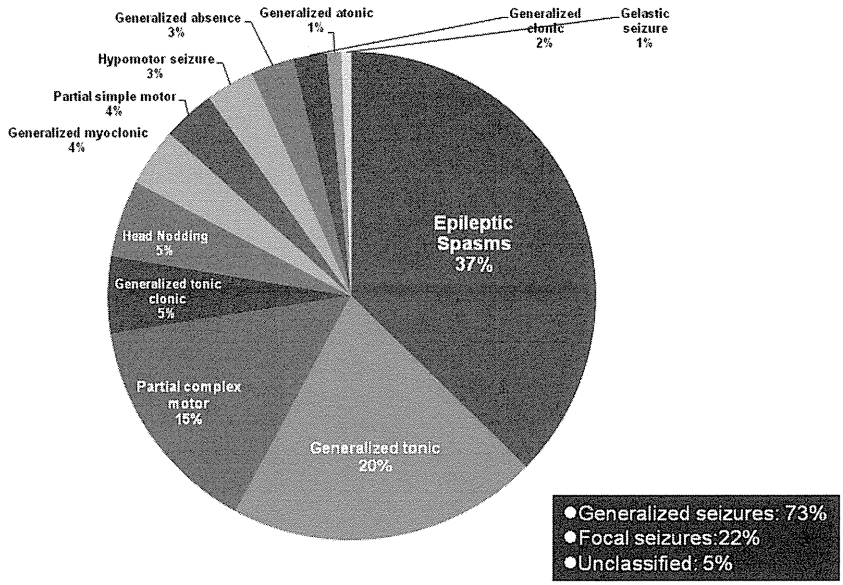

Fig. 2. Main seizure type classification ($n = 314$). The most frequent seizure type was epileptic spasms (ES), accounting for 37%, followed by GTS at 20%, and partial complex motor seizures at 15%. ES and GTS were the main seizure types in at least 57% of all patients.

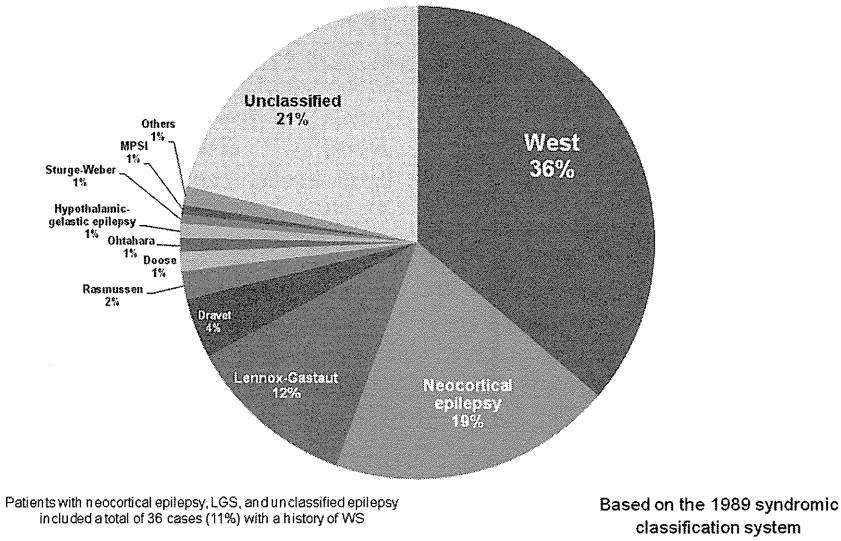

Fig. 3. Epilepsy syndromic classification at the time of the investigation ($n = 314$). The most frequent epileptic syndrome was West syndrome, which accounted for 36%, followed by unclassified epilepsy at 21%, neocortical epilepsy at 19%, and others. Patients with neocortical epilepsy, LGS, and unclassified epilepsy included a total of 36 cases (11%) with a history of WS.

15%, and tuberous sclerosis for 10%. However, etiology is still unknown in the remaining 40% of patients.

4.4. Psychomotor development

There were only two patients who were able to undergo Tanaka-Binet Japan-made IQ tests (IQ values: 65, 47). Thus, these two patients were judged to have mild and moderate retardation, respectively. The remaining 312 patients underwent psychomotor assessment. Among them, psychomotor development at the time of the first examination was normal in 15% of all patients, borderline to mild retardation in 23%, moderate retardation in 18%, severe retardation in 16%, and severe disabling in 28%. Thus, 38% of patients achieved normal to mild psychomotor development, while 62% exhibited already worse than moderate retardation at the time of the investigation.

Discussion

This study was the first multi-institutional collaborative study prospectively investigating many children with catastrophic epilepsy that developed at an age younger than 6 years old. The definition of catastrophic epilepsy was referred from other studies [3,12,13] and

had its own criteria of more than 10 seizures/month refractory to more than two antiepileptic drugs and ACTH therapy, resulting in the stagnation/deterioration of psychomotor development. Although it was arbitrary, this definition could cover the vast majority of refractory epilepsy syndromes as shown in the syndromic classification.

This large cohort study demonstrated that WS was the most frequent cause of catastrophic epilepsy in infancy and early childhood. In general, ACTH and various antiepileptic drugs have been administered to patients with WS, and have achieved long-term epilepsy remission in approximately half of these patients [14–17]. However, the remaining patients were mostly left with intractable epilepsy, often evolving to LGS and neocortical focal epilepsy, and also moderate to severe mental retardation. In this study, a total of 149 cases or 47% of all cases were classified either into WS or epilepsy with a history of WS. Oka et al. carried out an epidemiological survey in childhood epilepsy in Okayama prefecture in Japan and demonstrated that WS was the most frequent epileptic syndrome, accounting for 4.93% of all patients with epilepsy aged 1 month to 13 years of age [18]. This figure was 8-, 6.6-, and 62-times larger than the prevalence of LGS, and Dravet and Doose syndromes, three major representative intractable epileptic syndromes during early childhood, respectively.

