Original article

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Clinical features and electroclinical evolution in 22 cases with epileptic spasms without hypsarrhythmia

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ABSTRACT – *Aim.* This study aimed to investigate the general presentation of epileptic spasms without hypsarrhythmia (ESwoH) and retrospectively determine whether there are differences in treatment effects related to ACTH therapy, long-term seizure outcome, and evolution of EEG features according to pre-treatment EEG patterns.
Methods. According to the pattern of background activity, we divided our cohort into two groups: Group 1: normal background activity or with localized intermittent slow waves; Group 2: intermittent slow waves appearing generalized or in two or more lobes. Subjects included 22 children (Group 1: *n*=10; Group 2: *n*=12) diagnosed with ESwoH who received treatment from 2007 to 2017.
Results. The median age at onset of epileptic spasms was 5.5 months and the follow-up period lasted for 40.5 months. ACTH therapy was performed for seven patients from Group 1 and eight patients from Group 2. Only one patient from Group 2 responded to ACTH. Patients receiving effective treatments at early stages had excellent seizure outcome. Refractory cases included six patients in Group 1 and eight patients in Group 2; subsequent follow-up EEGs indicated hypsarrhythmia in one patient in Group 1 (17%) and six patients (75%) in Group 2, including one patient whose EEG pattern indicated progression to Lennox-Gastaut syndrome.
Conclusions. Overall, ACTH is ineffective for patients with epileptic spasms without hypsarrhythmia. The EEG may indicate possible future development of hypsarrhythmia if epileptic spasms are resistant to treatment, especially in patients with diffuse slow waves on pre-treatment EEG. The efficacy of treatment introduced at early stages from onset may predict long-term seizure outcome.

Key words: adrenocorticotropic hormone, electroencephalogram, hypsarrhythmia, infantile spasms, treatment, West syndrome

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According to the classification of seizure types proposed by the International League against Epilepsy (ILAE) in 2017, epileptic spasms (ES) are classified into three types: generalized, focal, and unknown onset. Although ES are the primary seizure manifestation of infantile spasms, patients with focal epilepsies also present ES during infancy. Caraballo *et al*. (2003) first reported a case characterized by a series of ES without hypsarrhythmia (ESwoH) in 2003 and Lux and Osborne (2004) presented the clinical entity of this condition, but its clinical features are still unclear. Some patients have been shown to respond to treatment, while others were resistant to the administered drugs. This drug resistance occurs in cases of refractory epilepsy, similar to some cases of ES with hypsarrhythmia including West syndrome (Caraballo *et al*., 2011). This type of ESwoH includes several forms of focal epilepsies with clinical features that are very similar to those of West syndrome. In previous studies, the characteristics of the EEG findings included various forms of electrical patterns, from hypsarrhythmia to almost normal electrical activities (Caraballo *et al*., 2003, 2011; Oguni *et al*., 2005). Neurophysiologically, hypsarrhythmia was thought to be associated with an increased EEG coherence at long inter-electrode distances (Burroughs *et al*., 2014) and is likely generated subcortically (Siniatchkin *et al*., 2007; Japaridze *et al*., 2013). We suspected that the prognosis and response to treatment may differ based on the neurofunctional connections in the early stages of this condition. This potential association was not considered in previous studies. Moreover, there are few published studies addressing the evolution of EEG in ESwoH patients. In this study, we investigated the general presentation of ESwoH and also retrospectively determined whether there are differences in treatment effects related to ACTH therapy, long-term seizure outcome and evolution of EEG features between the two groups with or without diffuse slow waves based on pre-treatment EEG.

