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# Effect of adrenocorticotropic hormone therapy for epileptic spasms developing after the age of 1 year

Miho Fukui [a], Shuichi Shimakawa [a,*], Ichiro Kuki [b], Hisashi Kawawaki [b], Yukiko Mogami [c], Yasuhiro Suzuki [c], Sayaka Nakano [d], Takeshi Okinaga [d]

[a] Department of Pediatrics, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan
[b] Department of Child Neurology, Osaka City General Hospital, 2-15-16, Miyakojima Hon-Dori, Miyakojima-ku, Osaka 534-0021, Japan
[c] Department of Pediatric Neurology, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodocho Izumi, Osaka 594-1101, Japan
[d] Department of Pediatrics, Osaka University Graduate School of Medicine, 2-15 Yamadaoka Suita, Osaka 565-0871, Japan

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ABSTRACT

*Purpose:* Epileptic spasms sometimes begin after the first year of life, and such seizures are recognized as late-onset spasms (LOS). The prognosis of LOS is poor, and a treatment strategy has not been established. This study aimed to assess the short- and long-term effects of adrenocorticotropic hormone (ACTH) therapy for LOS.
*Methods:* We investigated the rate of LOS in 22 patients (14 boys and 8 girls) treated with ACTH therapy. The age at onset of LOS and at the start of ACTH therapy ranged from 12 to 94 months (median, $31.6 \pm 22.1$ months) and from 12.5 to 116 months (median, $37.5 \pm 23.7$ months), respectively. We investigated the response rate of LOS treated with ACTH therapy, and compared the clinical features between responders (short-term) and nonresponders.
*Results:* Nine (41%) of the 22 patients showed cessation of epileptic spasms within 3 months. The epileptic spasms ceased in four of these nine patients for more than 1 year. The age at onset of LOS was significantly associated with short-term seizure cessation ($p < 0.05$). Patients who achieved short-term cessation of seizures received ACTH therapy within 6 months from the onset of LOS.
*Conclusion:* ACTH therapy is a potentially effective treatment when started within 6 months from the onset of LOS. A younger age at onset of LOS is associated with a favorable outcome.


## 1. Introduction

Epileptic spasms are often the primary seizure manifestation in patients with West syndrome. These spasms are age-related and usually begin in the first year of life. However, epileptic spasms are not specific to West syndrome; in some cases, they occur after the first year of life. Epileptic spasms starting after the first year of life were recently recognized as late-onset spasms (LOS).[1–3]

Pharmacological treatment of infantile spasms requires adrenocorticotropic hormone (ACTH) therapy, which leads to remission in 50–80% of cases.[4] In contrast, the prognosis of LOS is poor,[1,2,5] even when drugs that are efficacious for the treatment of infantile spasms are used.

With regard to ACTH therapy for LOS, Eisermann et al. and de Menezes and Rho reported treatment results in only eight and four patients of their series, respectively.[2,6] Oguni et al. indicated that ACTH therapy is worth attempting for patients with LOS without hypsarrhythmia.[7] However, interictal electroencephalography (EEG) of all 10 patients with LOS in the study of Oguni et al. showed no hypsarrhythmia. Interictal EEG can show hypsarrhythmia in LOS.[1,3] Therefore, the effect of ACTH therapy on LOS remains unclear.

This study aimed to assess the effect of ACTH therapy on LOS. We used ACTH therapy in 22 patients with LOS and retrospectively analyzed the effect of ACTH therapy among these patients.

## 2. Methods

We retrospectively analyzed the medical records and interictal EEG and/or video EEG data of 52 patients with epileptic spasms occurring after the age of 12 months between 1997 and 2012 at Osaka Medical College Hospital, Hirakata Municipal Hospital,

*Abbreviations:* ACTH, adrenocorticotropic hormone; Cortrosyn-Z, zinc hydroxide suspension of tetracosactide acetate; EEG, electroencephalography; LOS, late-onset spasms.

* Corresponding author. Tel.: +81 726 83 1221; fax: +81 726 84 5798.
*E-mail address:* ZVQ10523@nifty.com (S. Shimakawa).

