

## Distinguishing Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion from Prolonged Febrile Seizures by Acute Phase EEG Spectrum Analysis

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### ABSTRACT

**Background** To differentiate the features of electroencephalography (EEG) after status epilepticus in febrile children with final diagnosis of either febrile seizure (FS) or acute encephalopathy for an early diagnosis.

**Methods** We retrospectively collected data from 68 children who had status epilepticus and for whom EEGs were recorded within 120 h. These included subjects with a final diagnosis of FS ( $n = 20$ ), epileptic status (ES;  $n = 11$ ), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD;  $n = 18$ ), mild encephalopathy with a reversible splenial lesion (MERS;  $n = 7$ ), other febrile encephalopathies ( $n = 10$ ), hypoxic-ischemic encephalopathy ( $n = 1$ ), and intracranial bleeding ( $n = 1$ ). Initially, all EEGs were visually assessed and graded, and correlation with outcome was explored. Representative EEG epochs were then selected for quantitative analyses. Furthermore, data from AESD ( $n = 7$ ) and FS ( $n = 16$ ) patients for whom EEG was recorded within 24 h were also compared.

**Results** Although milder and most severe grades of EEG correlated with neurological outcome, the outcome of moderate EEG severity group was variable and was not predictable from usual inspection. Frequency band analysis revealed that solid delta power was not significantly different among the five groups (AESD, MERS, FS, ES and control), and that MERS group showed the highest theta band power. The ratios of delta/alpha and (delta + theta)/(alpha + beta) band powers were significantly higher in the AESD group than in other groups. The alpha and beta band powers in EEGs within 24 h from onset were significantly lower in the AESD group. The band powers and their ratios showed earlier improvement towards 24 h in FS than in AESD.

**Conclusion** Sequential EEG recording up to 24 h from onset appeared to be helpful for distinction of AESD from FS before emergence of the second phase of AESD.

**Key words** acute encephalopathy; acute encephalopathy with biphasic seizures and late reduced diffusion (AESD); electroencephalography; febrile seizure; spectrum analysis

The term acute encephalopathy (AE) encompasses various etiologies with acute insult to the brain and clinical manifestations of seizures, impaired consciousness and other neurological symptoms. This includes bacterial meningitis, viral encephalitis, hypoxic-ischemic encephalopathy (HIE), head injury, cerebrovascular disorders, and encephalopathies secondary to hepatic or renal failure.<sup>1,2</sup> Among others, AE as a complication of common viral (rarely bacterial) infections often affects young children and causes death or severe neurological sequelae. This subgroup of AE is a main cause of acute cerebral injury in Japan.<sup>3,4</sup> Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is

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Abbreviations: AE, acute encephalopathy; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; CNS, central nervous system; DQ, development quotient; EEG, electroencephalogram; ES, epileptic status; FFT, fast Fourier transform; FS, febrile seizure; HHS, hemiconvulsion-hemiplegia syndrome; HIE, hypoxic-ischemic encephalopathy; IQ, intelligence quotient; MERS, mild encephalitis/encephalopathy with a reversible splenial lesion; MRI, magnetic resonance imaging

the most frequent subtype,<sup>3,5</sup> characterized by no abnormalities on magnetic resonance imaging (MRI) at the disease onset, and evolution of second phase of encephalopathy following 4–7 days of latent period, accompanied by reduced diffusion due to cytotoxic edema.<sup>6–8</sup> It is often difficult to identify which patient represents the first phase of AESD, and which just manifests with a prolonged febrile seizure (FS) with favorable outcome. Given that a sustained increase in excitatory transmitters play a role in the provocation of second phase in AESD,<sup>8</sup> early initiation of treatment may lead to a better outcome. Therefore, early diagnosis of AESD is desirable for decision of treatment strategy that possibly prevents or ameliorates the second phase of AESD to improve the prognosis of this burden for previously healthy children.

Electroencephalogram (EEG) during the acute phase of AE shows diffuse slowing and attenuation/ flattening in encephalopathy due to various etiologies,<sup>1,9</sup> including AESD.<sup>10,11</sup> However, it is not easy to distinguish AE from prolonged FS or infection-induced epileptic status (ES), because diffuse delta activities are also often seen in these conditions for a few days after seizure onset.<sup>10,11</sup> The aim of this study was to examine whether qualitative analysis of EEGs during acute phase of AEs was able to predict the prognosis, and specifically to find any findings that distinguish EEGs of AESD from those of other disorders including FS and ES, through quantitative EEG analysis by using fast Fourier transform (FFT).

## SUBJECTS AND METHODS

### Subjects

This study enrolled children who manifested with acute symptoms of status epilepticus (SE) and impaired consciousness, who was referred to Tottori University Hospital, Shimane University Hospital, Seirei-Hamamatsu Hospital, Shimane Prefectural Central Hospital, Kyushu University Hospital, Kagoshima University Hospital, Matsue Red-Cross Hospital, Tsuyama Central Hospital, and Saitama Children's Medical Center between December 2001 and June 2014. Clinical data including the EEG tracings were retrospectively collected. SE was defined as any seizure > 30 min or a series of recurrent seizures beyond 30 min. In a narrow sense, AE in this study was defined according to the previously proposed criteria<sup>3–5</sup>: i) acute onset of impaired consciousness accompanied by seizures during a febrile infection; ii) exclusion of well-defined central nervous system inflammation, head trauma, cerebrovascular disease, toxic encephalopathy, and systemic and metabolic diseases and iii) normal cell count in CSF and negative viral and bacterial culture of CSF samples. AE subtypes were classified into AESD, acute necrotizing encephalopathy (ANE), hemiconvul-

sion-hemiplegia syndrome (HHS), Reye-like syndrome, and clinical mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) according to the previous reports.<sup>4,12,13</sup> Sixty-eight patients (mean age  $\pm$  SD;  $3.5 \pm 3.1$ , 38 males and 30 females) were identified, including 34 patients with AE, 20 with FS, and 11 with ES, 1 with hypoxic-ischemic encephalopathy (HIE), and 1 with intracranial bleeding (Table 1). All of these patients underwent EEG recording during acute periods. A control group ( $n = 13$ , aged  $4.8 \pm 3.2$  years, M:F = 8:5) was also selected whose EEG were recorded in Tottori University Hospital. They showed normal development without previous history of AE or other brain injuries; simple FS in 6, attention deficit hyperactivity disorder in 2, headache in 2, benign infantile convulsion in 1, breath holding spell in 1, shuddering attack in 1.

The study protocol was approved by institutional review boards.

### EEG recordings

Seventy two EEGs of 20–30 min were recorded in 68 patients during the acute phase, at period of 1–120 h (mean  $\pm$  SD;  $21 \pm 25$ ) from the onset of neurological illness. For the 4 patients (2 AESD and 2 FS) with repeated EEG recordings, the initial ones were used for visual and quantitative analyses. EEGs were recorded during sleep or unconsciousness state after antiepileptic injections; those at later periods up to 120 h were recorded during sleep induced by sedative agents. Electrodes were placed according to the international 10–20 system using at least 13 EEG channels (Fp1, Fp2, F3, F4, Cz, C3, C4, P3, P4, O1, O2, T3 and T4). Ground electrodes were attached to the forehead (Fpz). EEG data with bipolar montages were used for visual assessment and spectrum analysis to avoid the influence by artifacts due to body movements involving the scalp and earlobe electrodes. Recordings were carried out using the Neuropack EEG system (Nihon-Koden, Tokyo, Japan) and signals were downsampled at 1 kHz, then EEG was resampled at 200 or 500 Hz and stored on the hard disk for analysis. The sensitivity was set at  $10\mu\text{V/mm}$  with low-frequency filter of 0.5 Hz, high-frequency filter of 60 Hz. The notch filter was used at 60 Hz for data from western districts of Japan and at 50 Hz for data from eastern districts. Patients who had been evaluated for burst suppression and epileptiform activity (periodic or rhythmic spikes, sharp waves, spike-waves) were excluded in this study.

