Key Points

- The incidence of PEE following AESD was 23%, and the median interval between the onset of encephalopathy and PEE was 8.5 months.
- Epileptic spasms and startle focal seizures were common seizure types.
- The seizure types may be determined by the diffuse subcortical white matter injury in AESD and age-dependent reorganization of the brain network.

Acute encephalopathy/encephalitis in childhood is often caused by viral infections such as human herpesvirus 6 (HHV-6), influenza virus, and rotavirus, and is a leading cause of death or severe neurologic impairments, particularly in East Asia.[1] Six percent of affected children die and 36% of survivors have neurologic sequelae, including motor or cognitive impairment and epilepsy.[2]

Post-encephalopathic/encephalitic epilepsy (PEE) is a well-recognized, serious complication of acute encephalopathy/encephalitis. Previous studies have shown that 10–20% of affected children develop PEE, which occurs within 1 year after the onset of encephalopathy/encephalitis and is characterized by focal, intractable seizures. Risk factors for PEE are seizures (particularly recurrent seizures or status epilepticus) and electroencephalography (EEG) abnormalities during the acute phase of encephalopathy.[3–9] However, little is known about PEE following a specific acute encephalopathy syndrome known as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD).[10]

AESD is the most common acute infection–associated encephalopathy syndrome in childhood and has a higher incidence (66.2%) of neurologic sequelae than other acute infection–associated encephalopathy syndromes.[2] It is characterized by a biphasic clinical course and a magnetic resonance imaging (MRI) finding known as "bright tree appearance," which represents high signal intensity on diffusion-weighted imaging (DWI) in the widespread subcortical white matter, which has the appearance of tree branches. However, the characteristics of PEE after AESD have not been fully documented in the literature.

The aim of this study, therefore, is to clarify characteristics of PEE in children after AESD, paying particular attention to precise diagnosis of seizure types based on ictal video-EEG recordings.

Methods

Between April 2005 and December 2012, 262 children aged from 0 to 15 years newly diagnosed with acute encephalitis/encephalopathy were registered in a database of the Tokai Pediatric Neurology Society, which consists of pediatric neurologists from Nagoya University, Juntendo University, Nagoya City University, and the hospitals affiliated with these universities. Acute encephalitis/encephalopathy was defined as acute deterioration of brain function such as loss of consciousness that was not directly caused by seizures. Patients with inborn error of metabolism, hepatic encephalopathy, toxic-metabolic encephalopathy, traumatic brain injury, hypoxic-ischemic encephalopathy, or bacterial meningitis were excluded.

Among them, 36 patients were diagnosed with AESD. AESD was defined according to widely used diagnostic criteria[10] as an acute febrile encephalopathy with (1) prolonged seizures (status epilepticus in most cases) at onset, (2) transient improvement in consciousness followed by recurrence of seizures and deterioration of consciousness, and (3) reduced diffusion in the subcortical white matter on DWI 2–8 days after initial seizures, which was defined as late reduced diffusion. Biphasic seizures were defined as prolonged seizures at onset and recurrence of seizures at intervals of 3–5 days. Another 14 patients who fulfilled all criteria other than biphasic seizures were also included in this study because of recent evidence suggesting that this is the same entity as AESD.[11] Six patients who had neurologic abnormalities before the onset of encephalopathy were excluded because we could not distinguish neurologic sequelae of AESD from neurologic manifestations associated with preexisting neurologic disorders. Thus, the remaining 44 patients were included in this study.

We reviewed medical charts to investigate clinical data, MRI and EEG findings, and neurologic outcomes. MRI was performed at least once during the acute phase and once during the chronic phase of encephalopathy, and may have been performed more often according to the physician's demand. Three pediatric neurologists (Y.I., J.N., and H.K.) reviewed the MR images. High signal intensity on DWI was classified as bilateral or unilateral, and as with or without central sparing. Central sparing was defined as a lack of high signal intensity on DWI in subcortical white matter in the primary sensorimotor areas.[11]

The final evaluation of PEE was performed in January 2014. We examined the duration between encephalopathy and PEE, the type of seizures, the frequency of seizures, and seizure outcome with antiepileptic drugs. Patients who developed PEE underwent video-EEG recordings to identify seizure type. Three pediatric neurologists (J.N., T.N., and N.I.) reviewed the records and confirmed seizure types.