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Osaka University Hospital, Osaka Medical Center and the Research Institute for Maternal and Child Health, and Osaka City General Hospital. We excluded patients without ACTH treatment. As a result, 22 patients (14 boys and 8 girls) treated with ACTH therapy at these hospitals were enrolled in the present study. The onset of epileptic spasms ranged from the age of 12 to 94 months (median, 31.6 ± 22.1 months). All patients, except for one patient, underwent ictal video-EEG, which confirmed the presence of epileptic spasms. The remaining patient was diagnosed by an expert child neurologist who directly observed the patient's attack. The presumed etiologies of epilepsy were a genetic cause (CASK gene mutation, $n = 1$) and structural/metabolic causes ($n = 15$; post-encephalopathy [$n = 6$], cortical dysplasia [$n = 5$], chromosomal disorder [$n = 2$], giant arachnoid cyst [$n = 1$], and mitochondrial disorder [$n = 1$]). However, the etiology of epilepsy was unknown in the remaining patients ($n = 6$), despite the presence of severe psychomotor development disorder (Table 1).

ACTH therapy was started at the age of 12.5–116 months (median, 37.5 ± 23.7 months). Synthetic ACTH (a zinc hydroxide suspension of tetracosactide acetate [Cortrosyn-Z]) at a dose of 0.0125–0.025 mg/kg was injected every day or every other day for 2 weeks (maximum, 3 weeks). This dose was then tapered during the subsequent 1 or 2 weeks until discontinuation in a portion of the patients. The total dose of ACTH in each patient is shown in Table 2. The mean follow-up period was 49.6 ± 42.2 months (range, 6–166 months) after the ACTH therapy. Other antiepileptic drugs were administrated before ACTH therapy in all of the patients, except for one patient. The mean number of other drugs administered was 3.95 ± 3.50. ACTH therapy was performed more than once in three patients (two times, $n = 2$; three times, $n = 1$).

First, to ensure that there were no differences in the clinical characteristics between patients with LOS undergoing ACTH therapy and those with LOS not undergoing ACTH therapy, the clinical features (sex, underlying type of cause, age at onset, number of patients with other types of seizures, number of patients with clusters of epileptic spasms, and number of patients with hypsarrhythmia) were compared between both groups of patients. Clinical features were analyzed at the first treatment of ACTH therapy in the patients who underwent multiple ACTH treatments, and subsequent analyses were performed in the same manner.

To evaluate the clinical characteristics of patients with LOS undergoing ACTH therapy, we analyzed the following clinical data for each patient: sex, etiology, age at onset, other seizure types at onset of epileptic spasms, ACTH treatment lag, interictal and ictal EEG before and after ACTH therapy (just after ACTH therapy and at the last follow-up), antiepileptic drugs before ACTH therapy, total dose of ACTH, effect of ACTH therapy, duration of follow-up period, and mental outcome. To evaluate the effect of ACTH therapy on LOS, the timing of assessment was divided into the following two groups: (i) seizure cessation for 3 months after ACTH therapy (short-term effect) and (ii) seizure cessation for 12 months after ACTH therapy (long-term effect). The rate of seizure cessation in each period was then analyzed. Because two patients who were followed up for less than 12 months (6 and 8 months) after ACTH therapy were included in this study, we evaluated the long-term effect of therapy in the remaining 20 patients.

To identify the clinical features of responders, the patients were divided into the following two groups: (i) seizure cessation for 3 months (cessation group) and (ii) seizure persistence or relapse within 3 months (persistent group). The following data were then compared between the cessation and persistent groups: age at onset of LOS, underlying type of cause, interictal EEG findings, ACTH treatment lag, and total dose of ACTH. Furthermore, the effect of ACTH therapy was compared between treatments starting within 6 months from onset and 6 months after onset of LOS. The underlying type of cause was divided into genetic or structural/metabolic cause and unknown cause. We then investigated whether the presence of obvious etiology affected the efficacy of ACTH therapy.