Methods

The subjects included 22 children diagnosed with ESwoH and receiving treatment in the Division of Neurology, Saitama Children's Medical Center from 2007 to 2017. We classified the patients into two groups according to background activities based on pre-treatment EEG as follows: Group 1: normal background activity or limited to regional intermittent slow waves; Group 2: intermittent slow waves appearing diffused or in two or more lobes. Examples of the EEGs are presented in *figure 1*. With regards to epileptic discharges, focal or multi-foci epileptic discharges were visible in both groups. The EEG pattern for hypsarrhythmia is characterized by very high-voltage and irregular, asynchronous slow waves with intermixed multifocal independent epileptiform discharges (Gibbs, 1952). Interictal EEG recordings were performed in all patients during sleep Stages 1-2, because sleep is known to enhance the characteristics of hypsarrhythmia. Ictal EEG recordings were attempted in all patients and 18 patients showed ES on ictal video-EEGs, thus confirming the ictal manifestations and EEG patterns. In the remaining four cases, more than two epileptologists confirmed ictal manifestations of the attacks by direct observation or by videos taken by caregivers. ES were identified as brief (<two-second) axial contractions, appearing in clusters. Interictal EEGs were obtained for all patients before treatment. When several recordings were taken prior to treatment, the most recent recording was used as the pre-treatment recording for the patient. Interictal EEGs were recorded a number of times during the follow-up period and analysed three times at: three to six months, one to two years, and three to four years from the start of treatments at early stages.

Magnetic resonance imaging (MRI) was conducted for all patients to identify any structural abnormality. The patients' clinical data, including gender, age at onset of ES, other seizures prior to ES, aetiology, follow-up period, and response to treatment (including ACTH therapy), were investigated and analysed retrospectively.

The efficacy of treatment was evaluated based on the frequency of spasms and other seizures. Effective treatments and good response to treatments were defined as the resolution of all seizures, including ES, for more than a few months following initiation of treatment.

Results

General characteristics

A total of 22 patients were included in this study and divided into Group 1 (10 patients) and Group 2 (12 patients). *Table 1* presents the patients' characteristics and efficacy of the treatments. The median age at onset of the ES was 5.5 months in both groups. The median follow-up period was 40.5 months (range: 14-132) in Group 1 and 45 months (range: 14-136) in Group 2. The pre-treatment EEGs that were used to allocate patients to the different groups were evaluated at a median of seven months (range: 2-17) in Group 1 and six months (range: 3-41) in Group 2. The average period of latency between pre-treatment EEGs and the age at onset of ES was 1.3 months in Group 1 and 1.2 months in Group 2. Half of the patients in Group 1 and 3/12 cases in Group 2 experienced other seizures before or at almost the

Table 1. Clinical features and treatment of the 22 patients with epileptic spasms without hypsarrhythmia.

Patient/ Gender	Aetiology	Age at onset of ES (months)	Follow-up period (months)	Other seizure type	Effective treatments	Ineffective treatments	Seizure outcome
Group 1							
1/M	Unknown	2	44	-	ZNS	B6, TRH, IVIG, ACTH	Free for 34 m
2/F	Chromosomal aberration: 1p21del, 3q13del	11	16	PS (tonic seizure)	VPA	-	Free for 11 m
3/F	Hypoplasia of cerebellar vermis (Leprechaunism)	6	113	PS (tonic seizure, motion arrest)	PB, VPA	TPM, ACTH, LTG	Free for 94 m
4/F	Focal cortical dysplasia (L-T, P, O)	1	27	PS (eye deviation to R and motion arrest)	Surgery (left posterior disconnection)	VPA, IVIG, B6, ACTH, PB	Free for 22 m
5/F	Focal cortical dysplasia (R-F, C, T)	4	47	-	-	ACTH, IVIG, TRH, PB	Daily
6/F	Unknown	16	32	-	-	ACTH, VPA, CZP, PB, B6	Weekly/spasms
7/F	Aicardi syndrome	2	34	PS (tonic seizure)	-	B6, ACTH, IVIG, VPA, ZNS, LEV, CZP, KD	Daily/spasms
8/F	Polycystic encephalomalacia	5	14	-	-	ZNS	Daily/spasms
9/F	*CDKL5* mutation	3	132	PS (tonic seizure)	-	ACTH, VPA, ZNS, B6, CLB, CBZ	Daily/tonic
10/M	Subdural hematoma	9	61	-	-	B6, VPA, CZP, LTG, TPM	Unknown

Table 1. Clinical features and treatment of the 22 patients with epileptic spasms without hypsarrhythmia *(continued)*.