### Visual EEG assessment

EEG patterns used for power spectrum analysis were classified into five grades by an epileptologist (YM) who was blind to the clinical information, according to the

**Table 1. Clinical characteristics of the patients**

Patient	age of onset	Sex	Diagnosis	Accompanying symptoms and/or infectious agents identified	EEG from the onset (h)	Therapy for neurological symptom	Prognosis
1	3 y 7 m	M	AESD	–	44	DZP, MDZ	Most Severe (in -hospital death)
2	5 y 2 m	M	AESD	–	2	MDZ, PB	Most Severe (in -hospital death)
3	5 y 4 m	F	AESD	Fever, vomiting	33	DZP	Severe
4	11 m	F	AESD	Exanthema subitum	34	DZP, MDZ	Severe
5	1 y 5 m	F	AESD	Influenza	120	DZP, PB	Severe
6	1 y 1 m	M	AESD	Exanthema subitum	20	DZP, MDZ	Severe
7	1 y 11 m	M	AESD	Bronchitis	1	None	Moderate-mild
8	2 y 11 m	M	AESD	Influenza	2	None	Moderate-mild
9	1 y 10 m	M	AESD	Influenza	20	DZP, MDZ	Moderate-mild
10	1 y 4 m	M	AESD	Upper respiratory infection	66	fPHT	Moderate-mild
11–18	8 m–5 y	4 M/4 F	AESD	Exanthema subitum, gastroenteritis (Rotavirus), fever, nasal discharge, unclassified	1 to 101	DZP, MDZ, PB, fPHT, propofol or none in 5	Normal
19–25	1 y 0 m–9 y 0 m	5 M/2 F	MERS	Influenza, gastroenteritis (Rotavirus), adenovirus, fever, clouding of consciousness	3 to 39	DZP, MDZ, fPHT or none	Normal
26	11 m	F	Reye-like syndrome	Exanthema subitum	5	DZP	Most Severe (in -hospital death)
27	1 y 8 m	M	Reye-like syndrome	Upper respiratory infection	3	DZP, MDZ	Normal
28	8 m	M	ANE	Upper respiratory inflammation	77	DZP, PB	Normal
29	4 y	M	HHS	Influenza	3	fPHT, vitamin compounds	Normal
30–35	2 m–11 y 6 m	3 M/3 F	AE (unclassified)	Fever, vomiting	8 to 34	DZP, MDZ, TPL, PB, or none in 2	Severe
36	1 y 7 m	F	HIE	–	11	None	Most severe
37	1 y 4 m	M	Intracranial bleeding	Upper respiratory inflammation	19	PB	Most severe
38–57	11 m–9 y 3 m	9 M/11 F	FS	Influenza, upper respiratory inflammation, fever	1 to 105	DZP, MDZ, TPL, PB, or none in 4	Normal
58–68	1 y 3 m–16 y 11 m	6 M/5 F	ES	–	0.5 to 101	DZP, MDZ, or none in 1	Normal

–: symptoms other than fever and neurological manifestations were absent and no infectious agents were identified, AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; DZP, diazepam; ES, epileptic status; F, female; fPHT, fosphenytoin; FS, febrile seizure; HHS, hemiconvulsion-hemiplegia syndrome; HIE, hypoxic ischemic encephalopathy; M, male; m, month(s); MDZ, midazolam; MERS, mild encephalitis/encephalopathy with a reversible splenic lesion; PB, phenobarbital; none, no medication; TPL, thiopental; y, year(s).

scale reported by Synek et al.<sup>9</sup>: Grade 1; normal or mild abnormality with alpha activity but little, scattered theta activity, Grade 2; mild signs of encephalopathy with dominant activity in the theta frequency range, with some alpha and delta waves, Grade 3; moderate signs of encephalopathy characterized by dominant widespread delta activity, regular or irregular, with little activity in other frequency range, Grade 4; severe signs of encephalopathy with epileptiform discharges or with low-output EEG, Grade 5; signs of vegetative encephalopathy with frequent isoelectric EEG. The EEG data with bipolar montages (Fp1-F3, Fp2-F4, F3-C3, F4-C4, C3-P3, C4-P4, P3-O1 and P4-O2) were analyzed.

### Quantitative EEG analysis

For the quantitative analyses, EEG power spectrum was calculated with a fast Fourier transform (FFT) by the MATLAB software, R2013 student version (The MathWorks, Natick, MA). A representative, artifact-free five 5-second epochs were selected from each record and was averaged before absolute FFT. We excluded sudden deflection, such as epileptiform discharges and vertex sharp transients. Subsequently, the power spectrum was calculated for frequencies between 0.5 and 60 Hz with frequency step of 0.4 Hz in sampling 200 Hz and 0.2 Hz in sampling 500 Hz, and then averaged across the following bands: delta (0.5–3.9 Hz), theta (4.0–7.9 Hz),

alpha (8.0–12.9 Hz), beta (13.0–19.9 Hz), and gamma (20.0–39.9 Hz) frequency bands. The ratios of different EEG frequency bands reported by Stewart J et al<sup>14</sup>: the delta-alpha ratio (the delta band power divided by the alpha band power) and the (delta + theta)/(alpha + beta) ratio (the sum of delta plus theta band power divided by the sum of alpha plus beta band power) were also evaluated to enhance the identification of increased power of slow waves and decreased power of faster waves. These power values were averaged in each etiology group, i.e. AESD, FS, MERS, ES and controls, and used for analysis. We then selected patients with AESD ( $n = 7$ ) and FS ( $n = 16$ ) for whom EEGs were recorded within 24 h from onset, and compared the quantitative data to clarify whether any difference are present between these groups. In addition to the aforementioned FFT variables in average, we illustrated the temporal distribution of the variables through the 24 h, as well as the evolution in the 4 patients for whom EEGs were re-examined within 24 h.

### Neurological sequelae in clinical prognosis

The intellectual (IQ) or development quotient (DQ) later in the chronic phase was assessed in each patient by the Enjoji or Tanaka-Binet developmental scales. Neurological sequelae were graded into 4 categories: most severe; in-hospital death during acute periods, clinical brain death or vegetative state with brainstem dysfunction, severe;  $IQ/DQ < 35$ , moderate-mild;  $IQ/DQ = 35-69$ , and normal;  $IQ/DQ \geq 70$ .