Statistical analysis was performed using the Mann–Whitney $U$ test for comparison of age at onset between the patients with and those without ACTH therapy, as well as for comparison of age at onset, treatment lag, and dose of ACTH between the cessation and persistent groups. Differences in the other clinical data between groups were analyzed using Fisher's exact test. A $p$ value of $<0.05$ was considered statistically significant.

**Table 1**
Clinical data of the patients with LOS.

| | ACTH therapy (+) $n = 22$ | ACTH therapy (−) $n = 30$ |
|---|---|---|
| Gender (male/female) | 14/8 | 18/12 |
| Underlying type of cause | Genetic ($n = 1$)<br>Structural/metabolic ($n = 15$)<br>Unknown cause ($n = 6$) | Genetic ($n = 0$)<br>Structural/metabolic ($n = 23$)<br>Unknown cause ($n = 7$) |
| Age at onset of LOS (months) | 31.6 ± 22.1 | 46.2 ± 33.1 |
| With other seizures (%) | 8 (36.4%) | 8 (26.7%) |
| With cluster (%) | 22 (100%) | 23 (76.7%) |
| Hypsarrhythmia (%) | 7 (31.8%) | 8 (26.7%) |

LOS, late-onset infantile spasms.

## 3. Results

### 3.1. Characteristics of patients with ACTH therapy

None of the clinical features were significantly different between patients with and those without ACTH therapy (Table 1).

### 3.2. Effect of ACTH therapy

With regard to the short-term effect of ACTH therapy, nine (41%) of the 22 patients showed cessation of seizures, whereas the remaining 13 patients exhibited a poor response. With regard to the long-term effect of ACTH therapy, four of 20 patients achieved cessation of epileptic spasms. However, one of the four patients developed partial seizures 2 months after ACTH therapy. All of the remaining four patients experienced relapse of their epileptic spasms. Focal seizures also occurred in addition to epileptic spasms in two of the four patients, and tonic seizures occurred in addition to epileptic spasms in the remaining one patient. Epileptic spasms and other seizures did not cease in these three patients, despite the administration of antiepileptic drugs.

Before ACTH treatment, interictal EEG showed hypsarrhythmia in seven patients and diffuse high-voltage slowing (diffuse slow-wave discharges) associated with diffuse spike-wave discharges, temporofrontal spikes, or bilateral frontal spikes in one patient each. In the remaining 12 patients, interictal EEG showed diffuse spikes in two of 12 patients and focal abnormalities in 10 of 12 patients, with relatively preserved background activity. Among the patients with focal EEG epileptic abnormalities, these abnormalities were located in the frontal region ($n = 5$), temporal or temporofrontal region ($n = 3$), temporal and occipital regions ($n = 1$), and bilateral occipital and frontal regions ($n = 1$).

These EEG abnormalities disappeared just after ACTH therapy in five patients. EEG showed hypsarrhythmia in three of these five patients and bilateral temporofrontal spikes and frontal spikes in one patient each before ACTH therapy. Subsequently, epileptic EEG