The third largest group was neocortical epilepsy, accounting for 19%. More than two thirds of patients developed focal seizures younger than 12 months old. In this age range, the most severe epilepsy was most likely to develop in the form of diffuse epileptic encephalopathy irrespective of etiology. However, we previously reported that catastrophic focal epilepsy in patients less than 12 months old was characterized by multifocal seizure onsets and deleterious clinical courses with numerous focal seizures caused in part by metabolic/structural abnormalities [19].

As for the most disabling seizure type shown in 314 patients, ES and GTS, accounting for 42% and 20%, respectively, were the two most important seizure types, corresponding to both WS and LGS, respectively. The epilepsy onset age in 75% of all cases was 1 year or less when symptomatic epilepsy outnumbered idiopathic or cryptogenic epilepsy. Psychomotor development was already worse than a moderate degree in nearly two thirds of these patients at the time of investigation, which was not contradictory to the outcomes of WS, especially symptomatic outcomes [14,16,17,20].

A few studies investigated seizures in the first year of life excluding febrile seizures, and all of these demonstrated that WS cases accounted for nearly 50% of cases and seizure as well as intellectual outcomes were grave, not only in cases with WS but also in those with other seizure types [21–23]. In pediatric surgical series, one large ILAE-based cohort study investigating 543 children undergoing epilepsy surgery (age: 0–18 years) showed that the age at seizure onset was 1 year or less in 46% of patients, which increased up to 68% if patients were younger than 3 years. In this study, the most frequent etiologies were cortical dysplasia (42%), tumors (19%), atrophic lesions, and strokes (10%) [24]. In another report studying 116 patients undergoing epilepsy surgery in the first 3 years of life, the result was more distinct that the seizure onset was in the first year of life in 82% and the most frequent cause was a malformation in cortical development (49%), followed by tumors (19%) [25]. Although surgical series were biased to those with localized or hemispheric cortical lesions, they included those with true catastrophic cases.

In our cohort, cortical dysplasia and chromosomal anomalies were also two of the most frequent causes, although other causes were still unknown in nearly one half of all patients. Chugani et al. described that cortical dysplasia was found in many patients who underwent respective surgery based on PET despite the absence of recognizable MRI focus [1]. Cortical dysplasia type 1 has been recently shown to produce subtle high signal intensities and reductions in the volume of corresponding white matter only [26–30]. Most cases of unknown etiology may have been caused by cortical dysplasia type 1, which is difficult to visualize even with high-resolution MRI, and only repeated follow-up MRIs may demonstrate subtle white matter changes underlying a dysplastic cortex [31].

Epilepsy surgery for catastrophic epilepsy in children has been steadily increasing in not only the USA but also in the EU, Japan, and other Asian countries owing to the prevalence of neuroimaging modalities. Jonas et al. reported the most recent findings regarding the effectiveness of epilepsy surgery on children with either active infantile spasms (IS) or those with treated IS in whom epilepsy already evolved to other epilepsy types [32]. That study demonstrated a seizure-free rate of 62.5% at 1 year and 44.0% at 5 years, and 80.0% at 1 year and 36.4% at 5 years, respectively. Recently, Baba et al. also attempted corpus callosotomy in 51 infants with active and remote WS aged 24.4 months on average, and demonstrated a spasm-free rate of 33.3%, which represented more than an 80% reduction in spasms in 19.6% of infants, and more than a 50% reduction in 25.8% of infants [33]. These surgical procedures brought about not only seizure reductions but also improvements in psychomotor development.

In conclusion, the most frequent catastrophic epilepsy in infancy and early childhood of less than 6 years of age was WS and its related epilepsy, followed by neocortical epilepsy. Pharmacological and surgical treatments of these patients remain challenging [5,34]. We have to focus on identifying the underlying mechanisms involved and clearly visualize epileptic lesions in these

patients in order to develop new treatment strategies, thereby reducing the number of catastrophic epilepsy patients. Although our study has limitations associated with hospital-based multi-institutional investigations, these results should to be useful in further research to challenge catastrophic epilepsies in young children.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2013.02.004.

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Original article

A long-term, clinical study on symptomatic infantile spasms with focal features

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Abstract

Background: We studied the clinical, neuroradiological and EEG characteristics of patients with infantile spasms (IS) who showed focal features to reveal their long-term prognoses and treatment responses. *Subjects and methods:* Subjects included 69 patients with IS who consecutively visited our hospital. We tentatively classified the subjects into focal IS (fIS) and diffuse WS (dIS) groups based on the presence and absence of more than two of the following findings, respectively: (1) epileptic spasms (ES) that were asymmetric, (2) a focal epileptic EEG abnormality, (3) a lateralized neurological abnormality, (4) a focal brain MRI and (5) a focal SPECT abnormality. *Results:* We found 23 cases with fIS and 46 cases with dIS. ES responded more frequently in fIS than dIS group (100% vs. 80%; $P = 0.02$) to the initial ACTH trial although the subsequent seizure relapse occurred more frequently in fIS than dIS group (74% vs. 38%; $P = 0.0006$). The second course of ACTH trial brought a short as well as long-term remission in both groups (6/8 cases vs. 5/6 cases). Later in the clinical course, the fIS patients tended to display a focal epileptic EEG abnormality and to develop focal seizures. In our series, approximately one-third of patients with fIS later showed either only a focal epileptic EEG abnormality, a focal epileptic EEG abnormality with focal seizures, or bilateral asymmetric EEG foci with disabling seizures, respectively. *Conclusion:* It is useful to classify patients with IS into fIS and dIS groups based on various lateralizing signs because the classification provides practical information regarding the long-term outcome and treatment strategy.

