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Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis

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Objective –We conducted a nationwide multicenter study in Japan to elucidate the clinical and laboratory characteristics of acute encephalitis with refractory, repetitive partial seizures (AERRPS). *Materials and methods* – Clinical and laboratory features, treatment, and outcome were assessed using a structured questionnaire. *Results* –Twenty-nine children were enrolled in the study. Refractory and repetitive partial seizures accompanied by fever were the cardinal clinical features. Partial seizures consisted principally of eye deviation or facial twitching, being periodically repeated during the acute phase. These seizures were refractory to conventional anticonvulsants and were only suppressed by high-dose intravenous barbiturate administration. Rhythmic activities on electroencephalography and non-specific cerebral atrophy on neuroimaging were common. Serum or cerebrospinal antibodies against GluRε2 were positive in six patients. General prognosis was unfavorable due to intractable epilepsy and cognitive deficits. *Conclusion* – Based on the peculiar and homogenous features, AERRPS can be regarded as a distinct clinical entity.

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Introduction

Acute encephalitis/encephalopathy in children is often associated with seizures, and status epilepticus (SE) is one of the presenting symptoms. In most cases, seizures appear transiently during the acute phase and can be controlled by standard therapy. However, 2.7–6.7% of the central nervous system (CNS) infection results in the evolution of epilepsy (1). This 'post-encephalitic' epilepsy is characterized by intractable partial seizures associated with mesial temporal sclerosis and cognitive impairment (2). Post-encephalitic epilepsy is observed after a latent period of several months or years (3).

In contrast, in some cases with intractable epilepsy following encephalitis exists, without any latent period. This population was first recognized by Awaya et al. in 1986, and has been subsequently reported in Japan as 'acute encephalitis with refractory, repetitive partial seizures (AERRPS)' (4, 5). AERRPS has three cardinal features in common: (i) acute encephalitis of unknown origin, without underlying developmental delay or prior unprovoked seizures; (ii) presenting with repetitive and refractory partial seizures during the acute phase, referred to as 'refractory partial SE', which is followed by, (iii) continuous transition to intractable epilepsy without a latent period. It is distinct from encephalitis or acute neurological insults of known origin (shown in Table 1). AERRPS has not been perceived in Western countries, although it is widely recognized in Japan. Moreover, systematic analyses with regard to detailed clinical characteristics of AERRPS have not been performed.

In the present study, we describe the clinical characteristics of 29 patients with AERRPS based on the data of the first nationwide multicenter study conducted in Japan. These cases have some

Table 1 Differential diagnosis of AERRPS

Viral encephalitis and virus-associated encephalopathy
Herpes simplex encephalitis
Japanese encephalitis
Acute necrotizing encephalopathy
Acute encephalopathy with late reduced diffusion
Acute infantile encephalopathy
Predominating over frontal lobe
Acute limbic encephalitis
Paraneoplastic
Non-paraneoplastic
Anti-VGKC antibody associated
Anti-NMDA-R antibody associated
Miscellaneous
Metabolic encephalopathy
Organic aciduria
Urea cycle disorder
Fatty acid oxygenation disorder
Mitochondrial disease
Epilepsy
Rasmussen's encephalitis
Migrating partial seizures in infancy
Other known acute neurological insults

peculiar features in common; such as acute onset of extremely refractory and repetitive partial seizures, presumed autoimmune inflammatory pathomechanism, and poor neurological outcomes.

Patients and methods

Among acute encephalitis of unknown origin in childhood, AERRPS was defined as those fulfilling three aforementioned features. Acute neurological illnesses of known origin (shown in Table 1) were extensively studied and thus were excluded.

This is a retrospective, multicenter, questionnaire-based study. First, we inquired from principal medical institutions whether or not they had experience on cases identical to or analogous to AERRPS. Of 85 institutions consulted, 22 of them responded to us. Then, we sent a detailed multiple-choice-based questionnaire to these institutions, and they agreed to participate in our study. The items in the questionnaire included patient profiles, precipitating factors before onset, seizure types and their duration, concomitant neurological symptoms, blood and cerebrospinal fluid (CSF) studies, electrophysiological and neuroradiological findings, treatments and their efficacy, and outcomes.