### Statistical analysis

The EEG power spectra of each etiology group were analyzed using the Tukey way after using Kruskal-Wallis test. The proportion of patients for whom individual anticonvulsive agents in each etiology group, i.e. AESD, FS, MERS and ES was analyzed with Chi-square test. The comparison between AESD and FS was carried out by the Mann-Whitney U test. Regression lines for the spectrum data from AESD and FS during 24 h were drawn by the recording period as the independent variable and the power value as the dependent variable.  $P$  values of  $< 0.05$  were considered statistically significant. The IBM SPSS Statistics 20 (IBM, Tokyo, Japan) was used for these statistical tests.

## RESULTS

### Clinical characteristics

Of the 68 participants, 14 resulted in hospital death or neurological sequelae: classified as most severe prognosis in 5 patients (in-hospital deaths in 3 and vegetative state in 2), severe prognosis in 5 patients, and moderate-mild prognosis in 4 patients. The prognosis of AESD

was most severe in 2 patients, severe in 4 patients, moderate-mild in 4 patients, and normal in 8 patients. All 7 patients with MERS had a normal prognosis. Twenty FS and 11 ES patients all showed a full recovery (Table 1). Regarding the treatment for termination of initial SE, which may increase fast activity on the EEG, diazepam was used in 9 AESD, 2 MERS, 2 Reye-like syndrome, 1 ANE, 10 FS, 7 ES, and 1 unclassified AE. Midazolam was used in 7 AESD, 1 MERS, 1 Reye-like syndrome, 8 FS, 4 EP, and 1 unclassified AE. Both of these agents were administered in 5 AESD, 1 MERS, 1 Reye-like syndrome, 4 FS, 1 ES, and 1 unclassified AE. Phenobarbital was used in 4 AESD, 1 ANE, 1 intracranial bleeding, 3 FS, and 2 unclassified AE. The proportion of usage of these agents was not statistically significant among the AESD, MERS, FS and ES groups. Other medications included thiopental in 4, propofol in 1, fosphenytoin in 4, and vitamin compounds in 1. The medication used in the 5 most severe patients were diazepam in 2, midazolam in 2, phenobarbital in 3, and no medication in 1. All 5 severe patients were treated with diazepam in 5, midazolam in 3, and phenobarbital in 1. Two of 4 moderate-mild patients were treated with diazepam in 1, midazolam in 1, and fosphenytoin in 3.

### Visual EEG assessment

The severity grades of acute phase EEGs were variable in the AESD, FS, and ES groups, and distinction of these etiologies by visual inspection were impossible between EEGs of each grade (Fig. 1, Table 2). The EEGs in MERS was graded to 1–3, consistent with the favorable outcome of this patient group (Table 2). EEGs in some MERS patients were characterized by high amplitude theta activity with fronto-occipital predominance. As shown in Table 2, there was a considerable overlap among AESD, FS and ES groups, particularly in grades 3 and 4.

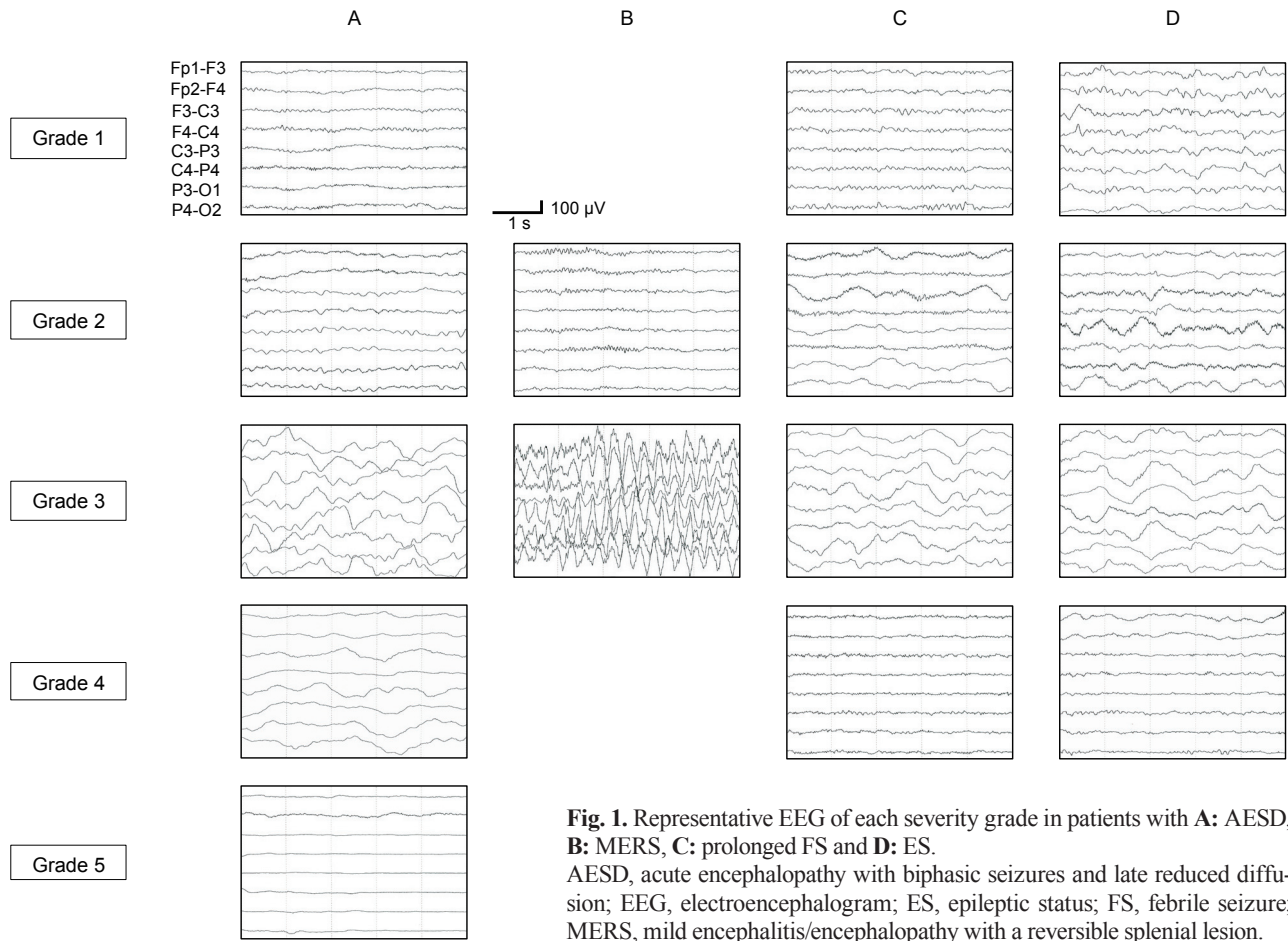
As for the correlation between the visual EEG grading and the neurological sequelae (Table 3), all but 1 patients (18/19, 95.0%) in grades 1 and 2 were normal and one patient had mild-moderate sequelae. In Grades 3, although most patients were normal, some patients (5/36, 14.0%) had neurological sequelae. In Grade 4, although 5 patients were normal, the other patients (5/10, 50.0%) had neurological sequelae. In Grade 5, all 3 patients were suffering from most severe sequelae.