**Table 2**
Clinical data of individual patients with LOS.

| No. | Gender | Etiology | Age at onset of LOS (mo) | Other seizure types | Antiepileptic drugs before ACTH therapy | Treatment lag of ACTH therapy | Interictal EEG (before ACTH therapy) | Total dose of ACTH (mg/kg) | Short term effects | Long-term effects (follow-up >1 year) | Residual EEG abnormality (just after ACTH therapy) | Follow-up period (months) | Residual EEG abnormality (last follow-up) | Mental outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male | Leigh encephalopathy | 18 | | VPA | 1 mo | Hypsarrhythmia | 0.175 | + | + | – | 81 | – | Se |
| 2 | Male | Down syndrome | 16 | | VPA | 4 mo | Hypsarrhythmia | 0.175 | + | + | Bi) F spike | 26 | – | Se |
| 3 | Female | Encephalopathy | 12 | CPS | LTG, CZP, TPM, VPA | 2 w | L) F spike | 0.175 | + | + | – | 30 | L) F spike | Se |
| 4 | Male | Psychomotor retardation | 30 | | VPA, TPM | 3 mo | L) F, R) mT spike | 0.175 | + | + | Bi) F spike | 30 | Bi) F spike | Se |
| 5 | Male | Psychomotor retardation | 12 | CPS | VPA,LTG,PB, GBP | 1 mo | L) T, R) O spike | 0.175 | + | – | Bi) P spike | 48 | L) pT-O-P, R) pT-P-O poly spike | Se |
| 6 | Male | Hypoxic–ischemic encephalopathy, biliary atresia | 12 | | ZNS, VPA, TPM | 6 mo | DSW, Bi) F–T spike | 0.175 | + | – | – | 40 | Diffuse spike | Se |
| 7 | Female | Focal cortical dysplasia | 18 | | VPA, CLB, TPM | 6 mo | R) F spike | 0.1125 | + | – | R) F spike | 40 | R) F spike | Se |
| 8 | Male | Mental retardation, autism | 62 | Myoclonic seizure | VPA | 3 mo | Bi) F spike | 0.21 | + | – | L) T spike | 58 | Diffuse spike | Se |
| 9 | Male | Cortical dysplasia | 17 | | VPA, ZNS | 4 mo | Hypsarrhythmia | 0.175 | + | N.D. | R) O spike | 6 | R) O spike | Se |
| 10 | Male | Chromosome disorder Dandy–Walker syndrome | 65 | | VPA | 3 mo | DSW, diffuse spike | 0.175 | – | – | Bi) F spike | 16 | Bi) F spike | Se |
| 11 | Female | Psychomotor retardation | 34 | CPS | VPA | 1 mo | Hypsarrhythmia | 0.175 | – | – | Diffuse spike | 12 | R) F spike | Se |
| 12 | Male | Focal cortical dysplasia | 12 | | – | 5 mo | Hypsarrhythmia | 0.175 | – | – | – | 118 | Diffuse spike | Se |
| 13 | Male | Focal cortical dysplasia | 14 | | VPA, CLB, B6 | 3 mo | Hypsarrhythmia | 0.175 | – | – | – | 137 | Diffuse spike | Se |
| 14 | Female | CASK gene mutation | 17 | | VPA | 2 mo | R) F, Bi) mT spike | 0.175 | – | – | L) O spike | 34 | Bi) O spike | Se |
| 15 | Female | Hemorrhagic shock and encephalopathy | 20 | | PB, VPA, PHT, ESM, ZNS, LTG, TPM | 9 mo | Bi) F spike | 0.14 | – | – | Diffuse spike | 50 | Diffuse spike | Se |
| 16 | Male | Hemiconvulsion hemiplegia epilepsy syndrome | 29 | Myoclonic seizure CPS | VPA, CLB, CBZ, ZNS, LTG, PRM, TPM, B6, ST, GBP, LEV, CLZ | 27 mo | Bi) F–T spike | 0.5 | – | – | Bi) F spike | 16 | Diffuse spike | Se |
| 17 | Male | Focal cortical dysplasia | 30 | | VPA, CLB | 9 mo | Diffuse spike | 0.175 | – | – | Diffuse spike | 44 | Diffuse spike | Se |
| 18 | Female | PRES | 34 | | VPA, CLB, TPM | 3 mo | Bi) F spike | 0.175 | – | – | Diffuse spike | 23 | Diffuse spike | Mild |
| 19 | Male | Arachnoid cyst | 36 | | VPA, CZP, ZNS, B6, NZP | 12 mo | Diffuse spike | 0.3 | – | – | Diffuse spike | 166 | L) C–P spike | Se |
| 20 | Female | Psychomotor retardation | 42 | GTC | CBZ, VPA, CLB, ESM, CLZ, ZNS, B6, PHT | 10 mo | DSW, Bi) F spike | 0.175 | – | – | L) F spike | 89 | Diffuse spike | Se |
| 21 | Male | Hemiconvulsion hemiplegia epilepsy syndrome | 72 | Myoclonic seizure CPS | CZP, ESM, PHT, ZNS, CLB, TPM, CBZ, ST, LEV, AZA, NZP, GBP, LTG | 44 mo | R) F, Bi) O spike | 0.34 | – | N.D. | R) F spike | 8 | R) F spike | Se |
| 22 | Female | Mental retardation | 94 | CPS | VPA, ZNS, LTG, CLB, LEV, ESM | 8 mo | Hypsarrhythmia | 0.5 | – | – | Hypsarrythmia | 18 | Hypsarrythmia | Borderline |