There were 39 cases collected from 22 hospitals between 1990 and 2006. After a careful review of the cases, 10 were concluded not to be identical to AERRPS and thus excluded for the following reasons: one had no partial seizure; four required neither intravenous barbiturates nor benzodiazepines to alleviate seizures; two did not develop subsequent epilepsy; three were diagnosed as acute limbic encephalitis; and one had insufficient medical records. Consequently, 29 patients fulfilled the criteria for AERRPS and were included in the study. Tables S1–S3 detail the clinical characteristics and investigations of the patients with AERRPS. Clinical details of Patients 22–24 have been reported previously (6). Case reports of patients 7, 9, 12, 14, 29, and 25 have also been published elsewhere in Japanese journals. Because of the retrospective nature of the study, written informed consent was not always acquired.

Seizures were classified according to the revised clinical and electroencephalographic classification of epileptic seizures from the Commission on Classification and Terminology of the International League Against Epilepsy (7). Routine blood and CSF studies, electroencephalography (EEG) and magnetic resonance (MR) imaging were performed in all patients. Serum and CSF antibodies against glutamate receptor epsilon 2 subunit (GluRε2) were analyzed as previously described (8). With respect to the efficacy of treatment, we used the following scale according to the reduction in seizure frequency: complete (seizure free), excellent (seizure reduction of 75% or more), good (50–75% reduction), and poor (50% or less reduction).

Results

Patient profiles

Among the 29 patients (M:F = 19:10), the age of disease onset ranged from 1 to 14 years (6.8 $\pm$ 4.0). Fourteen patients were at their school age. The family histories of the patients were unremarkable. Four patients had experienced febrile convulsions but none had underlying epilepsies or other neurological abnormalities.

Precipitating factors

Out of the 29 patients, 26 bore evidence of antecedent febrile illness before the onset of neurological symptom. The latency between antecedent fever and the onset of neurological symptoms was 4.9 $\pm$ 2.3 days (range: 2–10 days).

Characteristics in the acute phase

The acute phase was defined as the period during which patients presented with persistent fever or necessitated continuous anticonvulsant infusion to suppress seizures or both as described below. The duration of this phase ranged from 15 to 312 days.

Clinical manifestations – All 29 patients presented with fever at the onset of neurological symptoms, as well as throughout the acute phase. High-grade fever was observed in 23 patients (higher than 39°C), which was persistent in most cases. Intermittent fever concomitant with aggravation of seizures was also present.

The initial neurological manifestations were seizures in 20 patients, altered consciousness in seven patients, visual agnosia in one patient, and unidentified in one patient, whereas the manifestations in one patient could not be identified.

Seizures were constantly the most prominent and significant manifestation of AERRPS (Table 2). Partial seizure was invariable, and in the vast majority of cases, it was the predominant seizure type: Most commonly, these seizures took the form of eye deviation (69%) and hemifacial twitching (62%), with an occasional development to ipsilateral clonic seizure (48%). Autonomic manifestations such as apneic spell were not uncommon (28%). Seizures usually lasted 1–5 min (83%) and terminated spontaneously, but often occurred in clusters without recovery of consciousness during the interval periods. Within a week, they increased in frequency despite treatment and became full-blown, being periodically repeated every 5–10 min in 14 cases (48%).

Impairment of consciousness was also common. Other neurological symptoms included psychiatric and movement disorders, and memory impairment.

