Clinical commentary

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Successful treatment of early myoclonic encephalopathy using lidocaine and carbamazepine

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ABSTRACT – We report two female infants with early myoclonic encephalopathy (EME) whose intractable focal seizures were suppressed with lidocaine and carbamazepine (CBZ). Although EME is a form of early-onset epileptic encephalopathy characterised by myoclonus and focal seizures that are highly resistant to treatment, lidocaine and CBZ may prove effective in treating this disorder. Future studies should be performed in order to determine whether there are common specific mechanisms of seizure generation related to the sodium channel in these patients.

Key words: early myoclonic encephalopathy, focal seizures, lidocaine, carbamazepine

Early myoclonic encephalopathy (EME) is an intractable epileptic syndrome beginning in early infancy, mainly in the neonatal period (Aicardi and Goutières, 1978). It is categorized as an epileptic encephalopathy, in which the epileptic activity itself may be harmful in terms of cognitive function, along with other epileptic syndromes such as Ohtahara and West syndrome based on the revised classification of epilepsy (Berg *et al*., 2010). EME is characterised by myoclonus. Focal seizures occur concomitantly or later during the clinical course and they often become the cardinal seizure type. Some patients also experience epileptic spasms in series. Electroencephalography (EEG) shows a suppression-burst pattern which is less typical than that observed in Ohtahara syndrome (Ohtahara and Yamatogi, 2006). EME is a serious clinical problem because of its grim prognosis in terms of both seizures and development. No rational treatment for this disorder has yet been established. We herein report two infants with EME whose focal seizures were successfully ameliorated by treatment with lidocaine and carbamazepine (CBZ).

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Patient 1

A female patient was uneventfully born at 37 weeks and 4 days gestational age with a weight of 2,718 g. Her family history was unremarkable. Beginning on the first day of life, segmental myoclonus was erratically observed during both wakefulness and sleep, particularly in the face and all of the limbs, with the myoclonus gradually becoming more intense. Focal clonic seizures involving the eyelids and unilateral or bilateral upper extremities started to occur at 8 days of age with a frequency of up to more than 30 times per day. Neither blood biochemical examinations nor tests for congenital metabolic disorders revealed any specific abnormality. Additionally, cranial MRI disclosed no abnormalities. EEG showed multifocal spikes during wakefulness and a suppression-burst pattern during sleep with occasional asymmetry (*figure 1*). She was subsequently diagnosed with EME.

The focal clonic seizures mentioned above continued to occur frequently (about once every hour) in spite of treatment with phenobarbital (PB), of which the maximum dosage was 30 mg/day (10 mg/kg/day; blood level: 35.10 μg/mL) and zonisamide (ZNS), of which the maximum dosage was 45 mg/day (15 mg/kg/day; blood level: 36.3 μg/mL). At 1 month of age, in addition to PB and ZNS, continuous intravenous infusion of lidocaine was started, and the frequency of seizures decreased to less than three per day under this treatment, with an initial dose of 0.5 mg/kg/h (serum level of lidocaine: <1.0 μg/mL). The suppression-burst EEG pattern changed into a pattern of multifocal spikes (*figure 2*) on the day after lidocaine was started. Myoclonus gradually dissipated at 1 month of age. Although we attempted to replace intravenous lidocaine with oral administration of mexiletine 10 days after the start of lidocaine (maximum dosage: 15 mg/day) and then with clonazepam 5 days later (maximum dosage: 0.5 mg/day), these attempts were ineffective and caused an explosive increase of seizures. At 3 months of age, we discontinued intravenous lidocaine by replacing it with lidocaine tape treatment, with the consent of the parents. This caused focal seizures to occur several times per day and this effect was persistent. The lidocaine tape (Penles®, Nihon Lederle, Japan) used was a stamp-sized (30.5×50.0 mm) piece of tape containing 18 mg of lidocaine for local cutaneous anesthesia; four pieces of tape were used every eight hours (serum level of lidocaine: <1.0 μg/mL) (Mori *et al*., 2004). No side effects were observed during either lidocaine infusion or tape treatment. Focal seizures were observed several times each day, but the general condition of the patient was not influenced by the seizures.