### EEG spectrum analysis of different etiology groups (Fig. 2, Table 4)

The absolute value of spectrum band powers showed no significant difference among the 5 groups in the delta band (Fig. 2A). In the theta band, the MERS group



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**Table 2. Severity grades on visual assessment of EEGs in children after status epilepticus due to each etiology**

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AESD ( <i>n</i> = 18)	1	1	10	5	1
MERS ( <i>n</i> = 7)	3	2	2		
Reye - like syndrome ( <i>n</i> = 2)			2		
AE (unclassified) ( <i>n</i> = 6)			4	2	
HHS ( <i>n</i> = 1)			1		
ANE ( <i>n</i> = 1)			1		
HIE ( <i>n</i> = 1)					1
Intracranial bleeding ( <i>n</i> = 1)					1
FS ( <i>n</i> = 20)	1	6	11	2	
ES ( <i>n</i> = 11)	3	2	5	1	

AE, acute encephalopathy; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; EEG, electroencephalogram; ES, epileptic status, FS, febrile seizure, MERS, mild encephalitis/encephalopathy with a reversible splenial lesion, HIE, hypoxic-ischemic encephalopathy; HHS, hemiconvulsion-hemiplegia syndrome.

**Table 3. Relationship between the EEG severity grades during the acute phase and prognosis**

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Normal ( <i>n</i> = 54)	7	11	31	5	
Mild-moderate ( <i>n</i> = 4)	1		2	1	
Severe ( <i>n</i> = 5)			2	3	
Most severe ( <i>n</i> = 5)			1	1	3

EEG, electroencephalogram.

showed a significantly high power value in the frontal and centro-parietal areas (Fig. 2B). In the alpha band, the AESD group showed a significantly lower power value than the FS group in the fronto-central areas (Fig. 2C). In the beta band, the power value in the FS group was significantly higher than the AESD group in the F3-C3 area (Table 4). The MERS group showed a higher beta band power with frontal predominance (Fig. 2D). In the gamma band, the FS group showed a significantly higher power value than the other groups in the centro-parietal areas. Gamma band power in MERS was higher in the frontal areas compared to other groups (Table 4). The ratios of delta/alpha and (delta + theta)/(alpha + beta) in the AESD group were both higher than those in the other groups in the frontal and parietal predominance (Figs. 2E and F). In terms of the correlation between the band power and the prognosis, delta power was lower in the patients with the most severe outcome and higher in the patient group with mild—moderate sequelae in the frontal and right parieto-occipital areas (Table 5).

#### Comparison of EEGs in AESD and FS by spectrum analyses including temporal evolution

Despite the significant differences revealed in the spectrum analysis among the different etiologies in the patient groups, there was still overlap in the spectra from each group. To identify further information for management of individual patient for whom the distinction of AESD and FS was desired, we compared EEGs within 24 h from onset in AESD (*n* = 7) and FS (*n* = 15) patients. The delta power values of these groups were not significantly different in any areas. The AESD group showed lower band powers than the FS group in the F3-C3, F4-C4 and P3-O1 areas in the theta band, and in all areas in the alpha, beta, and gamma bands. The ratios of delta/alpha and (delta + theta)/(alpha + beta) were higher in the AESD group in all areas (Table 6).

We then plotted the temporal distribution of spectrum band powers from the 22 patients and found that absolute theta and alpha band power tended to increase, and delta/alpha and (delta + theta)/(alpha + beta) ratios

significantly decreased with time in the FS group (Fig. 3). In the 4 patients [2 AESD (Patients 7 and 8; see Table 1) and 2 FS (Patients 45 and 56)] for whom EEGs were repeatedly recorded within 24 h from onset, theta, alpha, and beta band powers were higher and/or increased with time, and the delta/alpha and (delta + theta)/(alpha + beta) ratios remained lower from the early stage in the FS patients (Fig. 4).

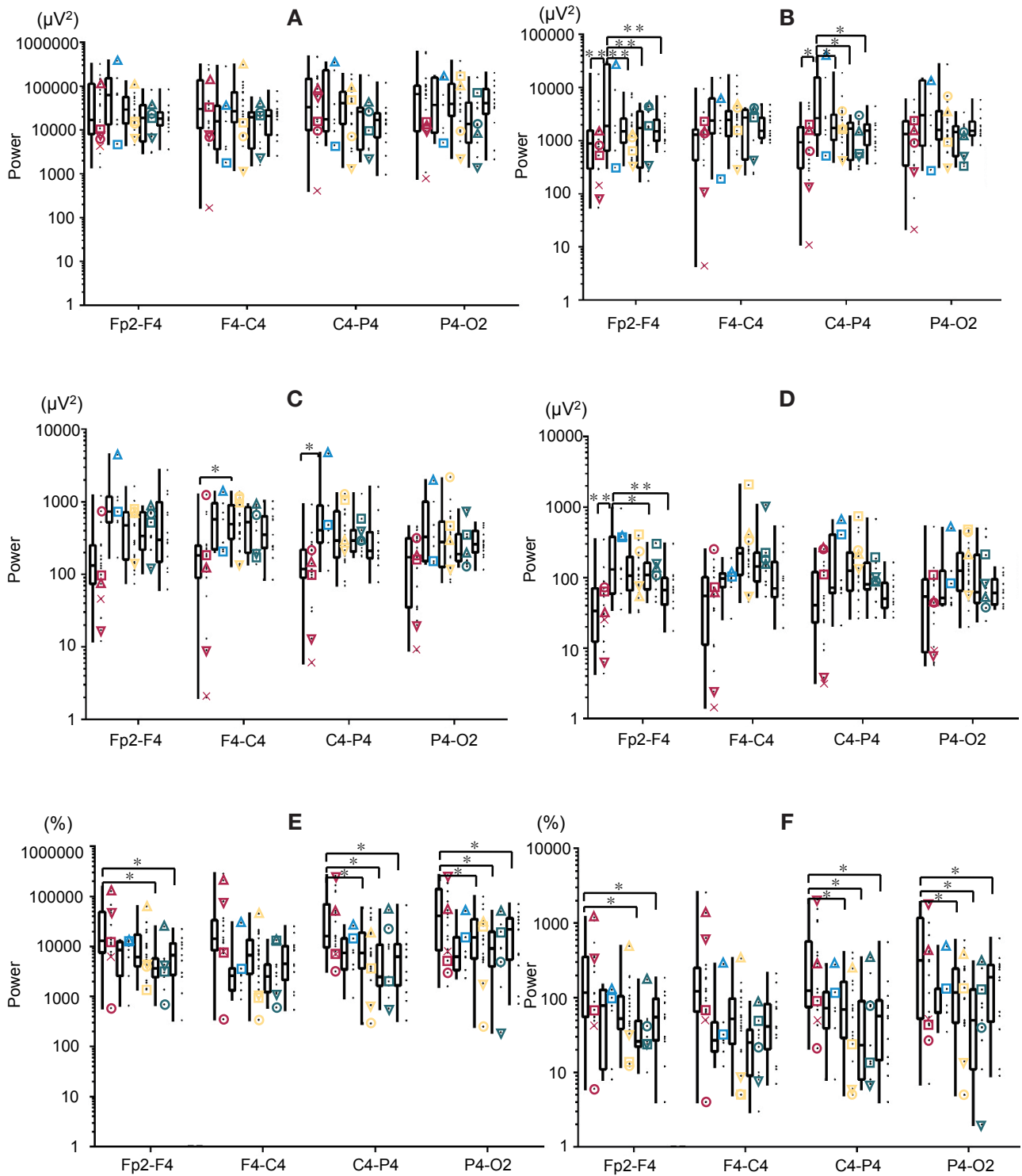
#### DISCUSSION

This is the first report that quantitatively analyzed acute phase EEGs in childhood infection-related AEs with band spectrum powers. Significance of usual visual inspection of EEG was limited to the expectation of the most severe or mild outcomes, common to the cases of the AEs in a broad sense: slow and/or low voltage background, lack of EEG reactivity to external stimuli, and epileptiform discharges are characteristic in acute cerebral injuries with outcomes of various severities due to hypoxia-ischemia, bacterial infections, hepatic coma, and head trauma.<sup>1, 2, 9</sup> Among others, isoelectric and/or discontinuous EEG patterns, which correspond to Grade 5 in this study, have been linked to the poorest outcome in these etiologies.

