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CLINICAL EVALUATION AND MRI FINDINGS IN EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY WITH SUPPRESSION-BURST

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INDEXING WORDS

early infantile epileptic encephalopathy; magnetic resonance imaging; suppression-burst on EEG; tonic spasms; dysmyelination

SYNOPSIS

The clinical courses and a follow-up study on the MRI findings in four cases with early infantile epileptic encephalopathy (EIEE) are reported. The patients consisted of one male and three females. The age at onset was before 15 days on life and the etiology was unknown in all cases. EEG improvement and a decrease in seizure frequency were seen after treatment with ACTH and anticonvulsants in three of the four patients, while no treatment was effective in the other patient who developed Lennox-Gastaut syndrome through West syndrome. Psychomotor development of all patients was severely retarded, and it was impossible for three cases to gain head control until 12 months old. MRI findings revealed dysmyelination of white matter in the cerebrum in three patients and asymmetrical myelination in the other patient. These results suggested that EIEE is based on brain immaturity combined with dysmyelination.

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INTRODUCTION

Early infantile epileptic encephalopathy with suppression-burst (EIEE) which was characterized by an early onset, frequent tonic spasms, suppression-burst on EEG, poor responses to various treatments and a grave outcome, was first described by Ohtahara in 1976.[9] Recently, there has been several reports on its etiology and clinical features,[5, 7, 8, 12, 13] while there has been few reports on magnetic resonance imaging (MRI) findings in EIEE. In the past three years, we have found four patients with EIEE (one male and three females) in whom the definite etiology was unknown. This study deals with the clinical courses and a follow-up study on the MRI findings in the four patients with EIEE to clarify the developmental process in EIEE brain.

PATIENTS AND METHODS

Patients

The profiles and responses to treatments of the four cases are summarized in the Table. The patients consisted of one male and three females. The age of onset was before 15 days of life in all cases, and the initial symptoms at onset were tonic spasms and tonic-clonic convulsions. The EEG at onset showed the suppression-burst pattern reported by Ohtahara.[9]

Table Profiles of early infantile epileptic encephalopathy with suppression-burst.

	Case 1	Case 2	Case 3	Case 4
Sex	Female	Male	Female	Female
Age at present (months)	36	27	21	18
Gestational age (wks)	38	38	40	41
Birth weight (gm)	3100	3130	2806	3715
Apgar score at 5 min.	9	9	9	10
Age at onset (day)	1	12	5	8
Effect of treatment				
Vit. B_6	-	-	-	-
ACTH	+	+	+	+
Ketogenic diet	-	N.T.	N.T.	+
γ-globulin	-	-	N.T.	N.T.
Anticonvulsants (VPA,NZP,PB,PHT)	-	+	+	+

+: effective, -: not changed, N.T.: not tried.

Methods

The MRI imager used in the present study was a magnetic resonance system (Picker International Co., Ohio, USA). The pulse sequences for inversion recovery (IR) and spin echo (SE) were as follows: time of inversion, 500 msec; time of echo, 80 msec; time of repetition, 2100 msec; image section, 10 mm thick; matrix size, 256 x 256; scan number, 128 times; and number of slices, 8.

Oligosaccharides in urine were determined by the methods of Michalski et al.[6)]

RESULTS

Follow-up study on the patients

Case 1 was a female infant born at full term, weighing 3100 gm, to a healthy primigravida who had no problems during pregnancy. There was no trouble during labour except for coiling of the umbilical cord around the neck, and the Apgar score at five minutes was 9. The family history was unremarkable. Tonic-clonic convulsions of the legs were noticed from just after birth, and tonic spasms with suppression-burst on EEG were seen from the eleventh day of life. No neurological abnormality was seen on physical examination at birth except for mild muscle hypotonia of the limbs. The results of aminoacid analysis of plasma and organic acid analysis of urine were within normal range. No abnormal spots of oligosaccharides were detected for urine. X-Ray computed tomography (CT) of her brain showed no abnormal findings on the third day of life. The suppression-burst pattern on EEG described by Ohtahara gradually changed to hypsarhythmia by five months of age and to generalized 2-2.5 Hz spike or polyspikes and wave by eleven months of age, as shown in Fig. 1. Accompanying the changes seen on EEG, the clinical seizure type gradually changed from tonic spasms in series to tonic seizures lasting several minutes. MR imaging on IR at three months of age showed scarcely any high signal areas in the white matter, which correspond to myelinated fibers. Several forms of therapy, including ACTH, a ketogenic diet, pyridoxal phosphate (Vit. B_6), γ-globulin and commercially available anticonvulsants, were unsuccessful. She could not even fixate her eyes on objects, and remained in bed all day at three years of age.

