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Case Report

A case of early myoclonic encephalopathy with intractable seizures successfully treated with high-dose phenobarbital

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Abstract

Background: Early myoclonic encephalopathy (EME) is an epileptic syndrome that develops in neonates, commonly within 1 month of birth. The condition is characterized by irregular, partial, and asynchronous myoclonus. The seizures in EME are generally refractory to antiepileptic drugs and no effective treatment for EME has been established. We encountered a case of EME in which oral high-dose phenobarbital therapy effectively alleviated seizures.

Case report: A male infant developed erratic myoclonus in the face and limbs, exhibited upward gaze and facial flushing 20–30 times a day since 1 week of age. Electroencephalogram (EEG) showed a burst-suppression pattern, and considering the clinical features, EME was diagnosed. Valproate and vitamin B6 treatments were initiated; however, they were not effective. At day 58 after birth, oral high-dose phenobarbital therapy was introduced which resulted in the suppression of seizures to one or two per week and disappearance of the burst-suppression pattern on EEG.

Conclusion: Oral high-dose phenobarbital treatment may be suitable for controlling seizures in EME.

Keywords: Early myoclonic encephalopathy; Epileptic encephalopathy; High-dose phenobarbital; Burst-suppression pattern

1. Introduction

Early myoclonic encephalopathy (EME) was first reported by Aicardi and Goutières in 1978 [1]. EME is an epileptic encephalopathy that develops within 1 month of birth and is characterized by irregular, partial, and asynchronous (erratic) myoclonus in the eyelids, face, and limbs. Seizures often become tonic at approximately 3–4 months of age. EEG consistently demonstrates burst-suppression patterns during wakefulness and sleep. This pattern often changes to hypsarrhythmia or multifocal spikes at approximately 3–5 months of age. Metabolic disorders, such as nonketotic hyperglycinemia, and genetic disorders have been reported as underlying causes of EME. Because seizures associated with EME are extremely refractory to antiepileptic drugs, an effective treatment has not yet been established. The prognosis for patients with EME is generally poor, resulting in severe psychomotor developmental delay [2,3]. Few reports on effective treatments of EME are available. Here, we report the case of a patient with EME in whom seizures were effectively controlled by oral high-dose phenobarbital therapy.

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2. Case report

A male infant was born to non-consanguineous parents at gestational age of 38 weeks. He was delivered by Cesarean section due to breech presentation without asphyxia. His birth weight was 2882 g, height 47.5 cm, and head circumference 34.5 cm.

At approximately 1 week of age, the infant developed erratic myoclonus in the face and limbs with upward gaze and facial flushing, which were observed during awake and sleep states. Because the frequency of seizures increased to 20 times a day, he was referred to our hospital at 45 days of age. On admission, he presented with irritability but no physical abnormalities, including muscle tonus and deep tendon reflexes. Complete blood counts, serum biochemistry, and blood gas measurements were within normal limits. Blood ammonia was 32 μmol/L and serum γ-GTP was 47 U/L. Cerebrospinal fluid (CSF) showed neither pleocytosis nor an increased protein concentration. Serum lactate, pyruvate, amino acid, and acyl-carnitine profiles, urine organic acid levels, and CSF/plasma glycine ratio were normal. Brain magnetic resonance imaging (MRI) results revealed no abnormal findings (Fig. 1A). Electroencephalogram (EEG) showed a burst-suppression pattern, which were more apparent during asleep phase (Fig. 2). Based on clinical features and EEG findings, EME was diagnosed.

Following admission to the hospital, the frequency of the infant's seizures increased to 30 times a day; and erratic myoclonus progressed to tonic seizures accompanied with upward gaze. We initially treated the condition with valproate (20 mg/kg/day) with minimal effect. As pyridoxine-dependent epilepsy was a possibility, pyridoxal calcium phosphate (vitamin B6) was administered instead of valproate at an initial dose of 20 mg/kg/day and then increased to 40 mg/kg/day. As this treatment was ineffective, when the infant reached 58 days of age, oral high-dose phenobarbital (PB) therapy was initiated with a loading dose of 20 mg/kg/day for 2 days, 10 mg/kg/day for 2 days, and 8–10 mg/kg/day thereafter. Following 3 days of high-dose PB therapy, the frequency of the patient's seizures decreased considerably to two incidents per week. Serum PB levels ranged between 50 and 60 μg/ml. The potential adverse effects associated with high doses of the drug, such as excessive drowsiness, poor feeding, hypotension, and liver dysfunction, were not observed. EEG showed that the burst-suppression pattern progressed to multifocal spikes in the bilateral frontal areas (Fig. 3). Whole exome sequencing was performed by using patient-parents trio samples. However, we could not detect any known genetic abnormalities which could explain the pathogenesis of epileptic encephalopathy.

