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CASE REPORT

Dextromethorphan in the treatment of early myoclonic encephalopathy evolving into migrating partial seizures in infancy

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Epileptic encephalopathy with suppression-burst in electroencephalography (EEG) can evolve into a few types of epileptic syndromes. We present here an unusual case of early myoclonic encephalopathy that evolved into migrating partial seizures in infancy. A female neonate initially had erratic myoclonus movements, hiccups, and a suppression-burst pattern in EEG that was compatible with early myoclonic encephalopathy. The seizures were controlled with dextromethorphan (20 mg/kg), and a suppression-burst pattern in EEG was reverted to relatively normal background activity. However, at 72 days of age, alternating focal tonic seizures, compatible with migrating partial seizures in infancy, were demonstrated by the 24-hour EEG recording. The seizures responded poorly to dextromethorphan. To our knowledge, this is the first reported case of early myoclonic encephalopathy evolving into migrating partial seizure in infancy. Whether it represents another age-dependent epilepsy evolution needs more clinical observation.

Introduction

Early infantile epileptic encephalopathy (EIEE) with suppression-bursts (Ohtahara syndrome) and early myoclonic encephalopathy (EME) are both characterized by

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suppression-burst pattern in electroencephalography (EEG) and intractable seizures in clinical presentations. EIEE is usually associated with brain structural anomaly, while EME is frequently associated with an inborn error of metabolism.[1] Nonketotic hyperglycinemia is one of the major causes of EME and the response to dextromethorphan (DM) treatment is good.[1,2] DM, a morphine derivative, is a commonly used antitussive drug, and it is also a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and voltage-dependent calcium and sodium channel blocker.[3] Although the use of DM is well established in patients with nonketotic hyperglycinemia, the use of DM in other types of epilepsy is not well known.[4–7]

Epileptic encephalopathy with suppression-burst pattern in EEG frequently evolves into other epileptic syndromes. Of these, EIEE can evolve into West syndrome, severe epilepsy with multiple independent spike foci, Lennox-Gastaut syndrome, and symptomatic partial epilepsy.[1] However, the evolution of EME is less documented. We report one patient with EME that was diagnosed at 40 days of age. The seizures were totally controlled by DM, and the suppression-burst pattern in EEG was changed to a nearly normal background activity. However, she developed alternating asymmetric tonic seizure 34 days later with characteristics of migrating partial seizure in infancy (MPSI) in both the clinical and EEG features. The response to DM was also poor at that time. The seizures were changed to infantile spasms 3 months later with the appearance of hypsarrhythmia in EEG.

Case report

A female baby was born smoothly by cesarean section to a G3P2SA1 mother aged 36 years; the baby had a gestational age of 36 weeks and a birth body weight of 1774 g.The head girth at birth was 30 cm (<third percentile). Myoclonus-like movements with hiccups were noted by the mother while the baby was awake and asleep ever since the patient was 20 days of age. The baby girl was then admitted for evaluation. On physical examination, there was no microcephaly, craniofacial dysmorphism, hepatosplenomegaly, and any other abnormality. The head circumference was 33.8 cm (third percentile). On neurologic examination, she had mild hypotonia, normoreflexia, and normal primitive reflexes, including positive grasping reflex, sucking, rooting reflexes, and Moro reflex. She also had normal cranial nerve examination with bilateral positive light reflex, gag reflex, and symmetric crying face, but she had poor eye contact. There was no optic atrophy or retinitis pigmentosa found during a fundus examination. During the admission period, metabolic evaluations