Keywords: Infantile spasms; West syndrome; Focal features; Focal cortical dysplasia; Focal seizures; Prognosis

1. Introduction

Infantile spasms (IS) or West syndrome (WS) is one of the most malignant epileptic syndromes that can occur during early childhood. IS are characterized by onset of epilepsy younger than 2 years of age and a combination of epileptic spasms (ES) in clusters, often associated with developmental arrest or regression and hypsarrhythmic EEG abnormality [1–3]. Seizures and intellectual prognoses are generally poor. In 20–30% of the patients, IS evolves to Lennox–Gastaut syndrome [4–6]. In the other 20–30% of the patients, IS either transforms into focal or multifocal epilepsy although only a few detailed studies on patients whose epilepsy evolved into focal epilepsy following IS have been documented [7–9]. Recently, several studies have been undertaken regarding the surgical treatment of patients with IS where detailed neuroimaging examinations were performed to identify the resectable focal lesion responsible for the ES [10–14]. Cortical malformation has received great attention as an etiology of IS, and recent progress in neuroimaging techniques and surgical intervention can visualize, in detail, the cortical and pathological abnormality consistent to cortical dysplasia. Thus, focal cortical dysplasia (FCD) has been suggested to be a cause of IS with focal features [15–17]. Some patients with IS who exhibited a focal

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PET abnormality have undergone surgery in specialized epilepsy centers when multiple medications failed to control the ES, and approximately half of these patients have gone into seizure remission [18]. However, the long-term, clinical course or prognoses of those with IS who show focal features remains unexplored in detail. We studied patients with IS and focal features and compared the results to patients with IS but without focal features.

2. Subjects and methods

The subjects of this study consisted of patients with IS who consecutively visited our hospital between the years 2000 and 2009. They all admitted to our hospital for detailed investigations and ES were confirmed by video-polygraphic study. We employed the case definitions and outcome measures in this study according to those proposed by the West Delphi Group [3]. The age at onset of ES was all younger than 2 years of age. We only included patients with IS without hypsarrhythmia and those with WS in this study. We retrospectively analyzed the medical charts, EEG findings and the following neuroimaging data: brain MRI, CT, single photon emission computed tomography (SPECT) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans. The following clinical factors were individually assessed: gender, etiology, age at which the onset of epilepsy and ES occurred, development before the onset of epilepsy, focal features of ES, associated seizure type, interictal EEG findings, and primary clinical as well as final electroclinical responses. In addition, the results of metabolic screening, chromosomal analyses and genetic testing were reviewed.

ES were investigated by means of simultaneous split-screen video taping and EEG–EMG polygraphic recording. The investigation was performed using either the Nihon-Kohden (Nihon Kohden Co., Shinjuku-ku, Tokyo, Japan) or Ceegraph SE (Bio-logic Systems Co., Mundelein, IL, USA) monitor system. Surface EMG activity data were collected from the trapezius, sternocleidomastoideus (SCM), and deltoid muscles. The interictal EEG examinations, which included waking and sleeping recordings, were performed using 10–20 international methods at 1–3-month after ACTH therapy and 6-month intervals thereafter. Brain MRIs were recorded using a 1.5 tesla, high-resolution MRI apparatus with T1, T2 and FLAIR methods. They were performed repeatedly if a focal lesion was suspected in the first recording. Lastly, a SPECT study was performed using either ^{123}I-iomazenil or ^{99m}Tc-ECD (ethyl cysteinate dimer). The development or IQ was measured either with Japanese Tsumori-Image developmental scale, modified Tanaka Binet IQ test or WISC-III depending on the patient's status.

Details of the treatment strategy used in our hospital were described elsewhere [19].

We tentatively classified patients into focal IS (fIS) and diffuse IS (dIS) groups; the former group was defined as patients having concordant focal signs in more than two examinations, and the latter group was defined as having one or no focal features in the following five examinations:

(1) Video-polygraphic examination: ES semiology was reviewed by video replay mode and consistent postural asymmetry was considered to be a focal feature. Asymmetric ES or unilateral ES were assessed when patients were resting on the symmetrical posture at least by two pediatric neurologists.
(2) Neurological examination: hemiparesis or monoparesis was considered to be a lateralized or focal sign.
(3) Interictal EEG: a focal feature was defined as either asymmetric hypsarrhythmia or exhibiting a difference between the sides in spikes, frequencies and amplitude that was greater than 25% confirmed by at least two consequent EEG examinations.
(4) Brain MRI and CT scans: localized structural abnormalities were evaluated, including features of calcification on CT scan even if the MRI scan was normal.
(5) SPECT or PET: IMZ-SPECT, ^{99m}Tc-ECD and FDG-PET (five patients) were evaluated for the presence of a focal abnormality. Neuroimaging was visually interpreted by one or two experienced radiologists who were blinded to all clinical information. We compared the onset age of epilepsy, age at the time of treatment intervention, lead-time to treatment intervention, primary electroclinical outcome, relapse rate, final electroclinical outcome and developmental outcomes at the final follow-up period between fIS and dIS groups. In this study, the primary electroclinical response is defined as cessation of spasms and resolution of hypsarrhythmia, the latter of which permits the presence of residual focal or generalized EEG spike discharges.

The proposed protocol was approved by the Ethics Review Board of the Tokyo Women's Medical University prior to the start of the study.

2.1. Statistical analyses

The chi-squared test and *t*-test were employed to compare the results between two variables. Fisher's exact test was used when the expected number was less than five. A comparison between more than three variables was performed using the chi-squared test with cross tabulation. We employed Bonferroni correction to calculate the *P* values to adjust for the multiple testing. A *P* value of <0.00625 (Bonferroni correction) was regarded as significant.