AZA, acetazolamide; B6, vitamin B6; Bi), bilateral; C, central; CBZ, carbamazepine; CLB, clobazam; CLZ, clorazepate; CPS, complex partial seizure; CZP, clonazepam; DSW, diffuse slow wave; ESM, ethosuximide; F, frontal; GBP, gabapentin; L), left; LEV, levetiracetam; LOS, late-onset infantile spasms LTG, lamotrigine; mo, months; mT, midtemporal; NZP, nitrazepam; O, occipital; P, parietal; PB, phenobarbital; PHT, phenytoin; PRES, posterior reversible encephalopathy; PRM, primidone; pT, post temporal; R), right; Se, severe; ST, sulthiame; T, temporal; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

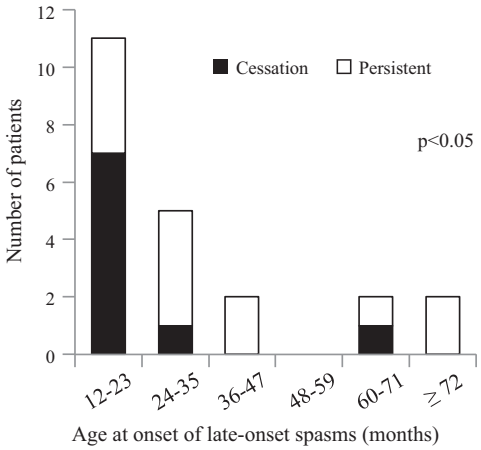


**Fig. 1.** Age at onset of LOS. The age at onset of LOS was significantly related to cessation of short-term seizures.

abnormalities were apparent during the follow-up period in four of the five patients. At the last follow-up, these epileptic EEG abnormalities disappeared after ACTH therapy in two patients. Although a residual epileptic EEG abnormality was identified in the frontal region just after ACTH therapy in one of these two patients, this abnormality disappeared 12 months after ACTH therapy. This patient achieved seizure cessation for more than 12 months. Epileptic EEG abnormalities before ACTH therapy were characterized by hypsarrhythmia in seven patients. Although this hypsarrhythmia disappeared in six of these seven patients after ACTH therapy, the interictal EEG after ACTH therapy was normal in only two patients; diffuse spikes and focal spikes were identified in the remaining two patients each. Hypsarrhythmia presented in only one patient without change after ACTH therapy at the last follow-up. Diffuse slow-wave discharges changed into a preserved background. Therefore, ACTH therapy was also effective for diffuse slow-wave discharges.

### 3.3. Clinical characteristics of responders

The age at onset of LOS in the persistent group (38.4 ± 23.6 months) was significantly higher than that in the cessation group (21.9 ± 15.1 months, $p < 0.05$) (Fig. 1). ACTH treatment lag did not show a significant difference between the persistent group (10.2 ± 11.8 months) and the cessation group (3.17 ± 1.94 months) (Fig. 2). However, all of the patients in the cessation group received ACTH therapy within 6 months after the onset of LOS. Patients who received ACTH therapy within 6 months from the onset of LOS