In previous reports, findings in EEG spectrum analysis from patients with AEs include a decreased (delta + theta)/(alpha + beta) ratio in severe bacterial infections,<sup>15</sup> and increased delta power and lower 50% spectral edge frequency in hepatic coma,<sup>14</sup> all of which did not show significant correlation with prognosis. Although diffuse asymmetrical slow waves in various AE etiologies,<sup>16</sup> and electrical storm in hemorrhagic shock and encephalopathy syndrome<sup>17</sup> are described as useful in outcome prediction, these appear to be applicable to rather specific conditions.

The band power analysis in this study among groups of different severity in outcomes revealed significant difference only in the delta frequency power bands in the frontal areas, which was lower in the most severe prognosis group and higher in the mild-moderate prognosis group. This may represent the low-voltage or isoelectric

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**Fig. 2.** Spectrum analysis of EEGs in different etiologies. Absolute power of **A:** delta (0.5–3 Hz), **B:** theta (4–7 Hz), **C:** alpha (8–12 Hz) and **D:** beta (13–19 Hz) frequency bands, as well as the ratio of band powers, **E:** delta/alpha and **F:** (delta + theta)/(alpha + beta), are shown. Five vertical bars for each area, e.g. Fp2-F4, represent the groups of AESD, MERS, FS, ES and control from the left to the right. Vertical squares on each bar show 25, median and 75 percentile values. Dots on the right of the bars represent the values of individual subject. The dots enclosed by blank signs represent the patients whose EEG tracings are shown in Fig. 1 (○: grade 1, □: grade 2, △: grade 3, ▽: grade 4, ×: grade 5). \* $P < 0.05$ , \*\* $P < 0.01$ . AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; EEG, electroencephalogram; ES, epileptic status; FS, febrile seizure; MERS, mild encephalitis/encephalopathy with a reversible splenic lesion.

**Table 4. Power spectrum values of EEGs in children after status epilepticus due to each etiology**

Frequency	Patient group	Locations		
		Fp1-F3	Fp2-F4	F3-C3
delta ( $\mu\text{V}^2$ )	AESD	76380 (892–513043)	59377 (1407–319824)	75346 (161–457518)
	MERS	80817 (3029–303123)	99577 (4824–378404)	62617 (3098–275621)
	FS	48315 (3210–171041)	37976 (4550–128664)	60494 (1472–326000)
	ES	23169 (7313–56033)	22168 (2994–82100)	28054 (1393–82363)
	Control	22200 (3186–69500)	23096 (3638–84100)	20603 (1740–68200)
theta ( $\mu\text{V}^2$ )	AESD	1956 (33–14977) **	2154 (55–17872)**	1750 (8–7779)*
	MERS	8973 (300–28335) **,*	9970 (312–29121)**	7754 (364–22529)*
	FS	2978 (236–19977) *	2381 (350–7910)**	4253 (139–18426)
	EP	1939 (426–5804) *	1983 (174–4904)**	1687 (258–4554)*
	Control	1574 (618–3140) **	1984 (630–6770)**	1845 (975–3660)*
alpha ( $\mu\text{V}^2$ )	AESD	221 (14–965)**	242 (12–1203)	308 (4–1380)
	MERS	1117 (232–3014)**	1233 (170–4453)	776 (87–2291)
	FS	506 (41–1902)	502 (74–1640)	672 (47–2016)
	ES	433 (98–1431)	453 (104–854)	453 (115–963)
	Control	667 (75–3269)	651 (62–2737)	507 (107–1520)
beta ( $\mu\text{V}^2$ )	AESD	70 (6–298)**	62 (4–347)**	77 (2–452)*
	MERS	677 (32–2927)**,*	286 (35–958)**,*	177 (23–567)
	FS	135 (23–586)**	134 (34–396)	247 (23–1260)*
	ES	154 (16–516)*	107 (45–162)*	202 (20–567)
	Control	72 (22–212)**	81 (17–302)**	134 (25–447)
gamma ( $\mu\text{V}^2$ )	AESD	29 (1–211)**	19 (1–99)**	18 (1–136)*
	MERS	500 (2–2346)**,*	233 (1–887)**,*	32 (1–84)
	FS	68 (13–311)**	66 (9–193)*	76 (8–309)*
	ES	67 (5–281)*	51 (9–164)*	79 (5–285)
	Control	31 (10–81)**	32 (6–78)**	24 (6–67)

Mean and the range of power values are shown in each cell. \* $P < 0.05$ , \*\*  $P < 0.01$ .

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ES, epileptic status epilepticus; FS, febrile status epilepticus; MERS, mild encephalitis/encephalopathy with a reversible splenial lesion.

**Table 5. Comparison of power spectrum values of EEGs between different severity groups of children after status epilepticus**

Frequency	Prognosis	Locations		
		Fp1-F3 ( $\mu\text{V}$ )	Fp2-F4 ( $\mu\text{V}$ )	F3-C3 ( $\mu\text{V}$ )
delta ( $\mu\text{V}^2$ )	Most severe	27134 (130–127928)*	20164 (135–91042)	11516 (62–56556)*
	Severe	40583 (2445–120609)*	48629 (1194–179730)	59618 (4309–251536)
	Moderate–mild	157172 (2273–513034)**,*	113672 (4365–319824)*	137676 (2807–457517)*
	Normal	42520 (970–303122)**	40677 (1406–378404)*	46431 (1392–326000)*
theta ( $\mu\text{V}^2$ )	Most severe	770 (15–3532)	592 (22–2471)	584 (7–2860)
	Severe	1416 (133–5236)	1517 (86–5554)	1939 (267–7779)
	Moderate–mild	1437 (401–4339)	1437 (670–3830)	1334 (499–3129)
	Normal	2860 (58–28335)	3064 (55–29121)	3043 (42–22529)
alpha ( $\mu\text{V}^2$ )	Most severe	172 (6–751)	150 (11–596)	101 (4–481)
	Severe	252 (34–964)	313 (17–1202)	347 (58–1380)
	Moderate–mild	218 (16–426)	253 (24–742)	343 (34–1073)
	Normal	509 (8–3270)	529 (7–4453)	508 (6–2292)
beta ( $\mu\text{V}^2$ )	Most severe	45 (6–69)	41 (4–88)	46 (14–86)
	Severe	65 (3–298)	61 (3–256)	35 (2–178)
	Moderate–mild	36 (9–70)	31 (8–87)	40 (8–92)
	Normal	192 (4–2928)	143 (3–958)	244 (3–4279)
gamma ( $\mu\text{V}^2$ )	Most severe	22 (2–88)	23 (2–85)	14 (1–65)
	Severe	13 (0–37)	12 (0–40)	12 (0–53)
	Moderate–mild	6 (1–14)	6 (1–18)	6 (1–19)
	Normal	113 (2–2347)	80 (1–888)	71 (1–1300)

Mean and the range of power values are shown in each cell. \* $P < 0.05$ , \*\*  $P < 0.01$ . EEG, electroencephalogram.