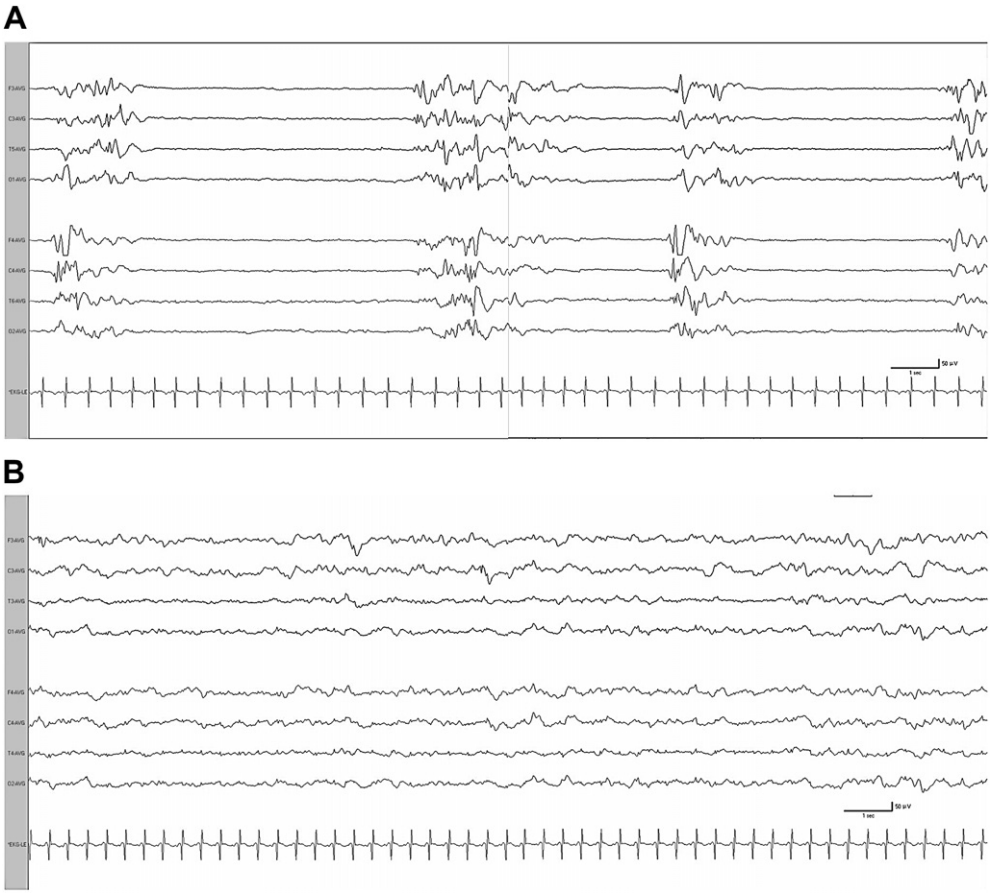

Figure 1 (A) Initial EEG evaluation showing the suppression-burst pattern at 40 days of age; and (B) the disappearance of the suppression-burst pattern with a nearly normalization of the background activity at 52 days of age after treatment with dextromethorphan. EEG = electroencephalography.

revealed negative results and included ammonia: 19 mol/L, normal blood gas, and urine sulfite. Plasma and cerebrospinal fluid tandem mass, urine organic acid study, plasma amino acids were unrevealing. Levels of very long chain fatty acid were normal. Cerebrospinal fluid examinations revealed a normal cell count and normal levels of neurotransmitters, 5-methyltetrahydrofolate, and glycine. Brain magnetic resonance imaging and spectroscope revealed negative findings. Brain auditory evoked potential was within the normal limit. The seizure characteristics were frequent, erratic, and massive myoclonus with hiccups, desaturation, and bradycardia, all of which were compatible with EME. The EEG revealed suppression-burst pattern in sleeping (Fig. 1A). Initial treatments, including phenytoin, phenobarbital, midazolam, and high dose pyridoxine, failed to control the seizures. DM (20 mg/kg/day) was then applied at 44 days of age for suspected nonketotic hyperglycinemia. The myoclonus greatly improved after treatment, and only occasional hiccups and bradycardia were found at 47 days of age. The follow-up EEG at 52 days of age revealed a nearly normal background activity with occasional focal spikes over the left frontocentral area (Fig. 1B). DM was tapered off due to normal cerebrospinal fluid glycine level at 61 days of age. However, the new seizure type developed 1 week later, and it was characterized with alternating asymmetric tonic seizures. A 24-hour video EEG revealed ictal attacks arising from the right-central temporooccipital areas that spread into the left hemisphere, followed by another attack arising from the left frontocentral and temporo-occipital areas (Fig. 2). The interictal EEG revealed multiple focal spikes in the bilateral central, temporal, and occipital areas, all of which were compatible with MPSI. Although multiple antiepileptic drugs were used, she still suffered from frequent asymmetric tonic seizures. DM was added again, but it still failed to control the seizures. After 3 months, the infant developed tonic spasms. EEG revealed hypsarrhythmia pattern, which was compatible with infantile spasms (Fig. 3). The seizures were resistant to different kinds of antiepileptic drugs, and she still has occasional tonic spasms at 2 years of age.

