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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.

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

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

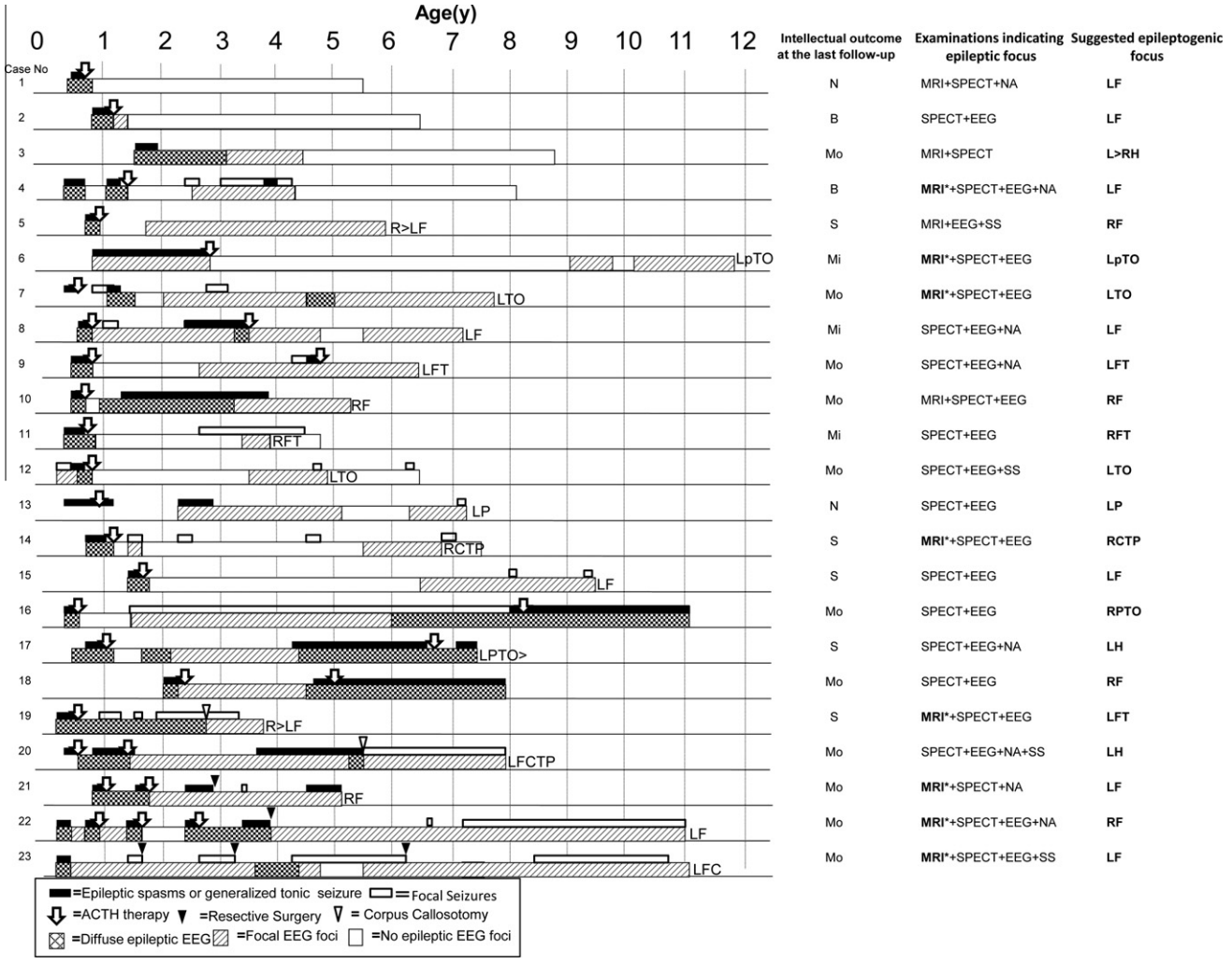

Fig. 1. The clinical and EEG courses of the 23 patients with fIS ($n = 23$). In the examinations indicating epileptic focus, bold-typed MRI* specified the presence of focal cortical dysplasia and hemimegalencephaly. *Abbreviations*: NA, Neurological abnormality; SS, Seizure semiology; RFT, Right frontotemporal 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 $\sim$ 70)	4 (17%)	4 (9%)
Mild (IQ = 69 $\sim$ 50)	8 (35%)	8 (17%)
Moderate (IQ = 49 $\sim$ 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

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

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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