At 3 months of age, epileptic spasms began to occur in series or in isolation, and the EEG pattern changed into hypsarrhythmia. One month later, spasms were suppressed and the EEG improved to show residual multifocal spikes following treatment with 50 mg/kg of sodium valproate (VPA) (blood level: 107.5 μg/mL). She thereafter continued to experience several focal seizures on a daily basis with a combination of PB (70 mg/day), VPA (450 mg/day), and lidocaine tape, until she was prescribed CBZ (50 mg/day) at 10 months of age. Her seizures gradually decreased as the dosage

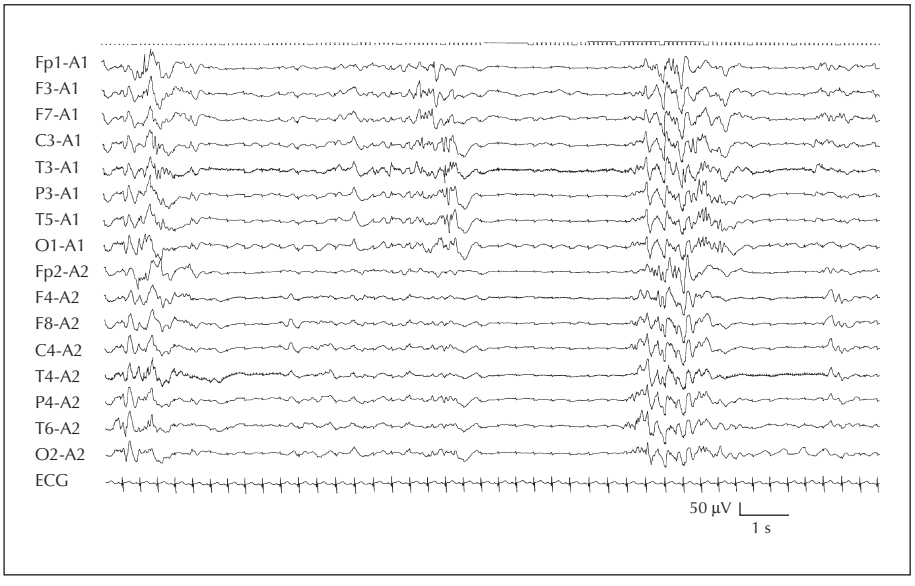

Figure 1. Interictal EEG before the administration of intravenous lidocaine in Patient 1. The EEG shows a suppression-burst pattern with occasional asymmetry during sleep.

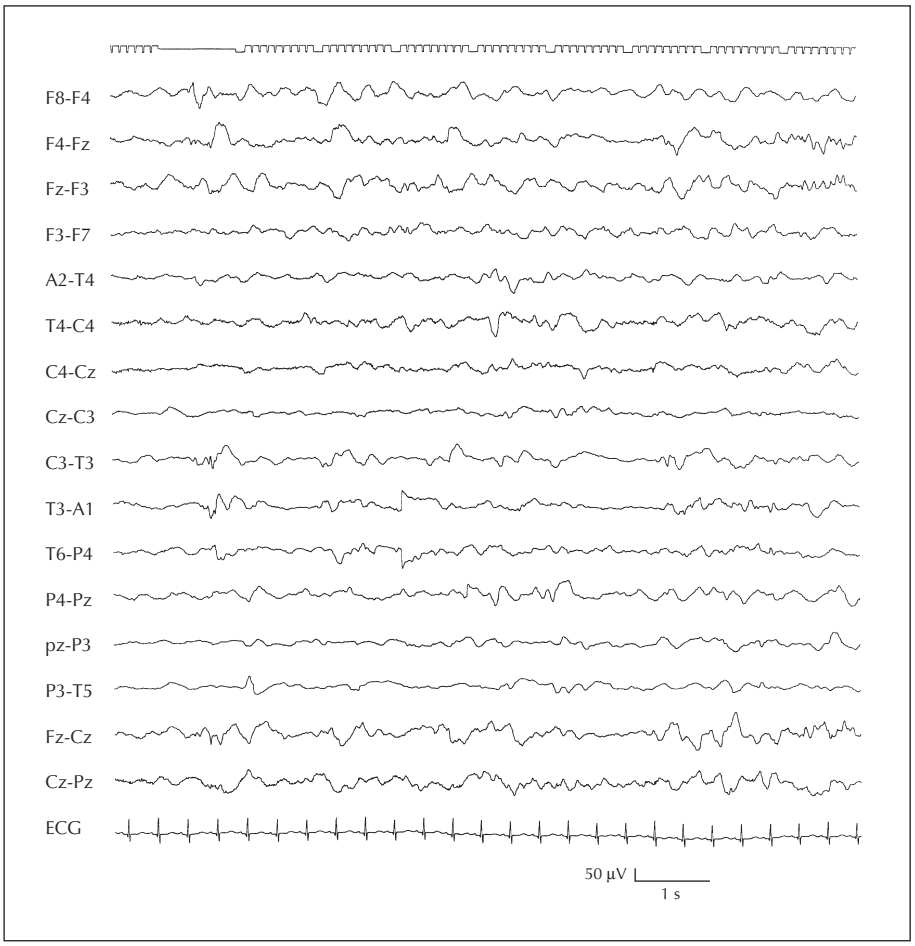

Figure 2. Interictal EEG during the administration of intravenous lidocaine in Patient 1.
The EEG recorded on the second day of lidocaine treatment shows multifocal spikes but no suppression-burst pattern during sleep.

of CBZ was incrementally increased, and the seizures finally disappeared at 18 months of age at a CBZ dosage of 125 mg/day (12 mg/kg; blood level: 7.96 µg/mL). There was no difference in EEG findings before or during the treatment with CBZ. She has remained seizure-free even with the discontinuation of lidocaine tape and PB, though her mental and motor development is severely retarded with no head control or visual following, as of the last follow-up visit at 5 years and 2 months of age.