Patient/ Gender	Aetiology	Age at onset of ES (months)	Follow-up period (months)	Other seizure type	Effective treatments	Ineffective treatments	Seizure outcome
Group 2							
1/M	Unknown	3	37	-	ACTH	B6	Free for 25 m
2/M	Unknown	10	76	-	B6	-	Free for 87 m
3/F	Unknown	39	31	PS (oral automatism +motion arrest)	VGB	ACTH, CBZ, CLB	Free for 20 m
4/F	Polymicrogyria around perisylvian fissure and in L-O	5	14	-	PB	B6, VGB	Free for 12 m
5/F	Dandy-Walker syndrome, colpocephaly	5	70	-	-	B6, ACTH	Daily/tonic
6/M	Microcephaly, polymicrogyria	4	37	-	-	B6, ACTH, VPA	Daily/spasms, tonic
7/M	Cerebral and cerebellar atrophy	12	136	-	-	VPA	Daily/spasms, clonic
8/F	Congenital hydrocephaly	6	94	-	-	VPA	Daily/spasms, tonic
9/M	Schizencephaly	4	53	-	-	B6, IVIG, ACTH	Monthly/tonic
10/F	Ulegyria (R-P, O)	6	94	-	-	B6, IVIG, ACTH	Monthly/tonic
11/M	Unknown	35	17	PS (eye deviation to R, sGTC)	-	B6, ACTH, VGB	Daily/spasms, tonic, atonic
12/M	Multiple congenital anomaly	4	18	PS (tonic seizure)	-	B6, ACTH, VGB	Daily/spasms

ACTH: adrenocorticotropic hormone therapy; B6: vitamin B6; PS: partial seizure; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; F: frontal; L: light; IVIG: intravenous immunoglobulin; KD: ketogenic diet; LEV: levetiracetam; LTG: lamotrigine; O: occipital; P: posterior; PB: phenobarbital; R: right; sGTC: secondary generalized tonic-clonic seizure; T: temporal; TPM: topiramate; TRH: thyrotropin-releasing hormone; VPA: valproic acid; VGB: vigabatrin; ZNS: zonisamide; m: month.