Table 2 Clinical features and laboratory findings

	No. of patients
Acute symptoms	
Seizure	
Simple partial	1
Complex partial	25
Secondary generalized	24
Generalized tonic–clonic	8
Tonic	8
Myoclonic	4
Impairment of consciousness	24
Psychiatric disorders	9
Movement disorders	12
Memory impairment	8
Laboratory findings	
Blood	
High ferritin	4/4 (221–2.370 mg/dl)
Positive anti-GluRε2 Ab	6/9
CSF	
Pleocytosis (>5/mm^3)	19/29 (6–25/mm^3)
High protein concentration (>45 mg/dl)	5/29 (46–85 mg/dl)
High neopterin	4/4 (246–1.154 nmol/ml)
High neuron specific enolase	2/6 (33–34 mg/dl)
Positive anti-GluRε2 Ab	5/9

Ab, antibody.

EEG findings – A total of 71 EEGs was studied (1–289 days of admission). During the first 14 days of neurological illness, pretreatment EEGs consisted principally of high-voltage slow background activity (7/9, 78%). At the later stage, all 29 patients developed interictal epileptiform discharges with a variety of spatial distribution. Multiple independent foci were observed in 15 patients (54%). Seven patients (24%) were found to have epileptic foci that migrated during the acute phase. Ictal discharges were recorded in 24 patients. They typically began with localized rhythmic activities consisting of spikes or sharp waves and progressively involved the adjacent areas, thus leading to secondary generalization. Ictal discharges disappeared spontaneously within a few minutes and then reappeared, being periodically repeated every 5–10 min.

Neuroimaging – Magnetic resonance imaging (MRI) was examined at least once in all patients. Those performed within 7 days after onset (14 cases) revealed mild brain edema in two patients but were otherwise normal. Subsequently, six patients showed hippocampal or amygdaloid hyperintensities on fluid-attenuated inversion recovery (FLAIR) without the evolution of epileptic foci at the corresponding area. Abnormal symmetrical T2 hyperintensity in the periventricular white matter and claustrum were found in four and two patients, respectively.

Laboratory examinations – The routine blood cell count and biochemistry, as well as blood levels of glucose, ammonia, and lactate were generally unremarkable. The data on inflammatory and autoimmune markers are summarized in Table 2. Plasma amino acid and urinary organic acid revealed no abnormalities. Extensive virological studies were also conducted. Herpes simplex virus was serologically negative or had remotely infected 27 patients who were examined. Serological studies for cytomegalovirus ($n = 16$), Epstein–Barr virus ($n = 20$), and human herpes virus 6 ($n = 11$) showed no serial elevation of antiviral titer. Viral cultures from CSF or throat swabs in 14 patients were all negative.

Treatment – Intravenous barbiturates were administered in 22 patients, of whom 13 showed complete, three excellent, and four good responses, while none were poor. Pentobarbital was most frequently used (15 patients), followed by thiopental (five) and thyamiral (four). The effective and maximal doses of pentobarbital were 4.22 ± 1.82 and 4.98 ± 2.06 mg/kg/h, respectively. The EEG backgrounds when seizure had been suppressed were high voltage slow wave in one, burst-suppres-

sion pattern in 14, and complete suppression in three. The duration of barbiturate infusion ranged from 4 to 312 days (52.3 ± 72.6 days).

Benzodiazepines, mainly midazolam, were administrated in 25 patients, of whom three showed complete, five good, and 17 poor effects. The maximal dose of midazolam was 0.47 ± 0.33 mg/kg/h. Diazepam was used in bolus injection successfully in five of 12 patients, which were only temporarily effective. The efficacy of intravenous lidocaine (1.5–6 mg/kg/h) and phenytoin (5–25 mg/kg/day) were limited (8% and 30%, respectively), transient, and incomplete.

Immunomodulatory treatments were challenged in some cases. Twelve patients were treated with corticosteroids mostly by intravenous methylprednisolone, of whom two were effective. Intravenous immunogloburin (IVIG) in 13 patients did not result to any improvement. One patient underwent plasma exchange, which was unsuccessful.