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3. Results

A total of 69 patients, consisting of 23 cases with fIS and 46 cases with dIS were enrolled in this study. The former and the latter included four and three cases with IS without hypsarrhythmia, respectively. The dIS group comprised 10 patients with nonsymptomatic IS. The median age at the onset of epilepsy in fIS and dIS groups was 150 days and 190 days, respectively, but the difference between these ages was not significant ($P = 0.93$).

3.1. Details of the focal features of the fIS group during initial examinations

A localized structural abnormality was found on the MRI and CT scans of 12 patients; seven had FCD, one had hemimegalencephaly, four showed a subtle FLAIR signal intensity abnormality on the white matter concordant to the estimated epileptic foci. There were 22 patients, 20 patients and eight patients showing focal SPECT abnormalities, focal EEG abnormalities and lateralizing neurological abnormalities (hemiparesis:7, monoparesis:1), respectively. Asymmetric ES was found in four patients. The combination of focal features in the fIS group is shown in Table 2.

Dominant epileptic foci, estimated by combining results from more than two examinations, was found in the left cerebral hemisphere ($n = 17$) and right cerebral hemisphere ($n = 6$). Furthermore, in 16 cases, foci were found in the anterior half of the brain; in five cases, foci were found in the posterior half of the brain; and in two patients, the locations of the foci were not determined due to widespread unilateral involvement. The age at the onset of epilepsy in patients who had epileptic foci in the anterior half of the brain was not significantly later than that of those who had foci in the posterior half of the brain ($22 \sim 554$ days vs. $77 \sim 245$ days; $P = 0.96$).

3.2. Etiology

The etiology of the fIS group consisted of FCD in seven patients, hemimegalencephaly in one patient, a metabolic disorder in one patient and unknown etiologies in the remaining 14 cases. For eight cases, a focal, structural lesion was found on the MRI to be located in the frontal lobe region, and in four cases, lesions were found in the temporal-occipital regions. In the dIS group, the etiology comprised perinatal hypoxic-ischemic encephalopathies in nine patients, chromosomal/genetic defects in three patients, congenital anomaly syndrome in two patients and diffuse polymicrogyria, tuberous sclerosis and diffuse cortical dysplasia each in one patient. In the remaining 29 cases, no known etiologies were found.

3.3. Primary electroclinical response

All fIS-group patients achieved primary electroclinical responses: 18 cases responded to ACTH, three cases responded to ZNS, and one responded to high-dose γ-globulin therapy (tried in the referral hospital). The age that first remission occurred ranged from 2 to 31 months (mean: 11.7 months; SD: 9.6 months). However, for the dIS group, 37 of the 46 cases (80%) showed primary electroclinical responses: 29 cases responded to ACTH, six responded to ZNS, one responded to VPA, and one responded to CLB. The remaining nine cases continued to have seizures despite various medical treatments. Overall, the primary electroclinical response appeared better for the fIS group than for the dIS group (Table 1).

3.4. Clinical course, EEG evolutional changes and seizure relapse after the initial treatment

During the clinical course, the seizures relapsed in 17 of the 23 fIS- group cases (74%) at 3–74 months (mean: 18 months) after the initial cessation of ES (Table. 1, Fig. 1). The relapsed seizure type demonstrated focal seizures in nine cases, ES in six cases, and generalized tonic seizures (GTS) in the remaining two cases. Alternatively, the seizures relapsed in 14 of the 37 cases (38%) of patients in the dIS group who had achieved seizure remission. Thus, the relapse rate was significantly greater in the fIS group than in the dIS group ($P = 0.0006$).

Among the 17 fIS-group patients who had relapsed seizures, eight cases underwent a second course of ACTH therapy for the treatment of ES ($n = 6$) and GTS ($n = 2$) between the ages of 2–7 years (mean: 43 months) because of resistance to all available antiepileptic drugs (AEDs). Three patients were in remission for longer than 1 year; three patients achieved a 6–12-month, short remission; and two patients showed no response. These two patients also failed to respond to ketogenic diet therapy. Finally, 11 patients developed focal seizures at onset ages ranging from 11 to 96 months, with a median of 31 months (Fig. 1: Cases 4,7,9,11–16,19,23). Seven patients had complex partial seizures with impairment in consciousness only, three patients showed tonic posturing, and one patient demonstrated unilateral clonic seizures. Among the 23 cases with dIS who continued to have seizures, six cases underwent a second course of ACTH therapy. Two of these patients achieved a longer than 1-year remission, three patients showed a 6–12-month remission, and one patient showed no response to therapy.

In eight patients with fIS who showed the relapse-free primary electroclinical response, a lateralized or focal epileptic EEG abnormality later emerged and became active, ranging in age from 25 to 109 months (with a median age of 42 months), (Fig. 1). The reappearance

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Table 1
Comparisons of demographic data between fIS and dIS.

N	fIS 23	dIS 46	*P*-value*
Gender (boys:girls)	11:12	21:25	
Follow-up period (month)	15 ~ 115 (median: 47)	11 ~ 120(median: 53)	0.19
Onset age of epilepsy (day)	22 ~ 740 (median: 150)	21 ~ 749 (median:190)	0.93
Age at the time of treatment intervention (month)	0.5 ~ 29 (median: 8)	2 ~ 34 (median: 9)	0.35
Lead-time to treatment intervention (month)	0 ~ 10 (median: 1)	0 ~ 23 (median: 3)	0.08
Number of patients showing excellent primary electroclinical responses	23 (100%)	37 (80%)	0.02
Number of patients who relapsed seizures	17 (73%)	14 (30%)	0.0006*
Number of patients showing excellent final electroclinical responses	10/23 (43%)	29/46 (63%)	0.13
Development outcomes (normal to mild/moderate/severe)	61/26/13	41/15/43	0.14

The chi-squared test and *t*-test were employed for comparisons.
* After Bonferroni correction, $P < 0.00625$ was significant.