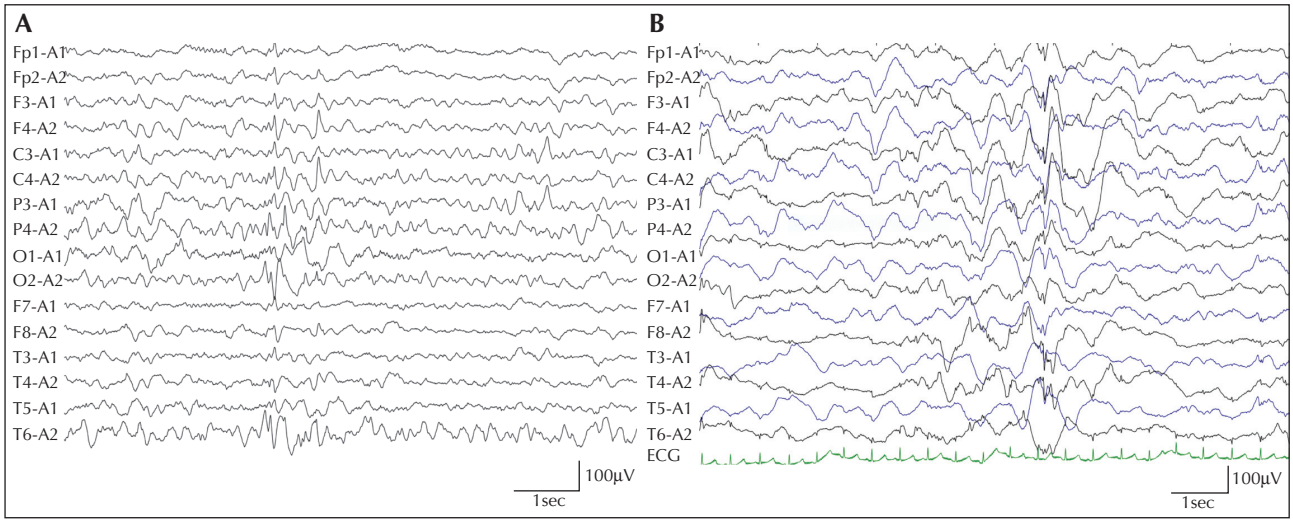

Figure 1. Interictal EEG recording before treatment showing (A) slow waves intermingled with paroxysmal spikes in the right occipitotemporal region and paroxysmal spikes in the left parietal region (Group 1; Patient 9), and (B) high-voltage diffuse slow waves with multi-focal spikes (Group 2; Patient 5).

same time as the onset of ES, which were mostly partial seizures with motor components. Structural involvement of the cerebral region was found in six of the patients of Group 1 and eight patients of Group 2. An unknown aetiology was determined for two patients in Group 1 and four patients in Group 2. ACTH therapy was initiated for seven patients of Group 1 and eight patients of Group 2, and only one patient (Group 2; Patient 1) with unknown aetiology responded to ACTH; there were no responders in Group 1. One patient (Group 2; Patient 5) showed a partial response to ACTH; the spasms of this patient disappeared, leaving only partial seizures. Three patients in Group 1 showed effectiveness of the antiepileptic drugs (AEDs), sodium valproate (VPA) and zonisamide (ZNS), and a combination of VPA and phenobarbital (PB) in one case. Two of the patients were initially given other treatments, including ACTH (*table 1*), but showed no improvement. In Group 2, AEDs included vigabatrin (VGB) and PB, as well as vitamin B6 which was effective in one case. Epilepsy surgery involving posterior disconnection was performed for only one patient (Group 1; Patient 4), resulting in resolution of the condition and diagnosis of the seizures.

Long-term seizure outcomes

The seizure outcomes were excellent in patients of both groups who showed a good response to the given treatments at early stages of epilepsy. However, when the effects at early stages were only partial or temporary, the seizure outcome was poor and the epilepsies developed into refractory conditions. At the last follow-up visit, in Group 1, spasms were reported in three patients, tonic seizures in one, and both spasms and tonic seizures in one patient. In Group 2, spasms were only noticed in one patient, tonic seizures in three, spasms and tonic seizures in two, and spasms and clonic seizures in one. Lennox-Gastaut syndrome (LGS) with tonic seizures, atypical absences, and spasms developed in one patient (Group 2, Patient 11) (*table 1*).

EEG findings before treatment and during subsequent follow-up

Table 2 shows the findings of interictal and ictal EEG recordings before treatment at early stages and at three timepoints during subsequent follow-up. In Group 1, the background activity of interictal EEG was either normal or limited to regional intermittent slow waves in six patients (*table 2*). Six patients (60%) had focal or regional epileptic discharges. In Group 2, intermittent slow waves on pre-treatment interictal EEGs showed a diffuse pattern in all but one patient (Patient 11) and appeared periodically in six. Ten patients (83%) showed multi foci epileptic paroxysmal discharges. Of the four patients in Group 1 (Patients 1-4) who responded to treatment, two patients showed normal EEGs at three to six months and one patient had a normal EEG after one year. The remaining patient underwent surgery involving left posterior disconnection, and her subsequent EEGs on the remaining brain section became normal. In all four cases who responded to treatment, the abnormal EEG findings included intermittent slow or paroxysmal discharges which disappeared after a year. In Group 2, all of the four responders (Patients 1-4) had normal interictal

Table 2. EEG findings before treatment and during subsequent follow-up, and seizure outcome.