Chronic phase

Course and prognosis

Two of the 29 patients dropped out, and therefore, the remaining 27 patients received follow-up, with a mean period of 60.9 months (ranging from 8 to 194 months). All patients had residual epilepsy. As defined in the diagnostic criteria, all patients showed continuous evolution from encephalitis to residual epilepsy without a latent period. The types of seizures were essentially the same as those in the acute phase except for scarce secondary generalization. Most patients had residual cognitive impairment. Intelligence quotients (IQs), measured using the Wisconsin Intelligence Scale for Children-III (WISC-III), were less than 70 in 16 patients and below 20 in 10 patients. All patients who had the antibody against GluRε2 were found to have residual cognitive impairment. Other residual neurological deficits included memory impairment (15%), autistic tendency (22%), hyperkinetism (15%), learning disability (15%), personality change (15%), and emotional instability (22%). One patient suddenly died of unknown cause 9 years after onset. Serial MRI scanning revealed diffuse brain atrophy after a month or more. Hippocampal or amygdaloid signal abnormalities remained unchanged in four of six patients.

Discussion

The clinical entity of AERRPS arose in 1986, when Awaya et al. described five cases of 'peculiar onset post-encephalitic epilepsy' (9). In his investigation into post-encephalitic epilepsy, he found a novel subtype of epilepsy characterized by refractory partial seizures persisting from the onset of encephalitis to the convalescent phase. Meanwhile, in 1989, Shiomi advocated a subgroup of encephalitis characterized by very frequent seizures that can be suppressed only by intravenous barbiturates. It should be noted that Awaya defined this illness as post-encephalitic 'epilepsy' and therefore, discussed mainly its epileptogenesis (4), while Shiomi classified it as a subtype of 'encephalitis' and put emphasis on the symptoms in the acute phase. These two clinical entities shared some characteristics: acute onset of illness, very frequent partial seizures, extremely refractory trait of seizures, inconspicuous switchover from encephalitis to subsequent epilepsy, and residual cognitive impairment. In 2001, we proposed the term AERRPS to integrate the characteristics of these entities (5). To date, more than 30 cases compatible to this condition have been accumulated in Japan (4).

We report the first multicenter collaborative study on acute encephalitis with refractory, repetitive partial seizures (AERRPS) to clarify its clinical features. The definitive features became evident as a result of this study. Several clinical aspects that seem to be characteristics of AERRPS are vital for the diagnosis, and these are listed in the diagnostic criteria (Table 3). EEG findings in AERRPS, particularly ictal recordings, are of diagnostic significance. The repetitive EEG pattern of ictal discharges has been described (6). In

Table 3 Diagnostic criteria for AERRPS

Mandatory:

1. Acute onset of seizures or consciousness impairment, in the absence of underlying developmental delay or prior unprovoked seizures
2. Extraordinarily frequent and refractory partial seizures, referred to as 'refractory partial SE': The patients usually show partial seizures characterized by eye deviation and facial twitching which repeat within an interval of 30 minutes or less, and necessitate long-term anesthesia (2 weeks or more) with intravenous barbiturates or benzodiazepines to attain burst-suppression coma on EEG
3. Continuous switchover to refractory epilepsy without a latent period

Supportive findings:

1. Antecedent febrile illness, which occurs 2–10 days before the onset of neurological symptoms
2. Persistent fever during the acute phase of illness
3. CSF findings: mild pleocytosis or slight increase in protein (inflammatory markers such as IL-6 or neopterin may be upregulated) or both
4. EEG: slow background during the acute phase and multifocal spikes during the chronic phase (ictal EEG reveals variable foci of epileptiform discharges and frequent secondary generalization)
5. MRI: no specific abnormalities except for occasional T2/FLAIR hyperintese signal of mesial temporal lobe
6. Profound neurological sequelae: cognitive deterioration, psychiatric disorders, and memory impairment, as well as occasional motor disability

contrast, MRI is not always helpful in establishing diagnosis because there are no specific neuroradiological abnormalities in AERRPS. Hyperintensities in limbic structures on MRI, which were observed in six patients in our series, are presumably due to refractory SE. This finding is consistent with a recent report on a Taiwanese series (10).