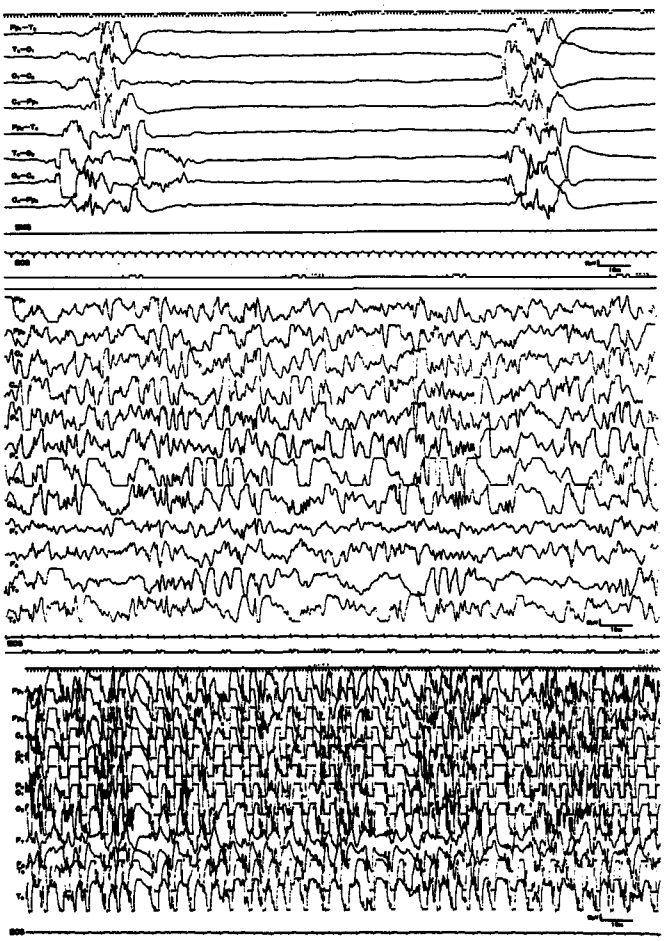

Fig. 1 EEGs of case 1 recorded in natural sleep show suppression-burst at two months old (Top), hypsarhythmia at 10 months old (Middle) and generalized 2-2.5 Hz spike-waves at 18 months old (Bottom).

Case 2 was a male infant, weighing 3130 gm, who was the product of a full-term uneventful delivery. The Apgar score at one minute ws 9 and the results of neurological examination at bitrh were unremarkable. Tonic spasms in series were seen from the 12th day after birth and a suppression-burst pattern on EEG was observed on the 30th day of life. The results of chemical analysis of the blood and urine, including aminoacid analysis, were within normal range. Organic acid analysis of urine showed a normal pattern. No abnormal spots of oligosaccharides were detected in urine. Treatment with Vit. B_6 was not effective at all, while ACTH

therapy with VPA and NZP was effective in reducing the frequency of tonic spasms. The suppression-burst pattern on EEG improved gradually together with a decrease in the frequency of tonic spasms, and the abnormal findings on EEG had disappeared by six months of age, as shown in Fig. 2. MR imaging of his brain at three months old showed no distinct abnormality. His psychomotor development was delayed in spite of the disappearance of tonic spasms, and he had not gained head control at two years old.