Patient/gender	Ictal EEG findings	Interictal EEG findings before treatment	Subsequent EEG findings		
			At 3-6 months	At 1-2 years	At 3-4 years
Group 1					
1/M	DSW	Multifocal spikes, fast waves, focal slow	Normal	Normal	-
2/F	DSW preceding R-P, pT spikes	Bil T,P,O spikes, focal slow	Normal	-	-
3/F	DSW	Normal	Bil F spikes	Normal	Normal
4/F	DSW	L-P, O spikes, focal slow waves, R-C, P spikes and fast wave	L-T, P, O spikes, R-C, P spikes	L-O, pT sharps, diffuse slow, R-P spikes,	-
5/F	DSW preceding R-F, C spikes	R-C,mT slow, spikes	R>L F, C, T spikes, diffuse HVS with fast wave, with periodicity	L-aT spikes, polyspikes, HVS with periodicity	L-aT spikes and polyspikes, periodic HVS
6/F	-	R-F spikes, fast waves	R-F spikes, diffuse HVS	Multifocal and polymorphic discharges	-
7/F	DSW	Multifocal spikes, focal slow, fast waves, with periodicity	Hypsarrhythmia	Hypsarrhythmia	-
8/F	R-F, C HVS	R-C, mT sharps,	R-O, pT spikes	R-C, O,mT, pT spikes, DIS	-
9/F	DSW	R-P, pT, L-O spikes	Bil.O polyspikes and HVS, periodic HVS with Bil O spikes	Bil O, F spikes, diffuse fast waves	R-O, pT Bil F spikes, DIS
10/M	-	Multifocal spikes, fast waves, focal slow, with periodicity	-	-	-

Table 2. EEG findings before treatment and during subsequent follow-up, and seizure outcome *(continued)*.

Patient/gender	Ictal EEG findings	Interictal EEG findings before treatment	Subsequent EEG findings		
			At 3-6 months	At 1-2 years	At 3-4 years
Group 2					
1/M	DSW	L-P, O > F, R-F, pT, DIS, with periodicity	Normal	Normal	-
2/M	-	Multifocal spikes and fast wave, DIS, with periodicity	Normal	Normal	-
3/F	DSW	Multifocal spikes of Bil F, O predominance, DIS, with periodicity	Normal	R-P,O L-P, mT,pT spikes	-
4/F	DSW with L-O predominance	Bil O (L>R), R-F,mT, L-pT, with periodicity, DIS	Normal	Normal	-
5/F	DSW with alternative hemispheric predominance	Multifocal spikes, DIS	Bil F spikes, DIS	L-F, aT,mT spikes, Bil F slow	L-P,mT, R-P spikes
6/M	DSW with Bil O predominance	Continuous fast waves in Bil P,O, DIS	Bil O spikes, poly spikes, HVS	Hypsarrhythmia	-
7/M	-	Fast waves and spikes in L-P, O, DIS, with periodicity	-	Hypsarrhythmia	Hypsarrhythmia
8/F	Electrical decremental activity	Multifocal spikes and fast waves in L-P,O, R-mT,pT, DIS	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia
9/M	EEG no change	Multifocal spikes of Bil P,O predominance, DIS in Bil C,P,O	L-P, O, pT, R-pT spikes, slow	Hypsarrhythmia	Hypsarrhythmia
10/F	DSW preceding R-C, P spikes	Multifocal spikes and fast waves of Bil P,O predominance, DIS	R-P, pT, L-C spikes, polyspike, slow	L-F, R-P spikes	L-F, Bil P, R-pT spikes
11/M	DSW with fast wave in Bil F, mT	HVS in Bil F predominance, Bil F,C,P spikes and slow	Bil F, C spikes, diffuse slow	Bil F, C slow spike wave, diffuse slow (LGS)	-
12/M	DSW	Polymorphic spikes and slow in Bil C, P, DIS, with periodicity	Bil O spikes, poly spikes with HVS	Hypsarrhythmia	-

Bil: bilateral; DIS: diffuse intermittent slow waves; DSW: diffuse slow waves; HVS: high-voltage slow waves ; LGS: Lennox Gastaut Syndrome; mT: mid temporal; pT: posterior temporal.

EEG after three to six months. Only one patient (Patient 3) showed regional paroxysmal epileptic discharges on the one-year follow-up EEG, but did not present any intermittent slow waves.