Table 2
Combinations of focal signs in fWS.

Combination of focal signs	*N*
SPECT + EEG	6
MRI + SPECT + EEG	5
SPECT + EEG + NA	3
MRI + SPECT + NA	2
MRI + SPECT + EEG + NA	2
MRI + SPECT	1
MRI + SPECT + EEG + SS	1
MRI + EEG + SS	1
SPECT + EEG + SS	1
SPECT + EEG + NA + SS	1
Total	23

NA, Neurological abnormality; SS, Seizure semiology.

of the epileptic EEG abnormality preceded the occurrence of focal seizures in seven of the eight patients.

During the final follow-up period, 10 patients (43%) in the fIS-group achieved the final electroclinical response for longer than 1 year. In the remaining 13 patients, six continued to have focal seizures at least once a month, and two had focal seizures once a week and ES once a day. Five of the 13 patients underwent epilepsy surgery after repeated ACTH trials or ketogenic diet therapy in addition to all available AED treatment failed. In these cases, three and two patients underwent focal resection and total corpus callosotomy, respectively. The three patients who underwent the resective surgery showed a transient disappearance of seizures and epileptic EEG abnormalities for longer than 1 or 2 years; however, both seizures and epileptic EEG abnormalities recurred afterward (Fig. 1). In all three cases, the relapsed seizures appeared to arise from the entire ipsilateral hemisphere, including the sensorimotor area, and the interictal EEG became diffusely widespread, especially in that hemisphere. The total corpus callosotomy in the two patients resulted in a moderate reduction in the intensity and frequency of seizures and in a complete lateralization of diffuse epileptic EEG abnormalities in both patients.

In the dIS group, 29 patients (63%) showed the final electroclinical response for longer than 1 year. Thus, there was no significant difference in the final electroclinical outcome between the two groups, despite that of the fIS group appearing to be worse (10/23 cases vs. 29/46 cases; $P = 0.13$).

3.5. Developmental outcomes during the final follow-up period

In the fIS group, normal to mild mental retardation was recognized in 14 patients (61%), while moderate and severe mental retardation was documented in six patients (26%) and in three patients (13%), respectively (Table 3). In contrast, there were 19 cases (41%), seven cases (15%) and 20 cases (43%), respectively, in dIS-group which included the 10 patients with nonsymptomatic IS. Thus, the fIS-group generally had better developmental outcomes than the dIS-group, despite these numbers being statistically insignificant ($P = 0.14$).

3.6. Summary of fIS outcomes

ES in the fIS-group patients tended to respond to the initial therapy, but later they typically recurred. However, a second ACTH therapy frequently resulted in a short-term or long-term remission of those seizures. Approximately one-third of patients maintained remission, despite focal epileptic EEG abnormalities, while another third developed focal seizures after reappearance of focal epileptic EEG abnormalities. The remaining one-third of the patients continued to have ES or GTS and bilateral asymmetric epileptic EEG abnormalities. Focal resection and corpus callosotomy brought only a short-term remission of seizures and epileptic EEG abnormalities.

4. Discussion

Infantile spasms (IS) have been etiologically classified into either nonsymptomatic or symptomatic in the

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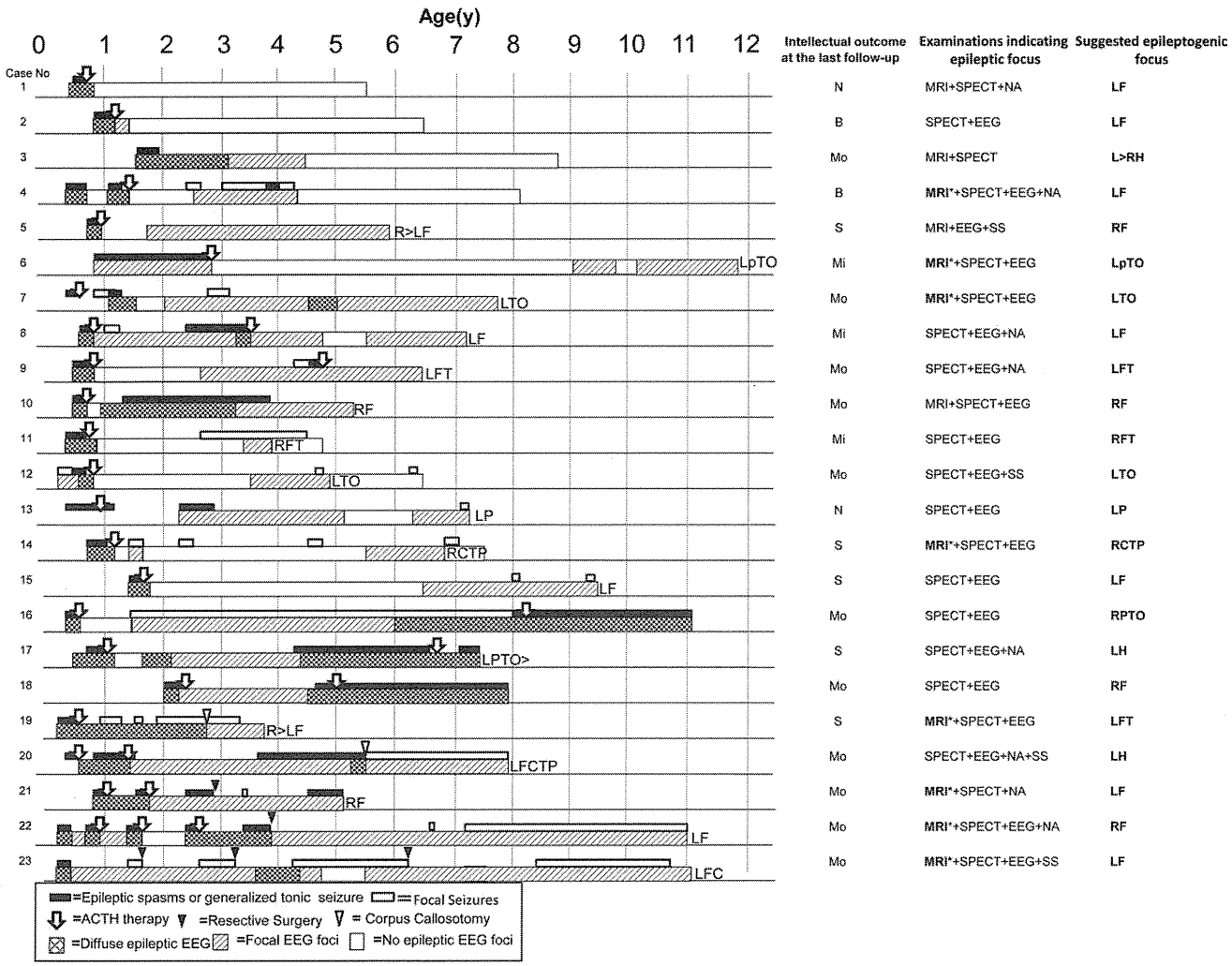