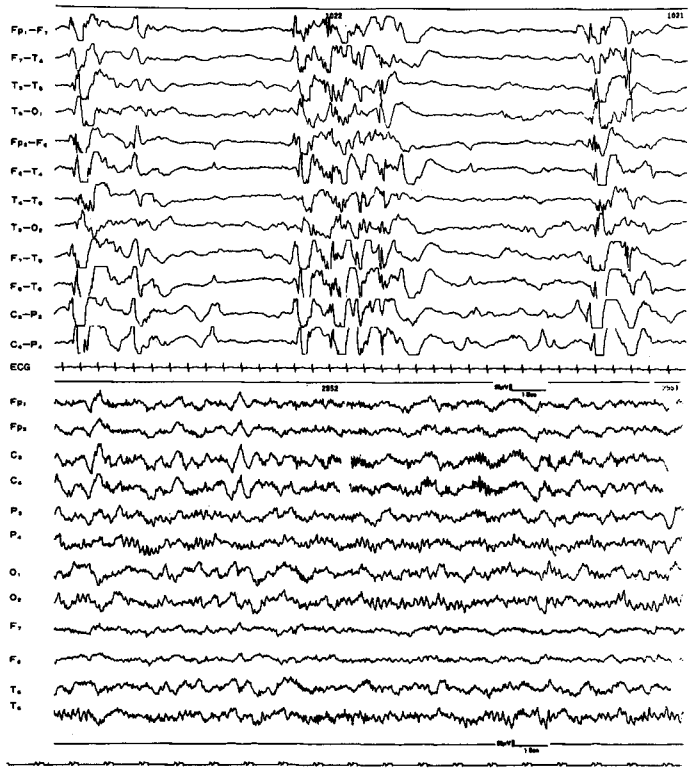

Fig. 2 EEGs of case 2 recorded in natural sleep show suppression-burst at one month old (Top) and no epileptic discharges at six months old (Bottom).

Case 3, with a birth weight of 2806 gm, was the product of a full term uncomplicated gestation, the mother being a young healthy woman who drank a bottle of beer daily until the first trimester. The Apgar score at five minutes was 9. There was no family history of neurological disease. Frequent tonic spasms with hemifacial twitching in series appeared from the fifth day of life. She was admitted to our hospital on the fifteenth day

because of an increase in the frequency of the seizures and the suppression-burst pattern on EEG. Neurological examination revealed no abnormality except for an old chorioretinitis observed on funduscopic examination, but serologic tests for viral titers including that of toxoplasmosis were all within normal range. The results of plasma aminoacid and urinary organic acid analyses were within normal range, and urine analysis for oligosaccharides showed a normal pattern. X-Ray CT on admission revealed no abnormal findings. MR imaging on IR revealed abnormal high signal areas in the right parietal and left occipital lobes at three months of age. ACTH with VPA and NZP therapy was effective in stopping the tonic spasms, but generalized tonic-clonic convulsions for a few minutes occurred twice a month thereafter. The suppression-burst pattern on EEG had disappeared gradually by three months old and focal spikes and/or polyspikes appeared frequently in the right parietal and left occipital areas, as shown in Fig. 3, corresponding to the abnormal high signal areas seen on IR On MRI. Left

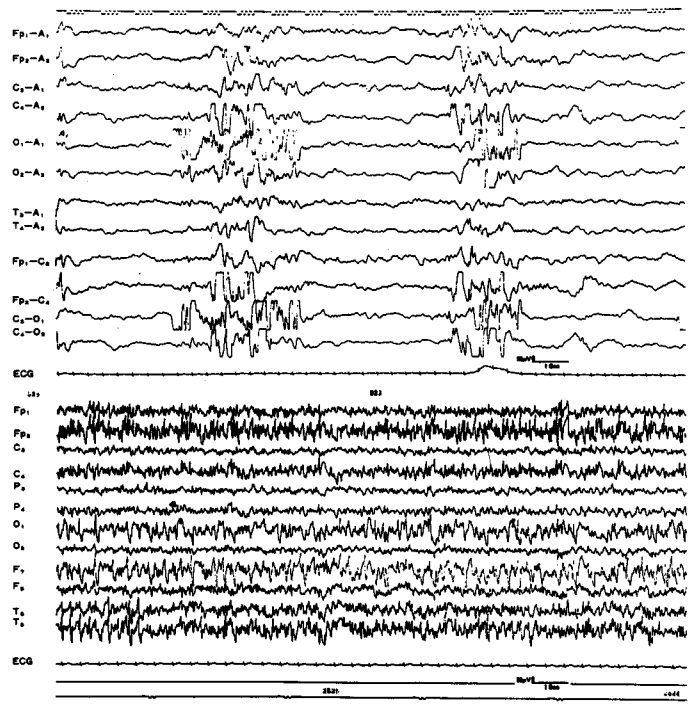

Fig. 3 EEGs of case 3 recorded in natural sleep show suppression-burst at one month old (Top) and frequent focal spikes in the right parietal and left occipital areas at five months old (Bottom).

sided hemiparesis was noted from three months old, but her psychological development was not so delayed compared to in the other three patients. She could sit with support at 18 months old.