Cognitive outcome was evaluated using the Tsumori-Inage Developmental Assessment Test, Enjoji Analytical Development Test, Kyoto Scale of Psychological Development 2001, or Tanaka-Binet Intelligence Scales, according to the age of the patient and feasibility of each test in each hospital. The severity of cognitive impairment was graded as mild (intelligence quotient or development quotient, 51–69), moderate (35–50), or severe (<35). Gross motor outcome was assessed by pediatric neurologists in each

Epilepsia, 56(8):1286–1293, 2015
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hospital. The severity of gross motor impairment was graded as mild (patient could walk without support), moderate (patient could sit without support but could not walk without support), or severe (patient could not sit without support), according to the Gross Motor Function Classification System.[12]

Statistical analyses were performed with SPSS software, version 22 (IBM, Chicago, IL, U.S.A.). The Mann–Whitney *U*-test was used to compare clinical variables, MRI findings, treatment in the acute phase of encephalopathy, and neurologic outcomes between patients with and without PEE. Statistical significance was established at $p < 0.05$.

This study was approved by the research ethics committee of Nagoya University Graduate School of Medicine. The patients' data were collected anonymously.

Results

Of the 44 patients after AESD, 10 (six boys, four girls) had PEE during the follow-up period. The demographics of the patients with and without PEE are shown in Table 1. The causative pathogen of AESD was not identified in 8 of the 10 patients with PEE. The causative pathogen was human herpesvirus 6 (HHV-6) in one patient and adenovirus in one patient. The causative pathogen of AESD in patients without PEE was HHV-6 in 10 patients, adenovirus in two patients, rotavirus in two patients, influenza virus in one patient, *Mycoplasma pneumoniae* in one patient, enterovirus type coxsackievirus A6 (CVA6) in one patient, *Escherichia coli O157:H7* in one patient, and unknown in 16 patients. Patients with PEE had more severe cognitive impairment as a sequela of encephalopathy than patients without PEE, and a greater proportion was treated with intravenous immunoglobulin. The remaining variables, including biphasic seizures and status epilepticus, were not significantly different between patients with and without PEE.

Characteristics of patients with PEE

Detailed characteristics of the 10 patients with PEE are provided in Table 2. In the acute phase of encephalopathy, all but one (frontal dominant) patient had bilateral diffuse DWI abnormality, and half of them had central sparing. In the chronic phase, all patients had some degree of cerebral atrophy in both gray and white matter on the follow-up MRI (Fig. 1). Age at the onset of PEE ranged from 10 to 57 months. The period between the onset of encephalopathy and onset of PEE ranged from 2 to 39 months (median 8.5 months).

Seizure type on clinical observation was focal seizure in five patients (n = 2 head turning with axial stiffness, n = 1 asymmetric tonic posturing, n = 1 hypermotor seizure, and n = 1 dyscognitive seizure), epileptic spasm in four patients (n = 1 clustered and n = 3 isolated), myoclonic seizure in three patients, tonic seizure in two patients, clonic seizure in one patient, and tonic–clonic seizure in one patient. Two patients had two types of seizures and one patient had five types of seizures. Six patients had startle seizures that were induced by sudden unexpected sounds. The startle seizures were focal seizures in four patients (n = 1 head turning with axial stiffness, n = 1 asymmetric tonic posturing, n = 1 hypermotor seizures, and n = 1 dyscognitive seizures), epileptic spasms in two patients (n = 1 clustered and n = 1 isolated), and myoclonic seizures in one patient. At the last follow-up time point, six patients had daily seizures that were uncontrolled despite taking more than two antiepileptic drugs. All patients with PEE had some degree of cognitive impairment after encephalopathy. Three patients had severe motor impairment, three had moderate motor impairment, and four had normal gross motor function.

Video-EEG recordings

Ictal simultaneous video-EEG recordings were performed in 6 of the 10 patients with PEE.

Three patients (patients 1, 2, and 8) were diagnosed with epileptic spasms. Ictal EEG in patient 8 showed a diffuse irregular complex of slow and sharp waves with diffuse fast wave activities (Fig. 2). Electromyography showed crescendo-decrescendo activities lasting about 1 s, and patients had head nodding with or without arm elevation. Spasms in patient 1 appeared in clusters, and spasms in patients 2 and 8 occurred separately.