Fig. 1. The clinical and EEG courses of the 23 patients with fIS ($n = 23$). In the examinations indicating epileptic focus, bold-typed MRI* specified the presence of focal cortical dysplasia and hemimegalencephaly. *Abbreviations*: NA, Neurological abnormality; SS, Seizure semiology; RFT, Right frontotemporal EEG foci; LF, Left frontal EEG focus; pTO, posterior temporal and occipital EEG foci; LFC, Left frontocentral EEG foci; LP, Left parietal EEG focus.

Table 3
Developmental outcomes of patients with fIS and dIS during the final, follow-up period.

	fIS ($n = 23$)	dIS ($n = 46$)
Normal (IQ $\geqslant$ 80)	2 (9%)	7 (15%)
Borderline (IQ = 79 ~ 70)	4 (17%)	4 (9%)
Mild (IQ = 69 ~ 50)	8 (35%)	8 (17%)
Moderate (IQ = 49 ~ 35)	6 (26%)	7 (15%)
Severe (IQ $\leqslant$ 34)	3 (13%)	20 (43%)

present ILAE classification. The latter generally shows neurodevelopmental delay, neurological deficits and neuroimaging abnormalities, which indicates antecedent brain damage before the onset of IS [20]. Recent progress in neuroimaging modalities and an increase in subsequent, surgical intervention have shown that cortical malformations are important etiologies that underlie IS and focal refractory epilepsies. Furthermore, FCD appears to be a frequent cause of IS with focal features [13,15]. Clinical and EEG pictures of epilepsy associated with cortical malformation have been shown to be diverse, manifesting not only with IS and focal epilepsy but also with IS with focal features that later evolved into focal epilepsy [16,21]. A few case reports showed the presence of focal spasms in patients with fIS, indicating that focal cortical lesions can produce asymmetric ES [22,23]. There have also been several reports indicating that surgical success largely depended on the localized MRI lesion that was responsible for generation of the seizures [11,13,14]. Among patients with IS and epilepsy with ES, a patient with a localized PET lesion or a combination of PET and MRI lesions was shown to be the most ideal candidate for resective surgery [13,15,18,24,25].

However, the natural course of patients with these epilepsies who had not responded to medical treatment was not sufficiently investigated before considering

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epilepsy surgery. Previous long-term, clinical studies of IS or WS have shown that alteration of seizure type, relapse after ACTH therapy, and abnormal neurological findings are risk factors for poor seizure and mental outcomes [5,7]. Kramer et al. [10] identified 22 (33%) of 67 cases of patients with WS and more than two focal features, which was similar to our result (23/69 cases). This study concluded that focal features did not correlate with the age at the onset of and outcome of epilepsy, but these features were associated with etiology of WS. In another study, patients with WS and focal features were described to run a different clinical course as compared to those without focal features [9]. It was also suggested that patients who developed focal seizures during the clinical course of WS had FCD which was responsible for both ES in infancy and focal seizures in later period [21].

In this study, we compared various clinical factors between patients with and without focal features. However, we were unable to reveal any structural lesions or only found a subtle FLAIR signal intensity abnormality on the white matter using high-resolution MRI examinations in nearly two-thirds of our focal cases. It has been reported that a focal cortical perfusion abnormality in a SPECT study was not correlated with seizure and developmental outcomes [26]. Although EEG and SPECT examinations can only identify a focal functional abnormality, these tests predicted later focal EEG abnormalities and focal seizures in five of the six cases in our series. It has been shown that FCD type I has only trivial MRI structural abnormality, hence this defect may be difficult to visualize using MRI [24]. Thus, it appears to be difficult to estimate the exact extent of an epileptogenic lesion on a structural basis in most patients with focal features and to determine whether it may extend to an entire hemisphere or involve both hemispheres.

In our follow-up EEG examinations of the fIS-group, the interictal epileptic EEG abnormality changed considerably with progressing age after the initial treatment. Although the epileptic EEG abnormality was completely suppressed after ACTH treatment, it tended to initially emerge in the form of a focal epileptic EEG abnormality at the median age of 42 months and as late as 9 years of age, and this abnormality most frequently involved the frontal or fronto-centro-temporal regions. It gradually became active, extending either to one entire hemisphere, or even to the contralateral hemisphere, when the focal seizures tended to develop. The location of a cerebral lesion has been shown to determine, in part, the age at the onset of ES [21]; lesions affecting the posterior half of the brain often generate seizures at an earlier age than those affecting the anterior half [7]. Although this was not validated statistically in our study, a further study including a larger number of patients is needed.