Case 4 was born at full term, with a birth weight of 3715 gm, to a young healthy primigravida after a normal pregnancy. The Apgar score at one minute was 10, though coiling of the umbilical cord around the neck was noted on delivery. There was no family history of neurological disease. The patient was admitted to our hospital on the fifteenth day of life because of frequent seizures and the suppression-burst pattern on EEG. She had frequent tonic spasms in series but other neurological abnormalities on physical examination were not seen at admission. The results of chemical analysis of blood and urine were within normal range. Aminoacid analysis of plasma and organic acid analysis of urine revealed normal patterns. No abnormal oligosaccharides were detected in urine. X-Ray CT on admission showed no abnormal findings. MR imaging on IR at two months of age disclosed almost normal high

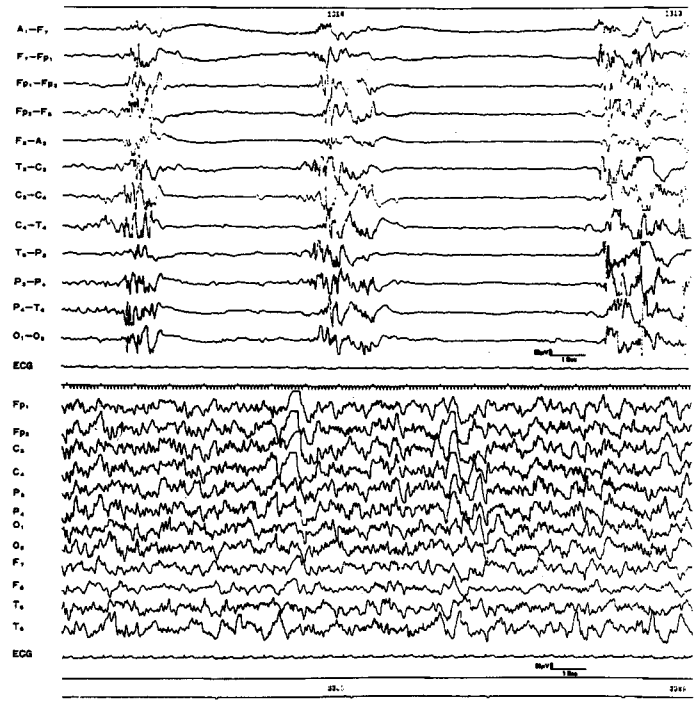

Fig. 4 EEGs of case 4 recorded in natural sleep show suppression-burst at two months old (Top) and no epileptic discharges at seven months old (Bottom).

signal areas in the white matter. Treatment with ACTH and Vit. B_6 did not improve her tonic spasms. Although a ketogenic diet enriched with median chain triglycerides was very effective for her, the treatment was stopped because she became jittery and lost her appetite. However, the tonic spasms had disappeared at four months of age with co-therapy with VPA, NZP and triclor-diphosphate monosodium (Tricloryl) after ketogenic diet therapy, but several fits of tonic seizure on one day have continued. The suppression-burst pattern on EEG had disappeared by nine months old, as shown in Fig. 4. Her psychological development was severely retarded in spite of the disappearance of tonic spasms and the EEG normalization, and she could not smile on social contact or had not gain head control at 15 months old.

Follow-up study on the MRI finding of IR

High signal areas in the cerebrum which represent myelination of white matter and basal ganglia were scarecely seen and brain atrophy was severe at nine months of age in case 1, as shown in Fig. 5. Although there was no distinct abnormality in the cerebrum