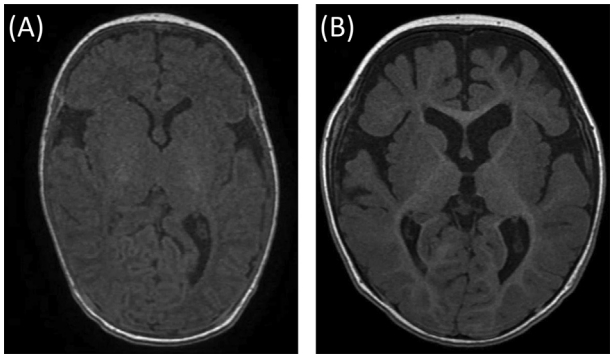

Fig. 1. T1-weighted MRI at 45 days (A) and 11 months (B) after birth revealed no abnormal findings and progressive cerebral atrophy, respectively.

At 18 months of age, the child presented with severe mental retardation and developmental delay. Head control and limb movement was poor and he could not form meaningful words. He was, however, gradually developing the ability to smile and the aptitude to pursue and eat puréed food. Tonic seizures of the upper limbs with upward gaze were observed once or twice a week with serum levels of PB at approximately <40 μg/ml. Serum γ-GTP fluctuated within a tolerable level, 50–100 U/L. MRI revealed progressive cerebral atrophy (Fig. 1B).

3. Discussion

Seizures associated with EME are generally refractory to antiepileptic drugs and are commonly treated in a trial and error manner. Nakano et al. reported two cases of EME in which the seizures were successfully treated with a combination of lidocaine and carbamazepine; however, psychomotor development was severely delayed [4]. In another study, Jan et al. reported on four infants with EME in whom MRI showed mild non-specific brain atrophy. After the introduction of topiramate, one patient became completely seizure-free and the others showed 50% reduction in seizures [5]. Cusmai et al. reported the treatment of three cases of EME with a ketogenic diet as the patients had nonketotic hyperglycinemia. The treatment resulted in >50% reduction of seizures; however, the patients exhibited severe delay in psychomotor development [6]. Treatment reports for EME are rare and a standardized therapy for this condition remains to be established. In our study patient, seizures were well controlled by high-dose PB therapy without apparent adverse events.

High-dose PB therapy has been previously reported to be effective in controlling intractable focal seizures [7] and Ohtahara syndrome [8]. PB is a barbiturate that depresses neuronal excitability by enhancing the γ-aminobutyric acid receptor-coupled response [9]. PB is considered to exert its neuroprotective effect in part by reducing cerebral metabolism and oxygen consumption [10]. Seizures are associated with increased metabolic demand and