With regards to the evolution of EEG of the non-responders in Group 1 (Patients 5-9), one patient developed persistent hypsarrhythmia (Patient 7) after three months from initial treatment, while the other four patients showed paroxysmal discharges with a predominance in the frontal or occipital regions. These findings remained the same at the one to two-year recordings. Two patients underwent EEG after three years; high-voltage slow waves on background activity with focal or multi foci paroxysmal discharges were observed, which were different from those observed with hypsarrhythmia (*figure 2*). In Group 2, hypsarrhythmia developed in five of the eight non-responders. One patient acquired hypsarrhythmia within three to six months and four patients acquired hypsarrhythmia within one to two years. Hypsarrhythmia remained after three to four years in three patients who were followed for more than three years. One patient (Group 2; Patient 11) developed LGS after the one-year follow-up period. Six of the eight non-responders (75%), including the patient with LGS, demonstrated epileptic encephalopathy of West syndrome or LGS based on subsequent follow-up EEGs.

Discussion

We classified patients into two groups based on the appearance of slow waves according to pre-treatment EEG recordings. Among the patients with diffuse intermittent slow waves on pre-treatment EEG (Group 2), progression to hypsarrhythmia or LGS was demonstrated in 75% non-responders based on subsequent EEGs. Siniatchkin *et al*. (2007) analysed epileptiform discharges and the slow waves of hypsarrhythmia separately, using simultaneous recordings of EEG and functional MRI. The authors demonstrated that multifocal interictal spikes caused cortical activation and slow wave activity that produced hypsarrhythmia-specific activation in the cortex and subcortical structures such as the brainstem, thalamus, and putamen. Shrey *et al*. (2018) examined the functional networks of patients with ES using cross-correlation techniques and evaluated the functional connectivity before and after treatment. The authors reported that the connectivity strength increased in non-responders. In our study, half of the patients of Group 2 had periodic diffuse intermittent slow waves on pre-treatment EEGs. Since the appearance of periodicity is suggestive of an association with a subcortical structure (Kuroiwa and Celesia, 1980), we therefore suspected that those cases may already have a functional connectivity even without hypsarrhythmia.

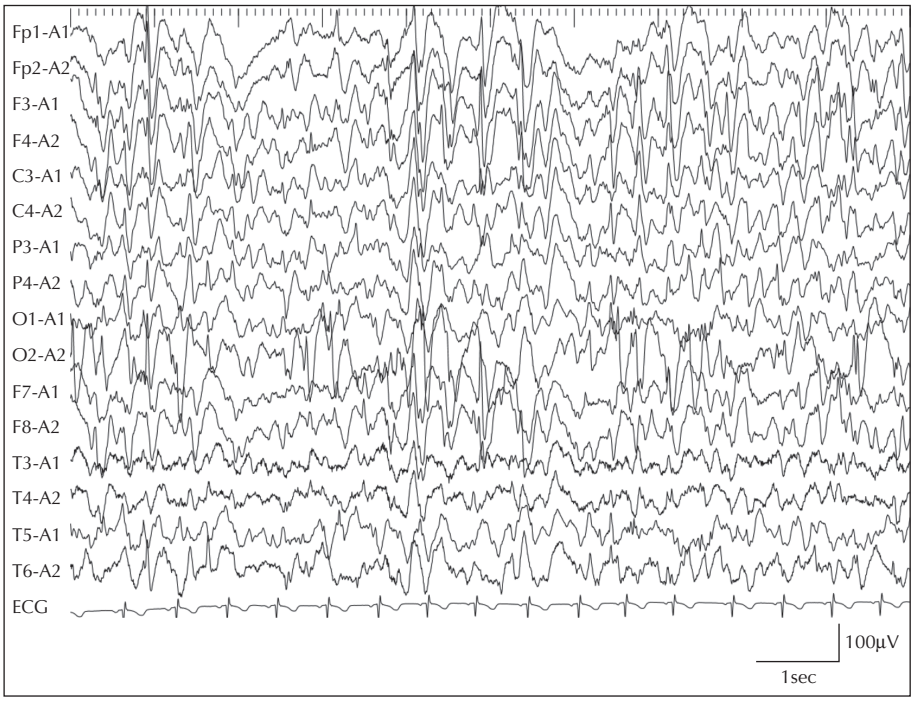

Figure 2. Interictal EEG recordings after three years (Group 1; Patient 9), showing high-voltage multi-focal spikes and diffuse slow waves with right occipital predominance.