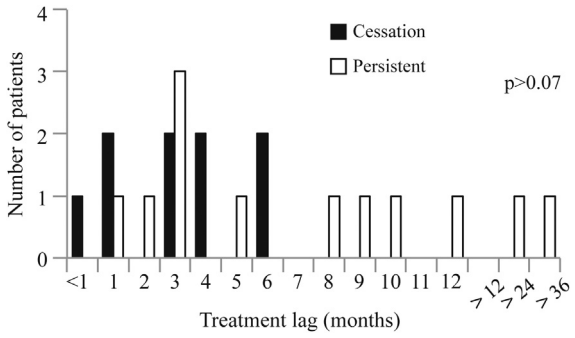


**Fig. 2.** Treatment lag was not associated with short-term cessation.

**Table 3**
Response to therapy according to treatment lag.

| | Cessation ($n = 9$) | Persistent ($n = 13$) |
|---|---|---|
| Within 6 months from onset | 9 | 7 |
| After 6 months from onset | 0 | 6 |

**Table 4**
Response to therapy according to etiology.

| | Cessation ($n = 9$) | Persistent ($n = 13$) |
|---|---|---|
| Genetic or structural/metabolic cause | 6 | 10 |
| Unknown cause | 3 | 3 |

reached short-term cessation of epileptic spasms at a significantly higher rate than those who received ACTH therapy more than 6 months from the onset of LOS (Table 3, $p < 0.02$). A total of 66.7% of LOS patients had genetic or structural/metabolic causes in the cessation group, and 76.9% of LOS patients had genetic or structural/metabolic causes in the persistent group. The rate of patients with an obvious etiology was not significantly different between the persistent group and the cessation group (Table 4). In the short term, interictal EEG showed hypsarrhythmia in three patients in the cessation group and four patients in the persistent group. Additionally, in the short term, interictal EEG showed focal epileptic EEG abnormalities excluding symmetrical bilateral EEG foci in four patients in the cessation group and two patients in the persistent group. The response to ACTH therapy was not significantly different between patients with and without hypsarrhythmia and focal features of epileptic EEG abnormalities. The total amount of ACTH administered was not significantly different between the persistent group (0.25 ± 0.12 mg) and the cessation group (0.172 ± 0.0237 mg, Fig. 3). However, in eight of nine patients, LOS ceased at an ACTH dose of less than 0.175 mg/kg (corresponding to 0.0125 mg/kg/day of ACTH injected every day for 2 weeks), whereas LOS persisted in all of the patients with an ACTH dose higher than 0.35 mg/kg (corresponding to 0.25 mg/kg/day of ACTH injected every day for 2 weeks).

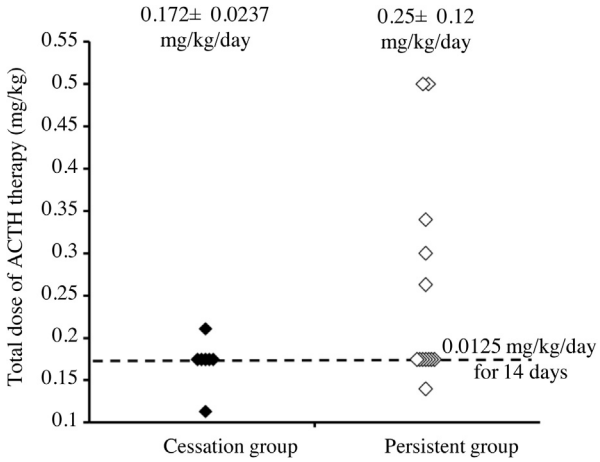


**Fig. 3.** Total ACTH dose was not different between the short-term cessation group and the persistence group. Solid squares indicate patients who achieved short-term cessation. Open squares indicate patients with persistent LOS.

## 4. Discussion

The prognosis of LOS is poor,[2] and a treatment strategy has not been established. In previous studies, the effect of ACTH therapy for LOS was evaluated in a small numbers of patients.[2,7] This is the first study on the effect of ACTH therapy on LOS. Nine (41%) of the 22 patients showed cessation of seizures within 3 months. At the last follow-up, four patients had achieved cessation of epileptic spasms for more than 1 year.