Three patients (patients 3, 4, and 5) were diagnosed with focal seizures of frontal onset. Ictal EEG in patient 3 revealed a startle seizure induced by sudden unexpected sounds, in which frontal-dominant fast wave activities lasted for 12 s, with a progressive increase in amplitude and decrease in frequency (Fig. 3). Immediately after a startle movement, the patient had motion arrest with axial stiffness in the sitting position and gradually turned her head to the left. This versive seizure was supposed to be of mesial frontal lobe origin, although the frontal-dominant fast wave activities were not well localized. Ictal EEG in patient 4 showed bilateral frontal-dominant fast wave activities lasting for 15 s. The patient showed tonic posturing with an extended right arm and flexed left arm that was induced by sudden unexpected sounds. His eyes were deviated to the right. Ictal EEG in patient 5 showed a startle seizure induced by sudden unexpected sounds, in which bilateral frontal-dominant sharp-slow waves appeared, followed by frontal-dominant fast wave activities lasting for 25 s with a progressive increase in amplitude and decrease in frequency. The patient had motion arrest for 3 s and then started jumping repetitively.

Discussion

In this multicenter cohort study of children with AESD, we report detailed characteristics of PEE. Our main findings are as follows: (1) the incidence of PEE was 23%, (2) the

Table 1. Clinical characteristics in patients with and without post-encephalopathic epilepsy (PEE)

	With PEE (n = 10)	Without PEE (n = 34)	p-Value
Sex, male:female	6:4	15:19	0.38
Age at onset of AESD (months), range (median)	1–47 (15)	4–55 (14)	0.40
Biphasic seizures	6	26	0.31
Status epilepticus	6	17	0.58
MRI findings during the acute phase			
Bilateral	10	25	0.071
Central sparing	5	22	0.41
Treatment			
Methylprednisolone pulse	7	25	0.83
IVIG	8	14	0.033
Follow-up period from the onset of AESD (months), range (median)	12–79 (36)	13–89 (36)	0.85
Neurologic outcome			
Cognitive impairment			
None	0	17	<0.001
Mild	1	9	
Moderate	3	1	
Severe	6	7	
Gross motor impairment			
None	4	17	0.24
Mild	0	6	
Moderate	3	8	
Severe	3	3	

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; PEE, post-encephalopathic epilepsy.

median interval between the onset of encephalopathy and PEE was 8.5 months, (3) epileptic spasms and startle focal seizures induced by acoustic stimulation were common seizure types, (4) patients with PEE had more severe cognitive impairments than those without PEE, (5) biphasic seizures and status epilepticus during the acute phase of encephalopathy did not influence the risk of PEE, and (6) PEE was intractable.

The most interesting finding in our study is that epileptic spasms and startle seizures as well as focal seizures were common in PEE. This is not consistent with previous studies, which showed without exception that focal seizure was the main seizure type of PEE regardless of condition, including in patients with acute disseminated encephalomyelitis,[13] acute meningitis,[3] herpes simplex encephalitis,[9] *Mycoplasma pneumoniae* encephalitis,[7] and febrile infection-related epilepsy syndrome (FIRES).[14] A similar study by Saito et al.[15] included 16 children with PEE after acute febrile encephalopathy with prolonged seizures during acute phase in a single tertiary epilepsy center in Japan. Four of the 16 patients had bright tree appearance on DWI and five of the 16 patients showed biphasic seizures during acute phase of encephalopathy. The authors reported various seizure types, including head nodding with motion arrest (n = 3 patients), epileptic spasm (n = 2 patients), versive seizure (n = 2 patients), brief tonic seizure (n = 5 patients, one with startle seizure), myoclonic seizure (n = 1 patient), and dyscognitive seizure (n = 1 patient). Nine of 16 patients underwent video-EEG to identify seizure type. We also found a variety of seizure types, including epileptic spasm, frontal versive seizure, dyscognitive seizure, myoclonic seizure, and tonic seizure. The main difference between the present study and the study by Saito et al. is that more patients had epileptic spasms and startle seizures in the present study. This is because 3 of 16 patients fulfilled all diagnostic criteria as AESD other than biphasic seizures and only one patient fulfilled all diagnostic criteria as AESD in the study by Saito et al. In addition, isolated epileptic spasms and subtle acoustic stimulation-induced seizures can be easily missed in clinical observation and require particular attention.