Discussion

Epileptic encephalopathy with suppression-bursts is divided into two syndromes, EIEE and EME. Patients with EIEE are frequently associated with different brain malformations,[1] and the condition has a consistent evolution into other epileptic syndromes. By contrast, patients with EME are occasionally associated with genetic factors or inborn errors of metabolism, such as nonketotic hyperglycinemia.[8] However, the underlying cause is usually not found in most patients with EME. EME occurs mainly in the neonatal period, with erratic myoclonus movement at first that may become tonic spasms later on. The suppression-burst in EEG is noted only during the sleep period. Although EME can—but rarely—evolve into West syndrome, severe epilepsy with multiple independent spike foci, and symptomatic partial epilepsy, most patients with EME do not have a consistent evolution.[1] There was no previous report of EME evolving into MPSI, which was a newly epilepsy syndrome addressed in the International League Against Epilepsy's commission report in 2001.[9] Ohtahara syndrome and EME share common clinical and EEG characteristics, such as onset in the first few months of life and a suppression-burst pattern on EEG, but there are several features that distinguish these two disorders.[8–10] These two syndromes can be differentiated mainly in the seizure types, underlying conditions, ictal EEG, and the seizure transition. However, occasional cases are truly difficult to separate because of the underlying cerebral malformation and metabolic/genetic disorders.[8,11–13] In our patient, she did not have a brain anomaly, and the seizure type was mainly erratic myoclonia. Therefore, EME is the diagnosis of this patient.

MPSI was first reported by Coppola in 1995,[14] and it is characterized by: (1) normal development before seizure onset, (2) seizure onset before 6 months without identified etiology, (3) migrating focal motor seizures at onset, nearly continuous, and becoming intractable, (4) intractability to conventional antiepileptic drugs and corticosteroids, and (5) profound psychomotor developmental delay. Some studies show a better prognosis with a better seizure control in patients without continuous seizures.[15] The ictal EEG shows focal rhythmic theta activity shifting from one hemisphere to the other and progressively involving adjacent areas like what was seen in the present case. Except for the presence of abnormal development, our patient had typical clinical and EEG features of MPSI, and she fulfilled the diagnostic criteria.[16] Whether EME that evolves into MPSI represents one special type of age-dependent epilepsy evolution is a question that requires more clinical observations to answer.

The therapy for MPSI has not yet been established. Conventional antiepileptics did not show any effect on MPSI by definition. Two patients reported by Okuda and colleagues [17] who were refractory to conventional antiepileptic drugs were eventually controlled with potassium bromide. Another two patients treated with combined clonazepam and stiripentol had some response.[17] New epileptic drugs such as zonisamide and topiramate were found to be ineffective, and, in one case, levetiracetam decreased seizure frequency and improved both the clinical picture and EEG recording.[18]