Clinical entities resembling AERRPS have also been reported elsewhere outside Japan. Kramer et al. (11) reported five cases of refractory SE which is presumably caused by encephalitis of unknown origin. In their report, they identified the preceding febrile illness, persistent seizures despite induced burst suppression coma, and negative results for the cause of seizures, as common features. They postulated that this severe refractory type of SE is due to relatively mild encephalitis. Mikaeloff et al. (12) reported 14 cases of 'devastating epileptic encephalopathy in school-age children', which is characterized by prolonged SE following non-specific febrile illness without any latent period. These cases are slightly different from AERRPS because they are limited to the cases with school-age onset and perisylvian involvement. These facts clearly demonstrate that the clinical entities similar to AERRPS are distributed all over the world.

Limbic encephalitis (LE) is characterized by limbic seizures, short-term memory loss, and psychiatric symptoms (13). Recent studies have revealed that acute non-paraneoplastic LE is related to the anti-voltage-gated potassium channel antibody (14, 15) or antibodies that reacted with the *N*-methyl-D-aspartate receptor (16, 17). AERRPS can be distinguished from LE for the following reasons. First, psychiatric disorders and memory impairment are uncommon and seldom present as initial predominating features in AERRPS. Second, no case has been described in which AERRPS was presumably caused by a neoplasm. Third, AERRPS, but not LE, shows a uniformly unfavorable outcome with neurological sequelae. Nevertheless, there is a report of an atypical clinical presentation of paraneoplastic LE with pharmacoresistant epilepsy lacking memory loss or psychiatric symptoms (18). Hence, there is a possibility of some overlap between AERRPS and LE.

The process of epileptogenicity in AERRPS is not well understood. Epilepsy secondary to encephalitis is reported to occur after a latent period of 3.82 ± 3.7 years (1). In contrast, there is no definite seizure-free period in AERRPS. We hypothesize that extraordinary epileptogenicity prolongs seizures even after the acute phase and therefore makes the initiation of epilepsy inconspicuous.

The etiology of AERRPS remains to be clarified. In the present study, several lines of evidence supported the hypothesis that some of AERRPS are associated with CNS inflammation. First, unlike epilepsy, neurological manifestations are preceded by febrile illness and are accompanied by persistent fever. Second, the levels of neopterin, which are known to be up-regulated in macrophage activation syndrome, are elevated in CSF; however, others seem to be irrelevant to the inflammatory process. Not all the patients showed increased mononuclear cells or elevated CSF protein concentration. In the previous reports, Kramer et al. maintained an 'inflammatory' theory (11), whereas Mikaeloff et al. objected to this (12). Taken together, it is possible that AERRPS and similar disorders are caused by multiple etiologies with a common clinical phenotype.

The involvement of the inflammatory process permits us to speculate that a specific infectious agent causes AERRPS; however, this is unlikely because extensive viral studies were all negative. Another possibility is an autoimmune mechanism. It is intriguing that the serum or CSF of some patients with AERRPS was positive for antibodies against GluRε2. Ito et al. first reported a patient with AERRPS who had this antibody (19). This antibody is not specific to AERRPS but is found in patients with various neurological diseases, including intractable epilepsy, Rasmussen encephalitis, and other forms of encephalitis (8). However, the early appearance (0–20 days after onset) of antibodies against GluRε2 in CSF suggests that GluR autoimmunity contributes to the onset of encephalitis (20).

In conclusion, a novel clinical syndrome designated AERRPS is characterized by definite hallmarks. AERRPS is currently defined solely by its clinical characteristics, and thus further investigation into its pathomechanisms is necessary.

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Supporting information

Additional Supporting Information may be found in the online version of this article:
Table S1. Clinical features.

Table S2. Laboratory, EEG, and MRI findings.
Table S3. Treatment and Outcome.

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