The specific seizure types of PEE in children following AESD might result from the pattern of brain injury and the age at onset of AESD. Although the precise pathogenesis of AESD remains unclear, MR spectroscopy studies indicate increased glutamine/glutamate complex concentration in the affected white matter, suggesting glutamate accumulation due to hyperactivity of excitatory neurons, which release glutamate, and hypoactivity of astrocytes, which take up glutamate and metabolize it into glutamine.[16] This is supported by other studies that have shown increased nitrite/nitrate levels and turnover rate of glutamate in the central nervous system.[17] Such infection/inflammation-induced excitotoxic injury by excessive glutamate with or

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Table 2. Characteristics of patients with post-encephalopathic epilepsy (PEE)

Patient/ Sex	Age at onset of AESD (months)	Pathogen	MRI findings during the acute period		Neurologic outcome		Age at onset of epilepsy (months)	Sz type	Startle sz	Sz frequency at the last follow-up period	Interictal EEG	Drugs at the last follow-up period
			Bilateral or unilateral lesions	Central sparing	Cognitive impairment	Gross motor impairment						
1/F	12	Unknown	Bilateral	No	Severe	Severe	16	Spasm[a]	Yes	Daily	R-F, L-F, R-CP, L-CP, L-O (sp, SW, spW)	VPA, TPM
2/M	47	Unknown	Bilateral	Yes	Moderate	None	49	Spasm[a]	Yes	None	B-F, B-P, G (spW, SWC, polyspW)	CLB, ZNS
3/F	18	Unknown	Bilateral	Yes	Mild	None	21	Focal sz[a]	Yes	None	L-T, L-PO, G (sp, spW, polysp, polyspW)	VPA, CLB
4/M	9	Unknown	Bilateral	No	Severe	Severe	18	Focal sz[a]	Yes	Daily	R-F, L-F, R-T, L-T, L-P, R-O (sp)	VPA, LTG
5/F	40	Unknown	Bilateral	Yes	Moderate	None	57	Focal sz[a]	Yes	Daily	L-F, R-T, L-T, R-C (sp)	CBZ, LEV
6/M	15	Unknown	Bilateral	No	Severe	Moderate	55	Myoclonic sz	No	None	R-F, L-F, R-T, G (spW, SWC)	PB
7/M	1	Unknown	Bilateral	Yes	Moderate	Moderate	10	Tonic–clonic sz	No	Yearly	R-FT, L-FT (sp, SW, SWC)	PB
8/M	35	Unknown	Bilateral	Yes	Severe	None	43	Focal sz Spasm[a]	No	Daily Weekly	R-T, L-T, R-CP, L-CP, L-O (sp, spW, SWC, polyspW)	VPA, ZNS, CLB
9/F	11	Adenovirus	Bilateral	Yes	Severe	Moderate	24	Myoclonic sz Brief tonic sz	No	Daily Daily	B-F, R-T, L-T (spW, SWC)	PB, TPM
10/M	14	Human herpesvirus 6	Bilateral	No	Severe	Severe	18	Focal sz Myoclonic sz Spasm Brief tonic sz Clonic sz	Yes (focal and myoclonic sz)	Daily Daily Daily Daily None	R-D (sp, SW, SWC)	TPM, LEV

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; CBZ, carbamazepine; CLB, clobazam; EEG, electroencephalography; F, female; LEV, levetiracetam; LTG, lamotrigine; M, male; PB, phenobarbital; PEE, post-encephalopathic epilepsy; polysp, polyspike; polyspW, polyspike and slow wave; sp, spike; spW, spike and slow wave; SW, sharp wave; SWC, sharp and slow wave complex; sz, seizure; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide; R, right; L, left; B, bilateral; F, frontal; C, central; T, temporal; P, parietal; O, occipital; D, diffuse; G, generalized.

[a]Seizures confirmed with ictal video-EEG recording.