Although widely used in patients with nonketotic hyperglycinemia, the experience of DM usage in children with epilepsy is limited.[2–7] DM is effective in elevating the threshold for the cough reflex, suppressing convulsions or their experimental correlate, and reducing the neuronal damage induced by ischemia or excitatory amino acids.[4] DM is demethylated to the D-isomer of levorphanol, dextrorphan (DX) *in vivo*. It is believed that the anticonvulsant effect of DM is due to NMDA-R inhibition, and DX is the predominant inhibitor of the NMDA-R *in vivo*. In recent studies, high dose of DM offered neuroprotection and improved neurologic recovery, and they also have effects in seizure reduction in both children and adults with epilepsy.[3,4] Very low doses (6—20 mg/day) of DM as an add-on therapy have also been shown to induce a significant reduction in seizure frequency and severity.[5] However, a low-dose (2 mg/kg/day) double-blinded, crossover, add-on study in nine patients with complex partial seizures showed no beneficial effects.[6] A study

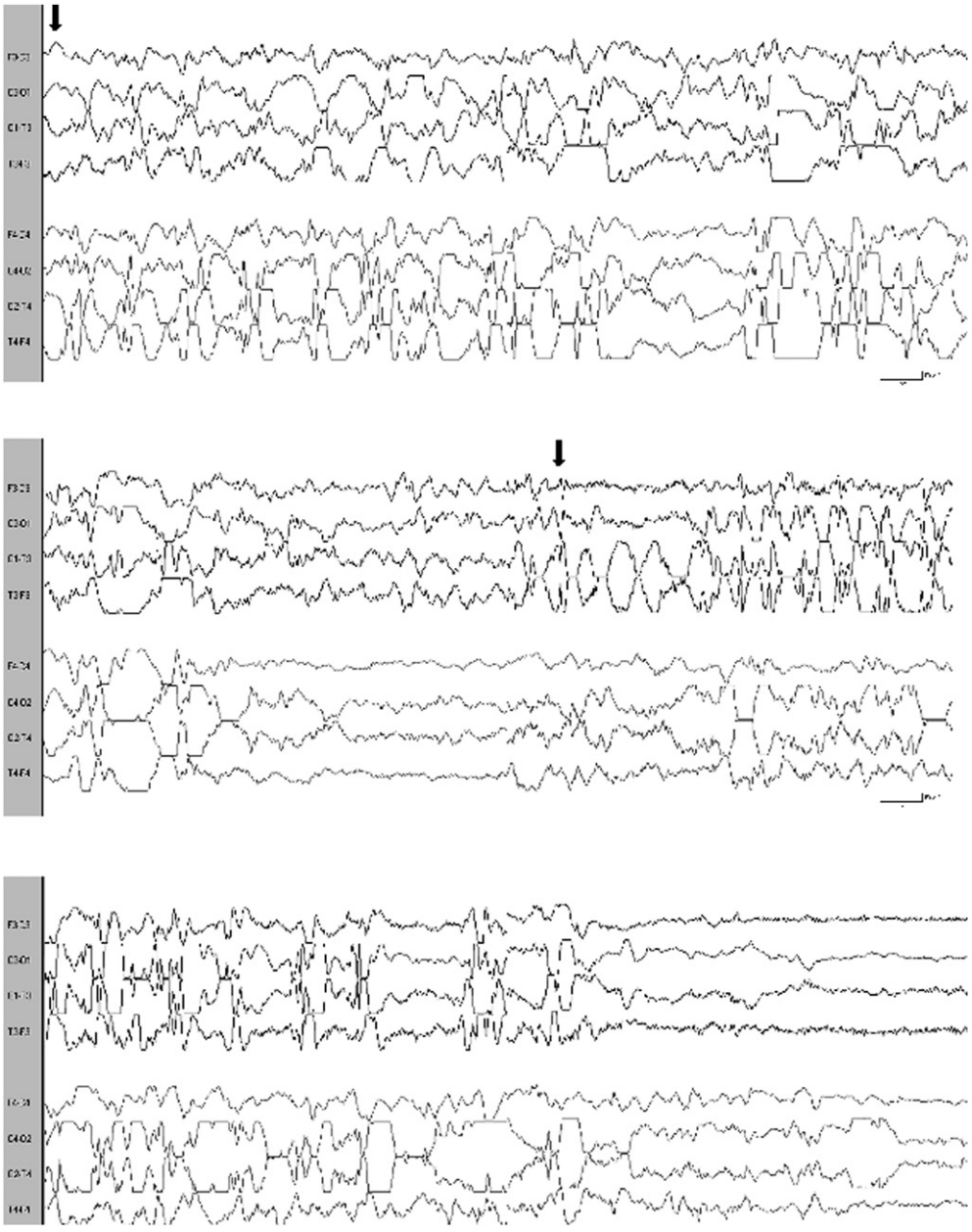

Figure 2 One episode of asymmetric tonic seizure in a 24-hour video EEG recording at 72 days of age showed focal spikes arising from the right-central temporooccipital area with spreading to the left hemisphere, which was followed by a relative flattening of right hemisphere. The clinical feature showed a left-side asymmetric tonic seizure. It was followed by a right-side tonic seizure, which is when the EEG revealed focal spikes over left the frontocentral and temporo-occipital areas. The presentation is compatible with migrating partial seizures in infancy. The arrows indicate the clinical onset of seizures. EEG = electroencephalography.