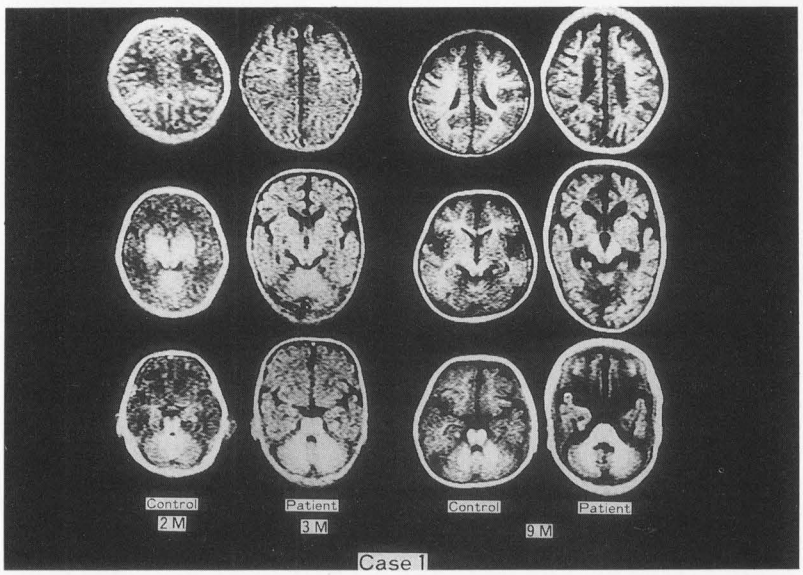

Fig. 5 MRI on IR (2100/500) scans in case 1 disclosed little high signal areas in white matter and basal ganglia at three month old (Left), and poor high signal areas in white matter with brain atrophy at nine months old (Right).

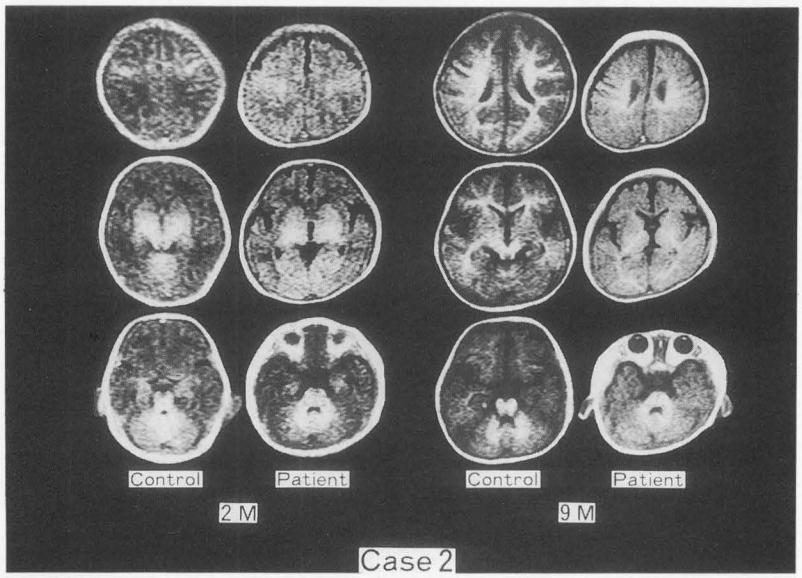

Fig. 6 MRI on IR (2100/500) scans in case 2 disclosed no abnormal findings at two months old (Left), and the delay in the myelination of white matter at nine months old compared with in an age-matched control (Right).

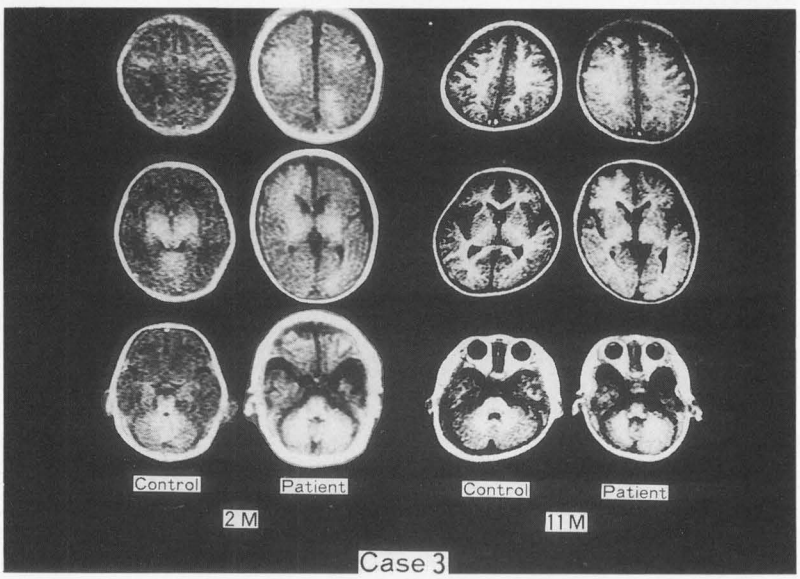

Fig. 7 MRI on IR (2100/500) scans in case 3 disclosed high siganl areas in the right front-parietal and left occipital lobes at two months old (Left), and asymetry of the myelination of white matter at 11 months old