In our case series, five patients underwent epilepsy surgery because repeated ACTH trials or ketogenic diet therapy had failed to control disabling seizures. All patients received benefits from the surgery, although none of them maintained a seizure-free state until the last follow-up period. Surgery for patients with IS and an MRI-based focal lesion has been encouraging based on the successful control of ES after the resection of a lesion [11,13,14]. However, because most reports described only the short-term outcomes and included a significant number of hemispherectomy cases, a long-term outcome study of patients with fIS and no hemiparesis is necessary to determine a precise indication for resective surgery.

Donat and Lo described that lateralized hypsarrhythmia, with or without asymmetric IS, occurred in the presence of bilateral structural lesions that were more abnormal in an area of greater EEG abnormality [27]. Thus, we could not rule out that our group of patients with fIS may have included those with epileptogenic lesions that were asymmetrically scattered in both hemispheres. In our series, approximately one-third of patients showed only a focal epileptic EEG abnormality, another one-third showed both a focal epileptic EEG abnormality and focal seizures, and the last one-third showed bilateral asymmetric EEG foci and disabling, either focal or generalized, seizures. Thus, it is reasonable that developmental outcomes were generally better in those with fIS than in those with dIS because the uninvolved hemisphere would have compensated for the developmental outcome. The developmental outcome would be further better in fIS group if cryptogenic IS were excluded from dIS. This result, together with those of previous studies, suggests the presence of a spectrum in the extent and intensity of cortical epileptogenesis in patients with IS. On one end of the spectrum is symptomatic IS with a unilateral, focal, discrete lesion; on the other end are bilateral, symmetrical, cerebral lesions; and various degrees of asymmetrical cerebral lesions exist between these two ends. Thus, in the two-thirds of the patients from our series who later showed a focal epileptic EEG abnormality and focal seizures, the localized epileptic focus became secondarily generalized during the infant period and was later localized again as the patient aged. The search for focal or lateralized features in patients with IS is practically important to predict seizure outcomes and to develop treatment strategies. This approach also allows physicians to search for the underlying etiology of the disorder and to make an etiological IS diagnosis (i.e., nonsymptomatic IS or symptomatic IS).

It was found that ACTH therapy for patients with fIS could bring a long-term seizure remission, irrespective of age. A few studies have been performed regarding ACTH therapy for patients with relapsed IS, ES without hypsarrhythmia, or Lennox–Gastaut syndrome [28]. The authors of these studies reported a favorable response to ACTH therapy regardless of patient age, even in

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patients with Lennox–Gastaut syndrome, if they had an immature, interictal epileptic EEG abnormality that was shared with hypsarrhythmia [25]. Thus, before considering surgical intervention, a second course of ACTH therapy should be utilized after a patient has relapsed following an initial ACTH trial. When resective surgery is being contemplated, the extent of the epileptogenic area should also be carefully evaluated; this area is expected to be much wider than the MRI lesion because of widespread involvement of the epileptic EEG abnormality.

Although the retrospective design of the study and relatively short observation periods limited the validity of our results, the clinical course of patients with fIS appeared distinctive from those with dIS. In conclusion, it is useful to classify those with IS into fIS and dIS based on various examinations because it provides practical information regarding the long-term outcome and treatment strategies for this challenging disorder.

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Chapter 65

Dravet syndrome (severe myoclonic epilepsy in infancy)

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INTRODUCTION

myoclonic epilepsy in infancy (SMEI; now known vet syndrome) was first described by Dravet and recognized by the International League Epilepsy as a syndrome in 1989 (Commission ssification and Terminology of the International Against Epilepsy, 1989). It is considered a rare with an incidence of less than 1 per 40 000 1990; Yakoub et al., 1992). As the knowledge epilepsy increases, the number of diagnosed likely is higher but it remains a rare disease. Re- Durá-Travé et al. (2007) found a rate of 1.4% in es of children aged < 15 years. It is characterized le and afebrile, generalized and unilateral, clonic -clonic seizures that occur in the first year of life otherwise apparently normal infant, without per- thological antecedents. They are later associated oclonus, atypical absences, and partial seizures. ure types are resistant to antiepileptic drugs. mental delay becomes apparent within the sec- r of life and is followed by definite cognitive im- and personality disorders. Many children have reported to have symptoms similar to SMEI but t myoclonias (Ogino et al., 1989; Dravet et al., Yakoub et al., 1992; Doose et al., 1998). These pa- may have different EEG features but they share e course and outcome as the patients with myo- s and present with the same syndrome, which s typical SMEI and borderline SMEI (SMEIB) et al., 2005). This is supported by genetic studies, have discovered an *SCN1A* gene mutation in s with and without myoclonias (Fukuma et al., Thus, it has been proposed to change its name avet syndrome." In the scheme proposed by the nal League Against Epilepsy (ILAE) (Engel, 2001) the Dravet syndrome is considered as an "epileptic encephalopathy," defined as "a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function." However, it is not proved that the cognitive decline observed in the first stage of the disease is mainly the consequence of the epilepsy.

The first neuropathological description of SMEI revealed microdysgenesis of cerebral cortex and cerebellum and malformation of the spinal cord (Renier and Renkawek, 1990) in a patient with no molecular genetics investigation, and no other such abnormalities have subsequently been reported. When they were performed, muscular and skin biopsies were negative (Guerrini and Dravet, 1998).