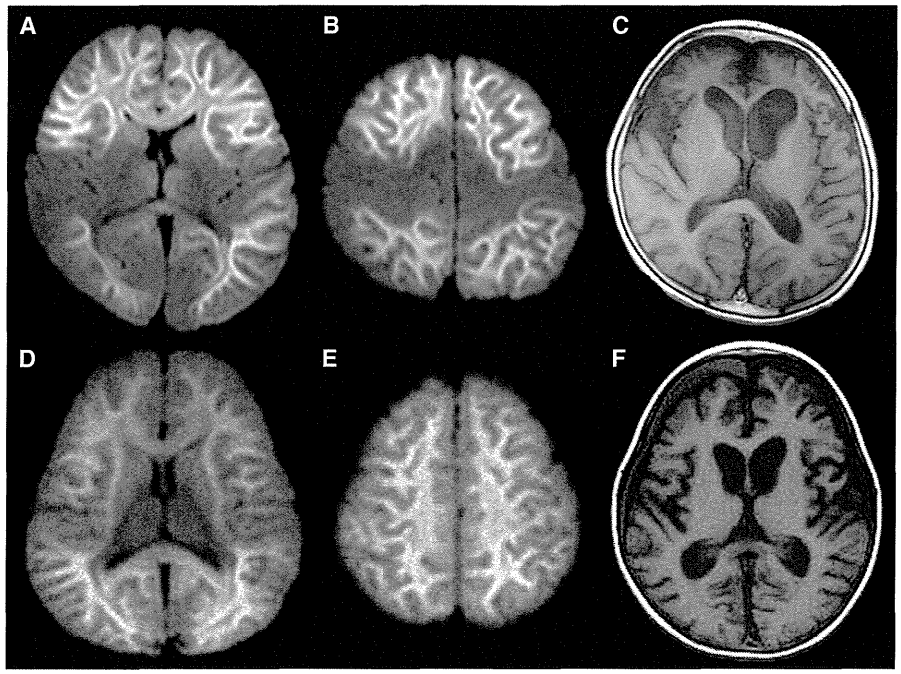

Figure 1.
MRI findings in acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). (**A**, **B**) Diffusion-weighted images from patient 6 obtained on day 6 after onset of encephalopathy showing high signal intensity in bilateral diffuse subcortical white matter with central sparing. (**C**) A T_1-weighted MR image from the same patient obtained 14 months after onset of encephalopathy showing diffuse cerebral atrophy. (**D**, **E**) Diffusion-weighted images from patient 4 obtained on day 6 after onset of encephalopathy showing bilateral diffuse subcortical high signal intensity without central sparing. (**F**) A T_1-weighted MR image from the same patient obtained 1 month after onset of encephalopathy showing diffuse cerebral atrophy. Note that a right frontal subdural hematoma is also present.

without nitric oxide injury may underlie the development of AESD. Furthermore, some genetic factors have been reported to predispose children to AESD.[18,19]

Another factor causing epileptic spasms in children following AESD is age-dependent reorganization of brain networks after the acute injury. Previous studies on infantile spasms have hypothesized that abnormal neural networks between the cortex and subcortical structures and the brainstem trigger spasms.[20–22] This is supported by another study with fluorodeoxyglucose positron emission tomography, which showed activation of the lenticular nuclei and brainstem with cortical hypometabolism.[21] In addition, Koo and Hwang[23] reported that the location of cortical lesions correlated with age at the onset of spasms. Occipital lesions were associated with the earliest onset of spasms and frontal lesions were associated with the latest onset. This pattern suggests that maturation of the white matter triggers the onset of spasms.[23] In our study, patients with PEE had diffuse subcortical white matter damage. In the repair of this diffuse white matter damage during the recovery period, abnormal neuronal networks between the cortex and subcortical structures will be constructed and may trigger epileptic spasms in a manner similar to that which white matter maturation triggers spasms in patients with infantile spasms.

Startle seizures after AESD may result from injury to a network different from that injured in patients with epileptic spasms. Startle seizures can be seen in patients with various etiologies, including perinatal brain injury, congenital infection, traumatic brain injury, and brain malformation.[24–26] Despite the etiologic differences, the results of magnetoencephalography, intracranial EEG, simultaneous EEG-functional MRI, and surgical resection studies indicate that the supplementary motor area is involved in the generation of startle seizures.[27–33] Based on this evidence, startle seizures could be generated by the frontoparietal network located over the mesial surface of the brain.[28,30] In the current study, all patients with PEE had diffuse subcortical white matter damage, including damage to frontal and parietal lobes, regardless of the presence or absence of central sparing. Acute injury in the subcortical white matter and the subsequent process of reorganization may contribute to the formation of abnormal frontoparietal networks, triggering startle focal seizures in PEE following AESD.