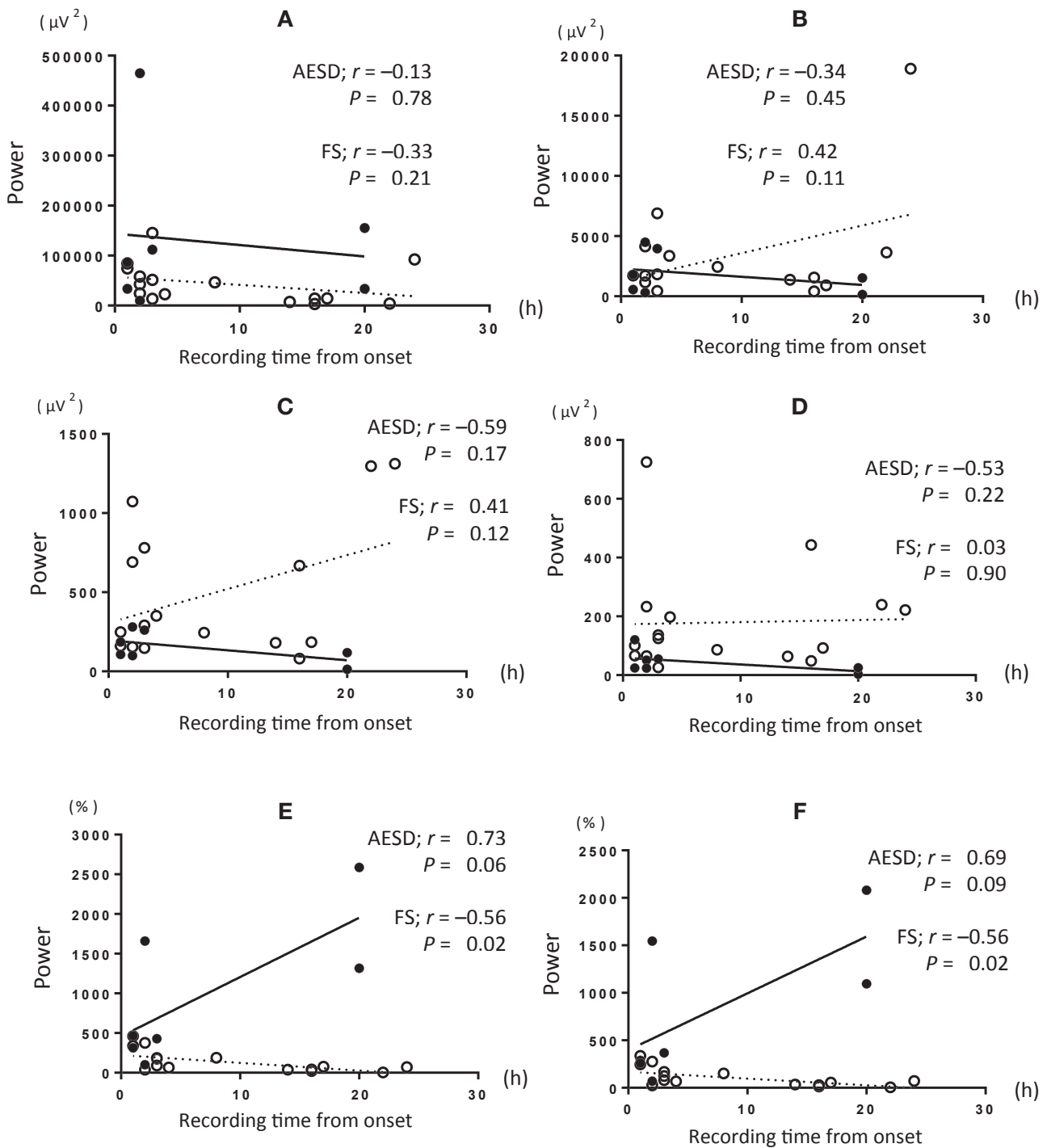


**Table 4-Continued**

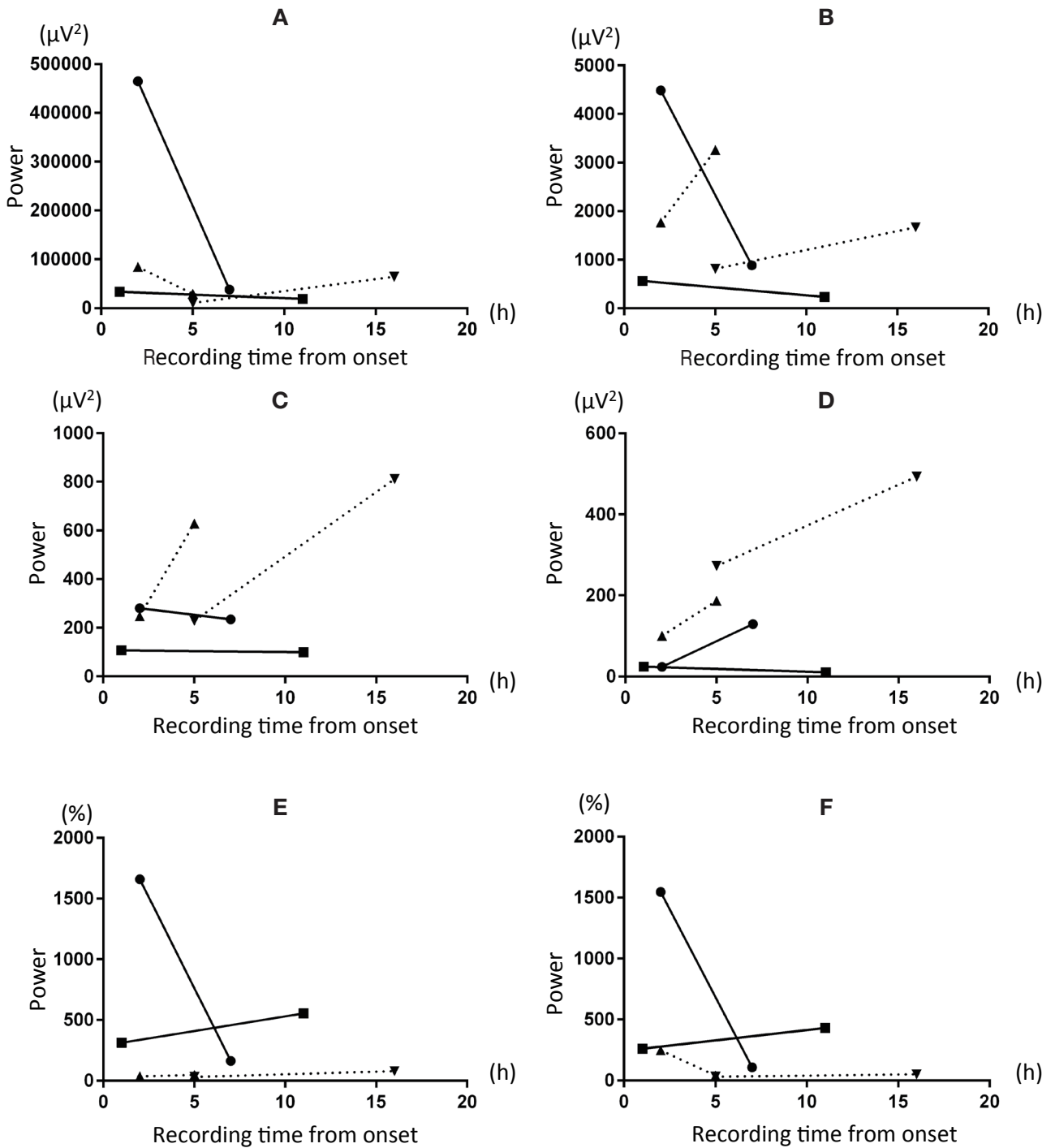
Locations				
F4-C4	C3-P3	C4-P4	P3-O1	P4-O2
66801 (168–309148)	65870 (71–420264)	92043 (412–472320)	109876 (122–580641)	113063 (784–601826)
52807 (1808–283534)	68914 (3054–344211)	94172 (4492–345928)	53371 (4603–136840)	64119 (5122–167628)
55717 (1218–310697)	58728 (2133–291000)	41958 (1444–145000)	111192 (4223–423000)	78466 (2312–376309)
18963 (1567–53800)	27627 (840–150000)	32622 (1984–177000)	27550 (2083–153000)	34188 (148–158000)
23757 (2570–77000)	21398 (1315–75902)	23337 (949–120517)	48173 (1676–119967)	59700 (2124–202674)
1662 (4–9400)	1533 (6–5752)*	1493 (11–5150)*	1835 (10–7307)*	1570 (22–5944)
4520 (198–15201)	5417 (251–22572)*	9032 (522–38951)*	7115 (230–24193)*	5962 (282–14508)
3714 (305–16900)	3189 (387–12800)	2965 (402–18900)*	3957 (429–21800)	3641 (322–27400)
2093 (235–3993)	1180 (243–2289)*	1448 (289–2937)*	1567 (234–4067)*	1351 (331–3408)
2044 (912–4750)	1635 (679–3950)	1558 (374–4438)*	2028 (894–5274)	2059 (825–5866)
269 (2–1257)*	220 (3–1293)	188 (6–920)*	218 (7–1552)	193 (9–457)
612 (206–1354)	770 (167–3132)	1028 (112–4635)*	605 (120–1185)	616 (143–1962)
623 (130–1370)*	429 (126–1099)	466 (70–1312)	433 (107–1652)	444 (78–2198)
519 (138–917)	277 (44–524)	389 (175–1293)	339 (55–1055)	304 (129–772)
444 (84–1020)	437 (119–1740)	372 (77–1610)	328 (141–903)	290 (116–510)
72 (1–247)	88 (2–500)	70 (3–254)	90 (3–564)*	83 (6–529)
82 (26–114)	108 (33–305)	188 (20–645)	454 (37–2285)*	116 (40–502)
290 (46–2072)	121 (37–8326)	166 (26–725)	132 (44–384)	154 (20–465)
243 (53–1076)	84 (7–176)	157 (27–678)	96 (11–328)	145 (24–493)
131 (19–531)	72 (26–228)	65 (27–164)	71 (25–150)*	68 (36–137)
21 (1–111)**	19 (1–94)**	20 (1–92)**	25 (1–110)	38 (1–335)
17 (1–36)*	16 (1–30)	30 (1–89)	252 (1–1611)	20 (1–72)
84 (21–277)** *	59 (8–268)** *	69 (10–265)** *	76 (6–352)	87 (10–362)
51 (18–162)	28 (2–60)	63 (6–277)	37 (3–135)	82 (5–399)
24 (6–55)**	22 (5–60)*	20 (5–64)*	26 (5–73)	24 (6–69)

**Table 5-Continued**

Locations				
F4-C4 (µV)	C3-P3 (µV)	C4-P4 (µV)	P3-O1 (µV)	P4-O2 (µV)