### 4.1. Effect of ACTH on epileptic spasms

With regard to infantile spasms, the epileptic spasm and hypsarrhythmia response rate to synthetic ACTH ranges from 42% to 76% in patients.[8,9] The efficacy of ACTH therapy for epileptic spasms persisting beyond infancy and epileptic spasms starting to occur after the first year of life is controversial. de Menezes and Rho found that conventional anticonvulsants (ACTH therapy and vigabatrin) were often ineffective in completely controlling unusual epileptic spasms.[6] Eisermann et al. described a favorable effect of ACTH therapy in only one of four patients.[2] Oguni et al. analyzed the effect of ACTH therapy for epileptic spasms without hypsarrhythmia.[7] In seven of 10 patients, epileptic spasms ceased for 3 months (short-term cessation) after ACTH therapy.[7] Although only six of these 10 patients could be followed up for more than 1 year, one of these six patients achieved freedom from seizures. In three of these six patients, only epileptic spasms disappeared, but other seizures developed.[7] In our study, nine (41%) of the 22 patients showed cessation of seizures within 3 months. Four (20%) of 20 patients achieved cessation of epileptic spasms for more than 1 year. During the follow-up period (30–81 months from ACTH therapy), three patients achieved freedom from seizures. The number of cases with unknown causes in the study of Oguni et al. is greater than that in our study, but the rate of patients who achieved freedom from seizures in our study is similar to that of Oguni et al. Although the response rate to ACTH was lower in patients with LOS than those with infantile spasms, 20% of patients with LOS achieved cessation of epileptic spasms and 15% of patients with LOS achieved freedom from seizures. Therefore, ACTH therapy is worth attempting in patients with LOS.

Hydrocortisone is also known to be effective for patients with LOS.[2] Seven of 21 patients achieved cessation of LOS with unknown causes. Because our study involved cases with an obvious etiology, it is difficult to compare the efficacy between ACTH and hydrocortisone. Further studies are required to determine whether hydrocortisone is more effective than ACTH therapy for LOS.

### 4.2. Effect of ACTH on interictal EEG

Interictal EEG showed hypsarrhythmia in seven patients. Eisermann et al. reported that no patients with LOS with an unknown cause had hypsarrythmia.[2] However, in the series of Auvin et al., one of three patients who developed LOS with unknown causes had hypsarrythmia.[3] In our series, two of seven patients with unknown causes had hypsarrhythmia. Therefore, electroclinical features are varied in patients with LOS with unknown causes.

Hypsarrhythmia was shown to disappear in 80% of patients with infantile spasms by synthetic ACTH therapy, regardless of the ACTH dose.[10] In our study, hypsarrhythmia disappeared in six of seven (85.7%) patients with LOS after ACTH therapy. The rate of disappearance of hypsarrhythmia in LOS is similar to that of infantile spasms. At the last follow-up period after ACTH treatment, epileptic EEG abnormalities disappeared in two of 22 patients, and these patients achieved freedom from seizures for more than 1 year. In a previous study, epileptic EEG abnormalities disappeared at 3 months in half of patients with LOS without hypsarrhythmia.[7] However, the subsequent interictal EEG findings were not provided in this previous study. ACTH therapy might be effective for interictal EEG abnormalities in patients with LOS. Further investigation of long-term EEG changes after ACTH therapy is required.

### 4.3. Clinical features of responders

#### 4.3.1. Age at onset

In the present study, a younger age at onset of LOS was significantly associated with a favorable outcome. For epileptic spasms developing in patients with West syndrome, the age at onset does not affect the final outcome.[11,12] Because patients with LOS usually have refractory epilepsy and no therapeutic strategy has been suggested, epileptic spasms developing as LOS are more refractory to antiepileptic drugs than are epileptic spasms developing as West syndrome.[1–4] The results of the present study provide the first evidence that age at onset of LOS affects outcome. However, the reason why a younger age at onset of LOS is associated with a favorable outcome remains unknown. The persistence of epileptic spasms may be a reflection of central nervous system (CNS) maturity.[13] This raises the possibility that patients who develop LOS at an older age have more severe developmental disorders and unchanged CNS maturity. However, in our study, all of the patients had severe developmental disorders, regardless of whether LOS achieved short- or long-term cessation. With regard to the presumed etiology of epilepsy, the rates of patients with encephalopathy, cortical dysplasia, and chromosomal disorders were not different between the cessation and persistent groups. Therefore, we could not determine whether drug-refractory LOS was related to CNS maturity.