The findings of the present study are limited by the small sample size, the short follow-up period, and the fact that not all patients with PEE had an ictal video-EEG recording. In addition, anti-*N*-methyl-D-aspartate receptor (NMDAR) or other autoimmune antibodies were

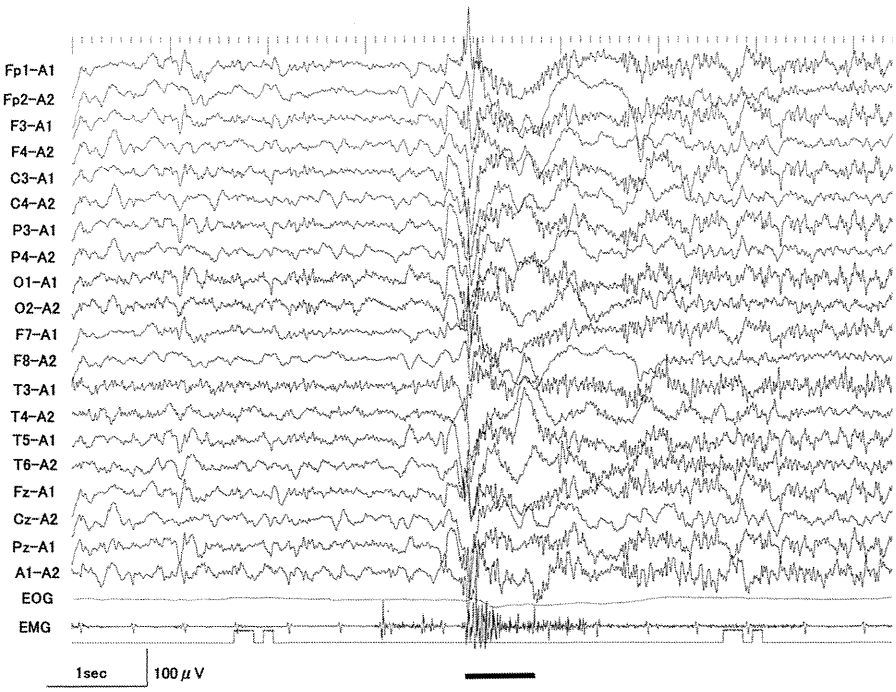

Figure 2.
Ictal EEG recorded during an epileptic spasm. Ictal EEG recorded from patient 8 during a spasm reveals a complex of diffuse irregular slow and sharp waves with diffuse fast wave activity. Electromyography shows crescendo-decrescendo activities lasting for 0.5 s. The bar under the EEG trace indicates the period of head nodding with elevation of arms.
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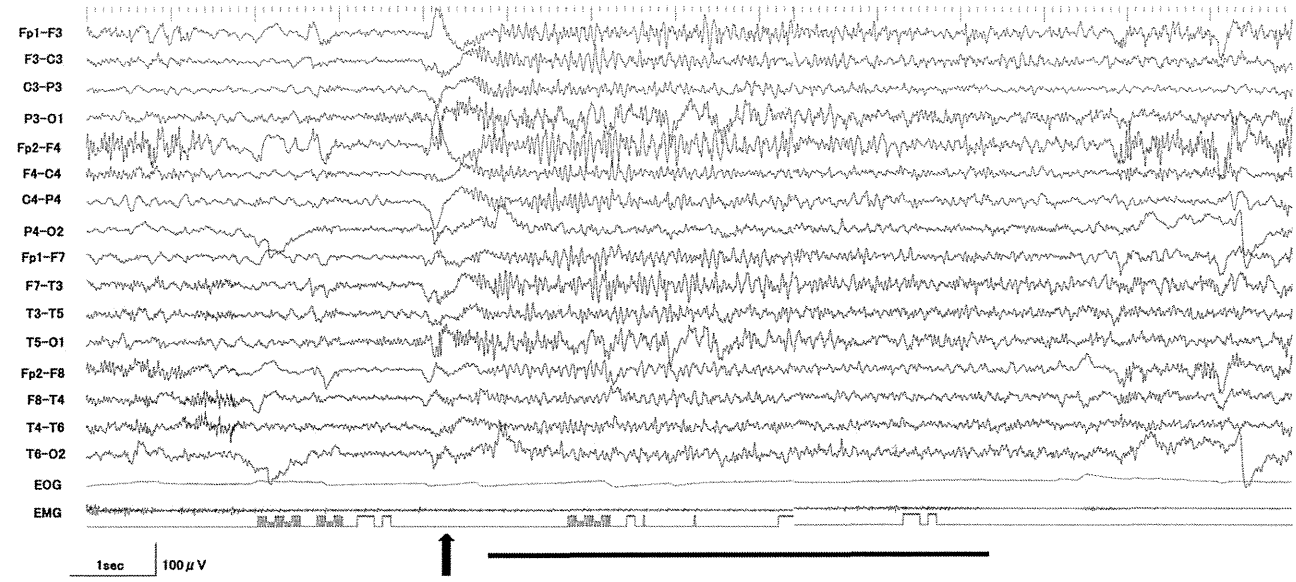