12285 (43–49985)	23365 (11–114752)	25319 (32–116038)*	23312 (20–115912)	33022 (85–163056)
59131 (6489–233011)	69001 (2825–242085)	115692 (1739–472320)	153993 (2278–580641)	147245 (3383–559450)
102912 (4467–309148)	105818 (5165–420263)	165972 (6766–464742)*	165137 (3859–569219)	185116 (9388–601826)
41084 (1217–310697)	47111 (839–344211)	46940 (949–345928)*	74752 (1676–479000)	65355 (1481–376308)
387 (4–1530)	928 (2–4469)	812 (9–3725)	1342 (4–6630)	757 (9–3651)
1175 (92–3429)	1877 (265–5752)	1510 (143–5150)	2487 (180–7307)	1295 (131–3417)
1305 (863–1667)	952 (184–2578)	1522 (369–4483)	1720 (205–6123)	2042 (338–5943)
2709 (45–16900)	2444 (242–22572)	2913 (182–38951)	2962 (70–24193)	2721 (129–27400)
102 (2–376)	208 (1–876)	199 (6–865)	205 (1–984)	197 (3–899)
237 (9–727)	358 (27–1293)	289 (12–920)	452 (20–1551)	216 (20–445)
380 (50–1256)	163 (8–407)	150 (34–280)	119 (19–241)	200 (33–330)
490 (7–1370)	394 (29–3132)	443 (21–4635)	364 (11–1652)	349 (17–2198)
69 (4–139)	68 (15–234)	75 (9–167)	30 (5–90)	31 (5–80)
36 (1–154)	65 (0–241)	66 (3–307)	55 (1–280)	64 (1–257)
48 (10–124)	27 (3–63)	42 (11–126)	32 (5–60)	40 (6–101)
188 (2–2071)	229 (7–8775)	135 (3–725)	148 (7–2285)	124 (8–529)
19 (0–73)	22 (0–66)	22 (1–80)	19 (1–78)	27 (1–85)
7 (0–25)	12 (1–46)	11 (0–35)	23 (1–62)	12 (1–28)
13 (1–54)	9 (1–41)	21 (2–92)	15 (1–56)	19 (0–68)
50 (1–277)	76 (1–2762)	47 (1–277)	70 (1–1611)	58 (0–362)



**Fig. 3.** Temporal distribution of spectrum band powers in AESD and FS within 24 h after the onset of seizures. Corresponding regression lines (the solid line for the AESD group and the dotted line for the FS group) are drawn for each of the 2 groups. The power value at C4–P4 area was chosen for demonstration. Blank and filled circles represent the FS ( $n = 15$ ) and AESD ( $n = 7$ ) patients. **A:** delta, **B:** theta, **C:** alpha, and **D:** beta frequency bands, and **E:** delta/alpha and **F:** (delta + theta)/(alpha + beta) ratios. Note that alpha power in FS significantly increases (C), and the ratios of delta/alpha and (delta + theta)/(alpha + beta) in FS decrease (E and F) with time. AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; FS, febrile seizure.