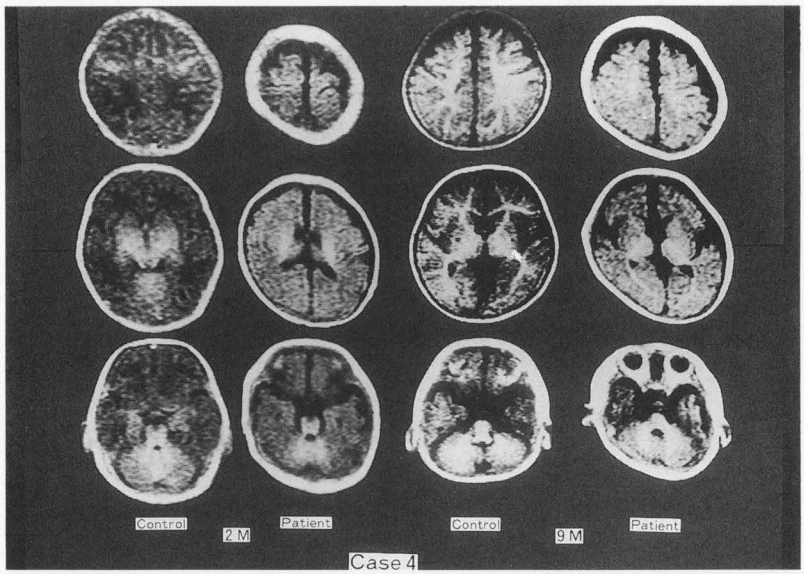

Fig. 8 MRI on IR (2100/500) scans in case 4 disclosed no abnormal findings at two months old (Left), and a delay in the myelination of white matter at nine months old compared with in an age-matched control (Right).

or cerebellum at two months of age in case 2, the increase in the high signal area of white matter in the cerebrum was delayed at nine months of age, as shown in Fig. 6. The abnormal high signal area in the right parietal and left occipital lobes, which were noted at two months, persisted at 11 months of age, while myelination of white matter in the cerebrum progressed with mild asymmetry in case 3, as shown in Fig. 7. MRI findings in case 4 revealed a delay in the myelination of white matter in the cerebrum at nine months of age, similar to that observed in case 2, as shown in Fig. 8.

MR imaging on SE in the four cases showed no characteristic findings except for the low signal areas in the cerebrum which coincided with the high signal areas seen on IR.

DISCUSSION

EIEE was first described as the earliest type of "age-dependent epileptic encephalopathy" by Ohtahara et al. in 1976.[9] Since then, this new clinico-electrical entity has been paid attention to clarify the etiology of epileptic encephalopathy, because in some patients the EIEE had evolved into West syndrome and then

Lennox-Gastaut syndrome.[10, 14] In the previous studies, many etiologies of EIEE were reported, i.e., brain anomalies,[9] necrotizing encephalopathy,[9, 13] bacterial meningitis[5] and intrauterine infections,[8, 12] but the definite etiology remained unknown in some cases. In studies on autopsy cases of EIEE, immaturity of myelination was diffusely observed in the cerebrum and cerebellum regardless of ACTH treatment.[12, 13]

On the other hand, early myoclonic epileptic encephalopathy (EMEE) was described as a new clinical entity by Aicardi and Goutieres.[1] Dalla Bernardina et al. reported that EMEE was usually based on metabolic disorders and, even in idiopathic cases of EMEE, EEG findings showed similar patterns to those in certain metabolic disorders, i.e., poliodystrophy and non-ketotic hyperglycinemia.[3] Michalski et al. reported that abnormal oligosaccharides were detected in the urine of patients with EMEE.[6] Furthermore, some authors mentioned that the presence of severe myoclonic fits was characteristic of EMEE.[2, 4]

Ohtsuka et al., therefore, insisted that EIEE was a different entity from EMEE because of the differences in the etiologies and clinico-electrical characteristics.[11] Although the etiologies in our four cases remain unknown, in spite of neuroradiological, biochemical and metabolic investigation, MR imaging on IR revealed such abnormal findings as the dysmyelination of white matter in three cases and asymmetrical myelination of white matter with high signal areas in the cerebrum in the other case. Moreover, no abnormal oligosaccharides were detected in urine in our four cases.

From the viewpoint mentioned above, it is suggested that EIEE is based on the immaturity of the brain combined with dysmyelination.

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