Figure 3.
Ictal EEG recorded during a startle focal seizure. Ictal EEG recorded from patient 3 during a startle seizure induced by sudden unexpected sounds. Frontal-dominant fast wave activities last for 12 s with a progressive increase in amplitude and decrease in frequency. Just after the startle movement (arrow), the patient had motion arrest with axial stiffness in the sitting position and gradually turned her head to the left (bar) during the seizure. This versive seizure was supposed to be of mesial frontal lobe origin, although the frontal-dominant fast wave activities were not well localized. The irregular slow wave at the time of the acoustic stimulation is an artifact caused by a startle movement.
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not examined in most of our patients. However, we could differentiate AESD from other types of acute encephalopathy/encephalitis with prolonged seizures in the acute phase, such as anti-NMDAR encephalitis or FIRES, by clinicoradiologic findings.[34–37] Biphasic seizures and late reduced diffusion on DWI are characteristic features in children with AESD, not in children with anti-NMDAR encephalitis or FIRES. Furthermore, our patients did not

have psychiatric symptoms, behavioral changes, or movement disorders that are commonly observed in children with anti-NMDAR encephalitis, and they did not have pharmacoresistant seizures in the acute phase that are observed in children with FIRES.

In conclusion, approximately one fourth of children with AESD developed PEE after a median interval of 8.5 months. PEE was intractable and not associated with biphasic seizures or status epilepticus during the acute phase of AESD, but was associated with poor cognitive outcomes. Epileptic spasms and startle focal seizures were common seizure types in PEE following AESD. Alterations in cortical-subcortical and/or frontoparietal neural networks after acute brain injury appear to trigger epileptic spasms and startle focal seizures.