#### 4.3.2. Treatment lag

In infantile spasms, a short treatment lag (less than 1 month) is associated with a good response to ACTH therapy.[14] Among patients with Down syndrome, those with infantile spasms with a treatment lag of less than 2 months have earlier treatment responses than those with a treatment lag of more than 2 months.[15] However, the difference in the treatment lag for hydrocortisone therapy is not related to cessation of LOS.[2] In the present study, significantly more patients who received ACTH therapy within 6 months from LOS onset achieved short-term cessation than those who received ACTH therapy more than 6 months from the onset of LOS. Therefore, ACTH therapy should be performed within 6 months from the onset of LOS.

#### 4.3.3. Characteristics of interictal EEG

Among patients with infantile spasms, seizure relapse occurs in patients with focal EEG epileptic abnormalities more frequently than in those without focal EEG abnormalities.[16] However, in our study, the response to ACTH therapy was not significantly different between patients with and those without focal epileptic EEG abnormalities. In a previous report, ACTH therapy was effective for patients with LOS without hypsarrhythmia.[7] Therefore, interictal EEG results before ACTH therapy cannot predict the disappearance of LOS after ACTH therapy.

#### 4.3.4. Underlying type of cause of LOS

Whether the underlying type of cause of LOS affects the efficacy of ACTH therapy for infantile spasms is controversial. The underlying type of cause did not affect the efficacy of ACTH therapy for infantile spasms in previous reports.[17,18] However, the long-term outcome (1 year) of seizures after ACTH therapy for infantile spasms in the unknown cause group was more favorable than that of the genetic or structural/metabolic cause group in the

series of Hamano et al.[19] In our study, the underlying type of cause of LOS did not affect the response to ACTH therapy. As described above, in seven of 10 patients, epileptic spasms ceased in the short-term after ACTH therapy in the study of Oguni et al.[7] However, only three cases with obvious etiologies were included in their study. Further investigation of the outcome of LOS with obvious etiology after ACTH therapy is required.

#### 4.3.5. Dose of ACTH therapy

The total amount of ACTH was not significantly different between the cessation and persistent groups. Eight of nine patients in the cessation group responded to less than 0.175 mg/kg of ACTH (corresponding to 0.0125 mg/kg/day injected every day for 2 weeks), and none of the patients treated with more than 0.35 mg/kg of ACTH (corresponding to 0.25 mg/kg/day injected every day for 2 weeks) achieved short-term cessation. In patients with infantile spasms, the daily dose of synthetic ACTH was not shown to influence the seizure outcome.[20] However, Oguni et al. suggested that epileptic spasms without hypsarrhythmia might require a larger dose of ACTH (0.0125–0.05 mg/kg/day injected every day for 2–3 weeks) than epileptic spasms of West syndrome.[7] Seven of 10 patients with LOS in the study of Oguni et al. achieved cessation of seizures within 3 months after ACTH therapy,[7] whereas only one of six patients with LOS achieved cessation of seizures after 1 year. Although a larger dose of ACTH for the treatment of LOS might be more effective in the short term, the rate of freedom from seizures for more than 1 year after ACTH treatment was not different between the study of Oguni et al. and our study. Further evaluation is required to elucidate the appropriate dose of ACTH for the treatment of LOS.

## 5. Conclusions

We assessed the effect of ACTH treatment for LOS among 22 patients. Nine (41%) of these 22 patients showed cessation of epileptic spasms within 3 months. Four (20%) of 20 patients achieved cessation of epileptic spasms for more than 1 year. With regard to the short-term effect of ACTH, a younger age at onset of LOS was significantly related to a favorable outcome. ACTH therapy is potentially effective if performed within 6 months from the onset of LOS.

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