with DM of ED50 (50% effective dose) and 2X ED50 doses had no effect on the nonconvulsive seizure in animal models of focal brain ischemia.[19] DM suppressed audiogenic seizure manifestation effectively in primed rats.[20] This effect of DM was consistent with its anticonvulsive effects, and the effective doses were below those reported in other models.[21,22] Although high dose DM (5—35 mg/kg/day) is routinely used with sodium benzoate in the treatment of nonketotic hyperglycinemia, rapid escalation of both hypertonia and seizures were found after discontinued DM use ,[7] indicating a significant role of DM in seizure reduction. Although the present case of EME was not secondary to nonketotic hyperglycinemia, DM was also effective in the control of seizures, leading to the disappearance of a suppression-burst pattern in EEG. However, DM was not effective for the control of migrating partial seizures in the present case.

In conclusion, we present a case of MPSI evolved from EME. The migrating partial seizures finally evolved into infantile spasms during the follow-up period. Although the patient did not have nonketotic hyperglycinemia, the erratic myoclonus responded very well to DM treatment.

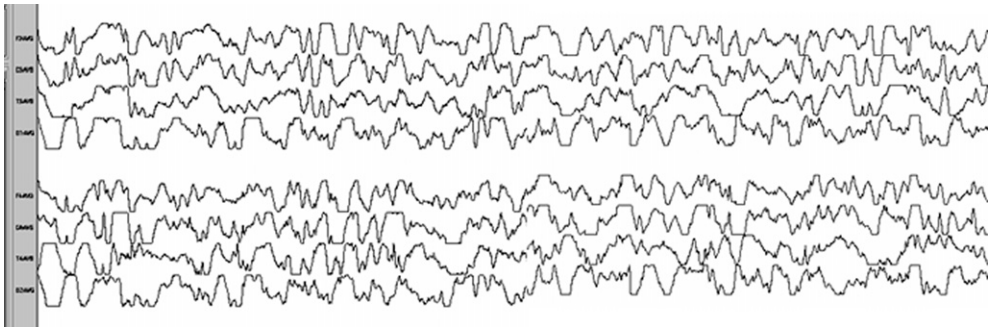

Figure 3 Follow-up EEG 3 months later revealed a hypsarrhythmia pattern compatible with infantile spasms. EEG = electroencephalography.

However, DM is not effective for the control of migrating partial seizures in the present case. The role of DM usage in neonatal seizure or status epilepticus even in those without nonketotic hyperglycinemia should, therefore, be reevaluated in the future.

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