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Disclosure

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

References

1. Mizuguchi M, Yamanouchi H, Ichiyama T, et al. Acute encephalopathy associated with influenza and other viral infections. *Acta Neurol Scand* 2007;115:45–56.
2. Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev* 2012;34:337–343.
3. Annegers JF, Hauser WA, Beghi E, et al. The risk of unprovoked seizures after encephalitis and meningitis. *Neurology* 1988;38:1407–1410.
4. Chen YJ, Fang PC, Chow JC. Clinical characteristics and prognostic factors of postencephalitic epilepsy in children. *J Child Neurol* 2006;21:1047–1051.
5. Fowler A, Stodberg T, Eriksson M, et al. Long-term outcomes of acute encephalitis in childhood. *Pediatrics* 2010;126:e828–e835.
6. Lee WT, Yu TW, Chang WC, et al. Risk factors for postencephalitic epilepsy in children: a hospital-based study in Taiwan. *Eur J Paediatr Neurol* 2007;11:302–309.
7. Lin JJ, Hsia SH, Wu CT, et al. Mycoplasma pneumoniae-related postencephalitic epilepsy in children. *Epilepsia* 2011;52:1979–1985.
8. Trinka E, Dubeau F, Andermann F, et al. Clinical findings, imaging characteristics and outcome in catastrophic post-encephalitic epilepsy. *Epileptic Disord* 2000;2:153–162.
9. Sellner J, Trinka E. Seizures and epilepsy in herpes simplex virus encephalitis: current concepts and future directions of pathogenesis and management. *J Neurol* 2012;259:2019–2030.
10. Takanashi J, Oba H, Barkovich AJ, et al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. *Neurology* 2006;66:1304–1309; discussion 1291.
11. Okumura A, Kidokoro H, Tsuji T, et al. Differences of clinical manifestations according to the patterns of brain lesions in acute encephalopathy with reduced diffusion in the bilateral hemispheres. *AJNR Am J Neuroradiol* 2009;30:825–830.
12. Palisano RJ, Rosenbaum P, Bartlett D, et al. Content validity of the expanded and revised gross motor function classification system. *Dev Med Child Neurol* 2008;50:744–750.
13. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. *Neurology* 2002;59:1224–1231.
14. Howell KB, Katanyuwong K, Mackay MT, et al. Long-term follow-up of febrile infection-related epilepsy syndrome. *Epilepsia* 2012;53:101–110.
15. Saito T, Saito Y, Sugai K, et al. Late-onset epilepsy in children with acute febrile encephalopathy with prolonged convulsions: a clinical and encephalographic study. *Brain Dev* 2013;35:531–539.
16. Takanashi J, Tada H, Terada H, et al. Excitotoxicity in acute encephalopathy with biphasic seizures and late reduced diffusion. *AJNR Am J Neuroradiol* 2009;30:132–135.
17. Kawashima H, Morishima T, Togashi T, et al. Extraordinary changes in excitatory amino acid levels in cerebrospinal fluid of influenza-associated encephalopathy of children. *Neurochem Res* 2004;29:1537–1540.
18. Shinohara M, Saitoh M, Nishizawa D, et al. ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus. *Neurology* 2013;80:1571–1576.
19. Shinohara M, Saitoh M, Takanashi J, et al. Carnitine palmitoyl transferase II polymorphism is associated with multiple syndromes of acute encephalopathy with various infectious diseases. *Brain Dev* 2011;33:512–517.
20. Chugani HT, Chugani DC. Basic mechanisms of childhood epilepsies: studies with positron emission tomography. *Adv Neurol* 1999;79:883–891.
21. Chugani HT, Shewmon DA, Sankar R, et al. Infantile spasms: II. Lenticular nuclei and brain stem activation on positron emission tomography. *Ann Neurol* 1992;31:212–219.
22. Juhasz C, Chugani HT, Muzik O, et al. Neuroradiological assessment of brain structure and function and its implication in the pathogenesis of West syndrome. *Brain Dev* 2001;23:488–495.
23. Koo B, Hwang P. Localization of focal cortical lesions influences age of onset of infantile spasms. *Epilepsia* 1996;37:1068–1071.
24. Yang Z, Liu X, Qin J, et al. Clinical and electrophysiological characteristics of startle epilepsy in childhood. *Clin Neurophysiol* 2010;121:658–664.
25. Tibussek D, Wohlrab G, Boltshauser E, et al. Proven startle-provoked epileptic seizures in childhood: semiologic and electrophysiologic variability. *Epilepsia* 2006;47:1050–1058.
26. Manford MR, Fish DR, Shorvon SD. Startle provoked epileptic seizures:features in 19 patients. *J Neurol Neurosurg Psychiatry* 1996;61:151–156.
27. Bancaud J, Talairach J, Bonis A. Physiopathogenesis of startle epilepsy (an epilepsy of the supplementary motor area). *Electroencephalogr Clin Neurophysiol* 1968;24:490.
28. Fernandez S, Donaire A, Maestro I, et al. Functional neuroimaging in startle epilepsy: involvement of a mesial frontoparietal network. *Epilepsia* 2011;52:1725–1732.
29. Garcia-Morales I, Maestu F, Perez-Jimenez MA, et al. A clinical and magnetoencephalography study of MRI-negative startle epilepsy. *Epilepsy Behav* 2009;16:166–171.
30. Job AS, De Palma L, Principe A, et al. The pivotal role of the supplementary motor area in startle epilepsy as demonstrated by SEEG epileptogenicity maps. *Epilepsia* 2014;55:e85–e88.
31. Nolan MA, Otsubo H, Iida K, et al. Startle-induced seizures associated with infantile hemiplegia: implication of the supplementary motor area. *Epileptic Disord* 2005;7:49–52.
32. Oguni H, Hayashi K, Usui N, et al. Startle epilepsy with infantile hemiplegia: report of two cases improved by surgery. *Epilepsia* 1998;39:93–98.
33. Serles W, Leutmezer F, Pataraia E, et al. A case of startle epilepsy and SSMA seizures documented with subdural recordings. *Epilepsia* 1999;40:1031–1035.
34. Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-*N*-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;162:850–856 e852.
35. Florance NR, Davis RL, Lam C, et al. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11–18.
36. Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. *Epilepsia* 2011;52:1956–1965.
37. van Baalen A, Hausler M, Boor R, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. *Epilepsia* 2010;51:1323–1328.

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