The increased strength over time, as a result of frequent attacks, results in the progression of clinical symptoms to epileptic encephalopathy. In patients of Group 1, even though non-responders except one did not develop hypsarrhythmia, subsequent follow-up EEGs indicated a change in intermittent slow waves, from a focal to a diffuse or periodic pattern. The type of seizure at the last follow-up visit consisted mainly of ES. ES themselves are thought to be caused by attacks involving the subcortical networks (Chugani *et al*., 1992) and the connectivity with subcortical structures may gradually strengthen with continued attacks. The diffuse and/or periodic appearance of intermittent slow waves may be a key finding in determining the existence or increase in connections to subcortical structures.

In this study we analysed 22 patients with ESwoH. In terms of treatment, only one patient (5%) responded to ACTH therapy and six patients (including a patient taking VGB) responded to AEDs (27%) who became seizure-free. Compared to the efficacy of treatment for ES with hypsarrhythmia including West syndrome (Demarest *et al*., 2017), the response rate of ACTH therapy was low and lower than that of AEDs in this study. Demarest *et al*. (2017) reported, based on an observational cohort study, that first-line treatment (VBG, prednisolone, ACTH) was by far the most important variable in determining likelihood of response to treatment of ES with or without hypsarrhythmia. The authors stated that hypsarrhythmia was not a determinant of the response to treatment and was therefore not predictive of a response to first-line therapy. Twenty-seven of 81 cases (33%) of ESwoH responded to first-line therapy in their study. In contrast to this study, there were no patients taking prednisolone in our study, and fewer patients were administered VGB since it only became available from March 2016 in Japan. Oguni *et al*. (2005) retrospectively analysed the short- and long-term effects of ACTH therapy in 30 patients with ESwoH. ACTH therapy regimen was efficacious in 63% of patients over short-term periods and 29% over long-term periods. Additionally, ACTH therapy is a valid therapeutic alternative in patients with resistant ES. These authors referred to paroxysmal discharges of interictal EEGs, but not to their background activities. We believe that a larger number of patients is needed to obtain conclusive evidence.

Our results show that long-term seizure outcomes were excellent in responders to treatments at early stages in both groups, but poor and unmanageable in non-responders. Callaballo *et al*. (2011) presented 16 patients with ESwoH; five patients with unknown aetiology responded to treatment and eventually became seizure-free. The remaining non-responding 11 patients became refractory to treatment. When patients do not respond to treatments at early stages, the seizure outcome may be unfavourable and the condition may progress to intractable epilepsy or ES with hypsarrhythmia. The patients in this study demonstrated a large variety of imaging abnormalities including acquired and congenital brain defects, and some with genetic epileptic encephalopathies. Although, certainly, these background factors could become more predictive of long-term seizure outcome, initial response to treatments could also be an important element in determining seizure outcome.

Conclusion

We retrospectively analysed clinical features and EEG evolution of patients with ESwoH. All patients, apart from one, were unresponsive to ACTH therapy, and seizure outcomes of patients who were resistant to all treatments at early stages were unfavourable. For patients with diffuse intermittent slow waves based on pre-treatment EEG, who were refractory to all treatments, hypsarrhythmia could develop based on subsequent follow-up EEGs. The efficacy of treatment at early stages may predict long-term seizure outcome, while the regional or diffuse intermittent slow wave appearance on pre-treatment EEG may predict subsequent EEG evolution in patients with ESwoH. □

Diclosures.
None of the authors have any conflict of interest to declare.

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