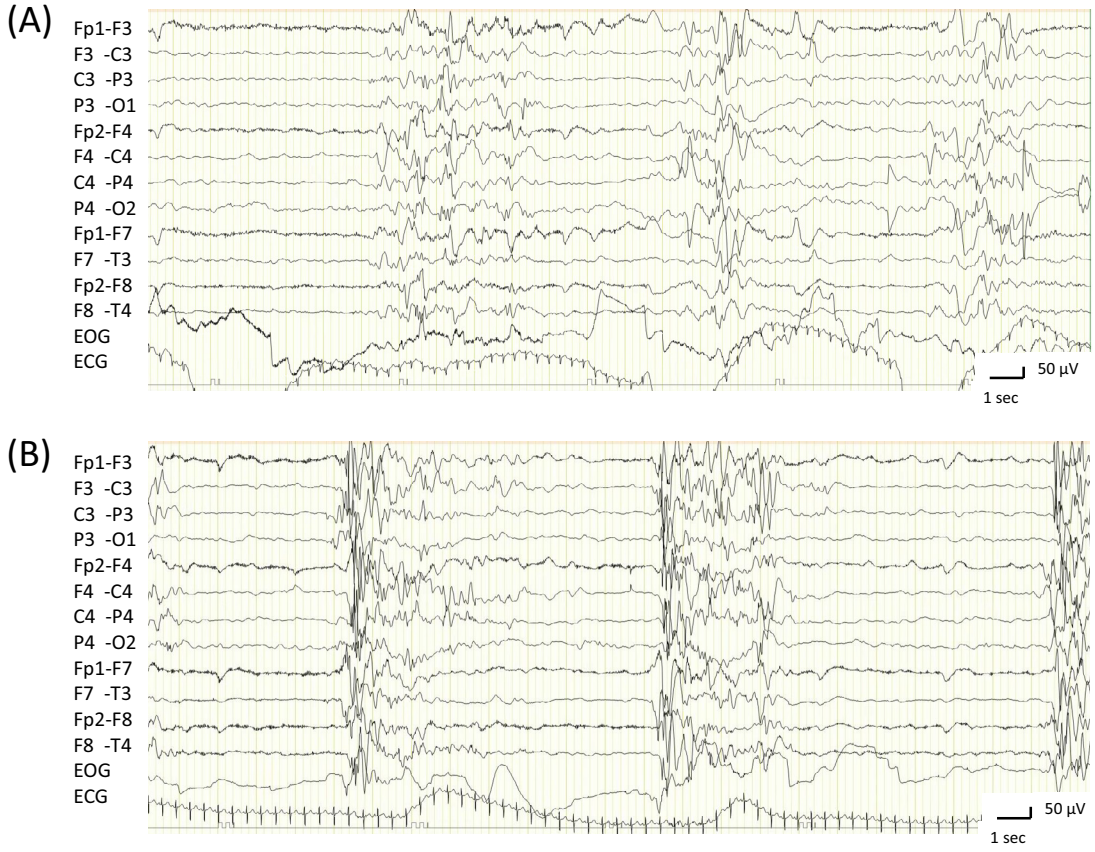

Fig. 2. EEG showed a burst-suppression pattern before high-dose phenobarbital therapy during awake (A) and sleep (B) states. Burst-suppression patterns were more apparent in the sleep EEG.

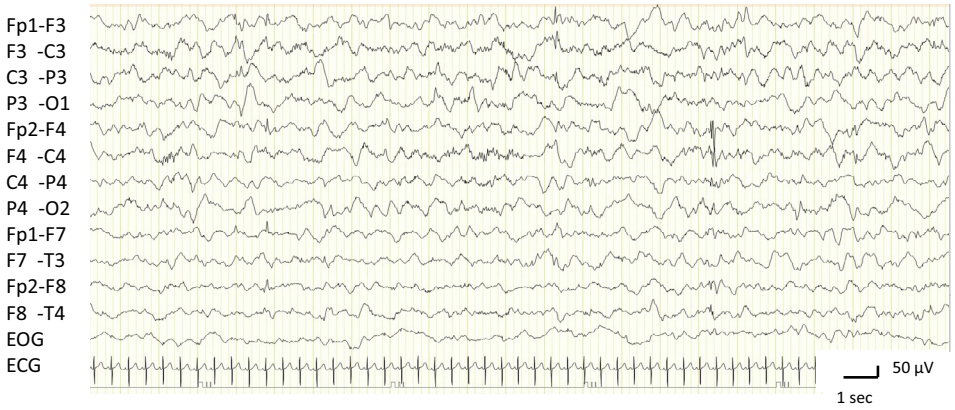

Fig. 3. EEG findings showed that the burst-suppression pattern developed into multifocal spikes following high-dose PB therapy.

may worsen neurologic injury of the brain in early infantile epileptic encephalopathy. In this context, high-dose PB therapy could be recommended to treat early infantile epileptic encephalopathy [8].

Excessive drowsiness, poor feeding, hypotension, and liver dysfunction are known to be adverse effects of high-dose PB treatment. The results for the study patient suggest that dose adjustment of PB to keep the serum concentration between 50 and 60 μg/ml may be important in controlling seizures without triggering detrimental side-effects.

Generally, long-term outcome for infants with EME is poor. Approximately half of affected infants die within the first year of life and the remaining eventually assume a vegetative state [3]. However, in our patient, as seizures were mostly under control by 2 months of age,

the patient had the potential to develop gradually. To enable developmental competence, early control of seizures may be essential.

In conclusion, oral high-dose PB treatment may be suitable as a method for controlling seizures in EME. Accumulation of data regarding similar cases treated with high doses of PB is required to establish the suitability of this therapy for the treatment of EME.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.04.007.

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