CLINICAL MANIFESTATIONS

The course of the epilepsy may be divided into three stages. The first stage is the "febrile stage." The onset happens in the first year of life, usually between 4 and 8 months, in an apparently normal baby who presents with one convulsive seizure, related or not (about 35%) to fever (infection, vaccination, etc.). Typically, it is a clonic seizure, either initially generalized, or starting in one part of the body and invading one entire side (hemiclonic seizure), or becoming generalized. Its duration is variable, often long, more than 15 minutes, sometimes evolving to a status epilepticus. It can be a focal, motor seizure, or a burst of myoclonic jerks which are not immediately recognized as epileptic in nature. EEG is usually normal as well as other investigations and this first seizure is considered as a complicated febrile seizure. Shortly after (2 weeks–2 months) other seizures occur, febrile or not, and are repeated, even in statuses, in spite of the anticonvulsive medication which is instituted

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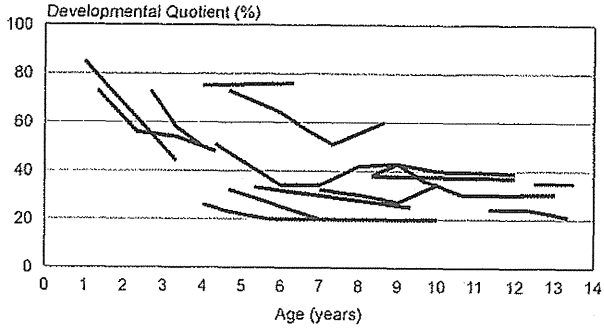

Fig. 65.1. Longitudinal neuropsychological data (global development quotient measured by the Brunet-Lézine scale, follow-up > 1 year) in 14 children. Reprinted with permission from Wolff et al. (2006).

at this time. Alternating hemiclonic seizures are the most characteristic ones. Rectal diazepam (DZ) is not always efficacious and the baby is frequently hospitalized.

The second stage is the "worsening stage". Different seizure types appear between 1 and 4 years: brief myoclonic seizures, atypical absences, with slight myoclonias and head nodding, more or less prolonged "obtundation status" (status with consciousness impairment of variable intensity), focal seizures, with motor (head deviation, stiffness or clonic jerks of one limb, hypotonia, etc.) and autonomic (pallor, flush, lip cyanosis, etc.) components, with or without loss of contact, and others that are difficult to classify. The psychomotor development becomes slower from the second year on (language, fine and gross motor skills). Attention disturbances, hyperactivity, and sometimes autistic features (stereotypies, poor eye contact) also appear. Figure 65.1 shows the decline in the developmental quotient during and after the second year of life, resulting from the stagnation of the psychomotor development, in 14 children studied by Wolff et al. (2006). Ragona et al. (2011) confirmed this decline but showed it was variable in degree of severity. Neurological signs are observed in some of the patients: ataxia (60%), moderate pyramidal signs (20%), and myoclonias (36%). This period with frequent seizures and statuses and behavioral deterioration lasts from the age of 1 year to that of 5 years approximately.

Usually after 5 years, the child enters the "stabilization stage": the convulsive seizures decrease and occur mainly in sleep, myoclonias and absences can disappear, and focal seizures persist or decrease. The psychomotor development and the behavior tend to improve but a cognitive impairment persists, which is variable among the patients.

EEG

The EEGs are often normal at the onset and progressively become abnormal but they change during the course of the epilepsy and there is not a typical EEG pattern as in the Lennox–Gastaut syndrome (LGS) for example. The interictal background activity is variable, either normal or slow. Paroxysmal activities consist of generalized spike-waves and polyspike-waves and focal and multifocal anomalies, during awake and sleep. Photosensitivity is frequent (more than 40%), sometimes early in the life, sometimes associated with pattern sensitivity. The ictal aspects depend on the seizure type: clonic, tonic–clonic, and hemiclonic seizures have no peculiarities (Dravet et al., 2005). Later on, the background may be either slow or normal. The generalized spike-waves tend to disappear whereas focal and multifocal anomalies persist. Photosensitivity is fluctuating, may disappear.

DIFFERENTIAL DIAGNOSIS

Since the first clonic seizures in SMEI are often associated with fever, distinction from febrile convulsions is important. In SMEI (1) the onset is early (before 1 year of age), (2) the seizure type is clonic and often unilateral instead of generalized tonic or tonic–clonic, (3) the seizure episodes are more prolonged and frequent, even when treated, and (4) the body temperature is not very high. The diagnosis can be established if other seizure types (myoclonic seizures – except in SMEIB – atypical absences, partial seizures, obtundation status) or photically induced spike-waves appear (Dravet et al., 2005).

Lennox–Gastaut syndrome (LGS) is virtually excluded by a history of febrile clonic seizures in the first year of life. Its characteristics are different: drop attacks, atypical absences, axial tonic seizures, and specific electroencephalographic abnormalities, with rapid, low-voltage rhythms during sleep. However, some patients with SMEI present with tonic seizures in the course of the disease. Usually they are different from those of the LGS. They are not repeated in clusters, often during night, and the interictal EEGs do not show the typical rapid rhythms. But a recent paper (Nabbout et al., 2008) reported a sleep EEG pattern resembling that of LGS in five adolescent patients, three of whom had febrile seizures, which could raise the question of an evolution to LGS. The authors agree that this was not the case and this aspect did not require a treatment shift to drugs which could aggravate the situation.

Difficulties may arise in differentiating SMEI from myoclonic–astatic epilepsy. In some cases of the latter, febrile convulsive seizures precede by several months nonfebrile atonic and myoclonic–astatic seizures which are the hallmark of the disorder. During the course of the epilepsy there are neither partial seizures nor focalization on the EEGs, and the main seizure type is myoclonic–astatic (Guerrini et al., 2005), whereas drop attacks are unusual in SMEI.