**Fig. 4.** Evolution of band powers in individuals for whom EEGs were recorded twice within 24 h after the onset of seizures. The power values at C4–P4 area are shown. Solid and dotted lines represent the AEDS and the FS patients, respectively. and **A:** delta, **B:** theta, **C:** alpha and **D:** beta frequency bands, and **E:** delta/alpha and **F:** (delta + theta)/(alpha + beta) ratios. AEDS, acute encephalopathy with bi-phasic seizures and late reduced diffusion; EEG, electroencephalogram; FS, febrile seizure.

**Table 6. Comparison of AESD and FS power spectrum value in EEGs within 24 h from onset**

Frequency	Patient group	Locations		
		Fp1-F3	Fp2-F4	F3-C3
delta ( $\mu\text{V}^2$ )	AESD	139812 (6575–513043)	97891 (6557–319824)	131689 (703–457517)
	FS	55493 (3210–171041)	42645 (4550–128664)	69815 (5188–32600)
theta ( $\mu\text{V}^2$ )	AESD	3340 (133–14977)	3633 (86–17872)	1935 (27–7345)
	FS	3639 (236–19977)	2894 (417–7910)	4764 (495–18426)
alpha ( $\mu\text{V}^2$ )	AESD	170 (5–341)	171 (17–524)	200 (10–634)
	FS	559 (41–1902)	563 (74–1640)	738 (107–2016)
beta ( $\mu\text{V}^2$ )	AESD	36 (7–84)	30 (6–70)	37 (6–92)
	FS	147 (23–586)	150 (34–396)	275 (46–1259)
gamma ( $\mu\text{V}^2$ )	AESD	9 (1–35)	8 (1–28)	6 (1–20)
	FS	73 (13–310)	73 (9–192)	79 (13–309)
delta/alpha(%)	AESD	685 (81–1710)	629 (78–1520)	881 (64–2990)
	FS	144 (12–778)	121 (13–629)	107 (3–359)
(delta + theta)/(alpha + beta) (%)	AESD	577 (59–1586)	515 (55–1192)	743 (46–2744)
	FS	112 (15–609)	96 (12–492)	82 (6–276)

Mean and the range of power values are shown in each cell. \* $P < 0.05$ , \*\* $P < 0.01$ .

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; EEG, electroencephalogram; ES, epileptic status epilepticus; FS, febrile status epilepticus; MERS, mild encephalitis/encephalopathy with a reversible splenial lesion.

EEGs in the most severe group. As for the differences among the background conditions, higher theta band power was characteristic in the MERS group. AESD group showed higher delta/alpha and (delta + theta)/(alpha + beta) ratios in the frontal and parieto-occipital areas than the FS group. In contrast, delta band power was comparable between FS and AESD groups. These could be interpreted that EEGs in AESD are more monotonous with decreased power of alpha and beta bands compared to those in FS. Thus, significant difference was found between AESD and FS but there was some overlap when focusing on individual patients (Fig. 2) based on the EEG within 120 h from the onset of first seizures.

Interestingly, Synek et al.<sup>9</sup> found that EEGs at 24–48 h from onset of anoxic and traumatic cerebral injury was reliable than those during earlier phases in prediction of outcome. Temporal evolution of EEG may also be indicative of the etiology and severity of the childhood infection-related AEs. This prompted us to compare the EEGs in AESD and FS within the first 24 h in terms of time-dependent changes. Although the number of EEGs in AESD between 5 and 24 h were limited, increase of alpha and beta power bands with time was apparent on EEGs in FS compared to those in AESD (Figs. 3 and 4). These suggest that serial EEGs up to 24 h after the onset would enhance the quality in early diagnosis of AESD before the emergence of second phase. Initial EEG earliest after admission would be also helpful for identification of most severe cases of AESD.

A nationwide survey identified 282 AESD cases

per 3 years in Japan,<sup>3</sup> which is presumably higher than other countries. The prevalence of FSs in Japan<sup>18</sup> is higher than Caucasian countries,<sup>19</sup> which may suggest a link between FS and AESD.<sup>5</sup> On the other hand, FS is more prevalent in boys than girls,<sup>18, 20, 21</sup> whereas the male-predominance was not observed in AESD (M:F = 114:167).<sup>3</sup> This is suggestive of certain genetic predisposition factors for AESD other than those for FSs in general. These may include certain genotype of carnitine palmitoyl transferase II,<sup>22, 23</sup> *SCN1A*,<sup>24</sup> *SCN2A*,<sup>25</sup> *ADORA2A*,<sup>26</sup> and *TLR3*.<sup>27</sup> These vulnerability factors to AESD may result in the persistent increase of excitatory transmitters assumed in the pathogenesis of AESD.<sup>8</sup> Subclinical status epilepticus has been identified in an AESD patient at the onset of the second phase.<sup>28</sup> This phenomenon was not found in the present patient series; however, considering the pathogenesis of AESD, early diagnosis could lead to improve the prognosis through early decision of treatment with some agents reported as potentially effective for AESD. These include fosphenytoin,<sup>28, 29</sup> L-carnitine and vitamins,<sup>30</sup> and erythropoietin.<sup>31</sup> The present study supports that follow-up EEGs up to 24 h from the onset would be helpful for early identification of AESD patients. EEG findings of AESD between 5 and 20 h from the onset, as well as any effect of the aforementioned treatment options, would be worth for further examination.

*The authors declare no conflict of interest.*



Table 6-Continued

Locations				
F4-C4	C3-P3	C4-P4	P3-O1	P4-O2
110619 (7152–309148)	99733 (1922–420263)	127946 (9967–464742)	130996 (122–569219)	152357 (1079–601826)
62161 (4249–310697)	60333 (4160–291000)	43634 (3240–145000)	123128 (4223–423000)	80667 (5526–376308)
2181 (92–9399) ]*	1247 (156–2981)	1824 (143–4483)	1668 (28–6123) ]*	1859 (83–5943)
4198 (644–16900) ]*	3392 (421–12800)	3265 (402–18900)	4385 (759–21800) ]*	3924 (614–27400)
213 (9–676) ]**	120 (27–190) ]**	151 (13–280) ]*	90 (19–241) ]**	46 (20–331) ]*
688 (139–1370) ]**	428 (126–1099) ]**	491 (80–1312) ]*	455 (190–1652) ]**	467 (101–2198) ]*
43 (2–101) ]**	39 (12–126) ]**	43 (3–120) ]**	24 (7–52) ]**	43 (6–101) ]**
328 (58–2071) ]**	123 (37–326) ]**	179 (26–724) ]**	140 (60–384) ]**	166 (20–464) ]**
9 (1–21) ]**	9 (1–40) ]**	9 (1–31) ]**	6 (1–12) ]**	11 (1–36) ]**
91 (20–276) ]**	59 (8–268) ]**	71 (11–264) ]**	82 (6–351) ]**	91 (10–362) ]**
900 (117–2836) ]**	898 (12–2531) ]*	981 (100–2587) ]**	1120 (6–2361) ]*	1212 (15–2610) ]*
102 (3–450) ]**	168 (4–829) ]**	138 (3–462) ]**	350 (2–901) ]**	262 (3–990) ]**
727 (91–2586) ]**	734 (7–2376) ]*	815 (69–2080) ]**	903 (4–2110) ]*	991 (7–1888) ]*
77 (5–337) ]**	138 (6–727) ]*	107 (5–336) ]**	250 (5–637) ]*	183 (5–589) ]*

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