Patient 2

A female patient was born with a weight of 2,614 g with normal delivery at exactly 37 weeks gestational age, after an uneventful pregnancy. There were no abnormalities in her family history. She exhibited subtle myoclonic movements in the limbs and trunk beginning on the first day of life, but otherwise appeared healthy for the first 15 days. At 16 days of age, she began to have frequent tonic or clonic convulsive seizures involving all extremities that lasted approximately 30 seconds and occurred several times per hour. Her blood biochemical examinations and tests for congenital metabolic disorders were normal, and cranial MRI revealed no abnormality. Interictal EEG showed multifocal spikes during wakefulness and a suppression-burst pattern during sleep (*figure 3*). She was subsequently diagnosed with EME.

Intravenous PB did not suppress the seizures (blood level: ≤35.49 µg/mL), and administration of vitamin B6 was ineffective. Recalling our previous experience, we started intravenous infusion of lidocaine at 1 month of age and the seizures immediately disappeared at an initial dose of 0.5 mg/kg/hour (serum level: <1.0 µg/mL). The sleep EEG pattern changed from suppression-burst to multifocal spikes (*figure 4*). Myoclonus also gradually disappeared. We were able to withdraw continuous intravenous

lidocaine by gradually replacing it with oral CBZ (dose: 11 mg/kg; blood level: 6.92 μg/mL) with no relapse of seizures at 2 months of age. The patient has been seizure-free with CBZ treatment. There was no difference in EEG findings before or during the treatment with CBZ. She could sit unaccompanied but could neither stand nor speak meaningful words as of the last follow-up visit at 2 years and 7 months of age.

Clinical findings, the results of examinations, and the treatment of the two patients are summarised in *table 1*.

Discussion

Generally, the seizures in EME patients are extremely intractable and do not respond to conventional antiepileptic drugs, intravenous benzodiazepines, or adrenocorticotropic hormone (ACTH); rare exceptions include dextromethorphan and ketogenic diet in EME associated with non-ketotic hyperglycinaemia (Hamosh *et al*., 1992; Cusmai *et al*., 2012). Focal seizures are frequent and devastating, and begin to occur shortly after birth in many patients with EME. In

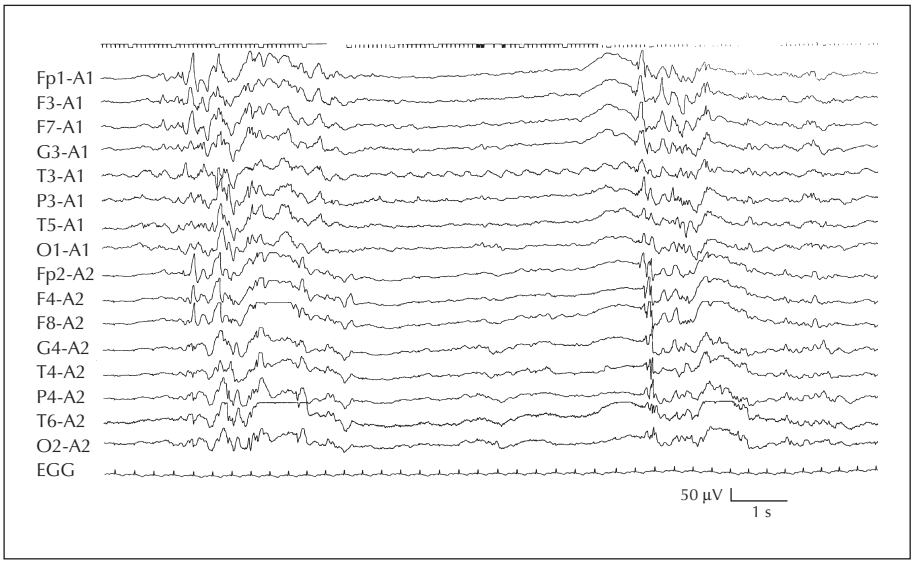

Figure 3. Interictal EEG before the administration of intravenous lidocaine in Patient 2.
The EEG shows a suppression-burst pattern during sleep.

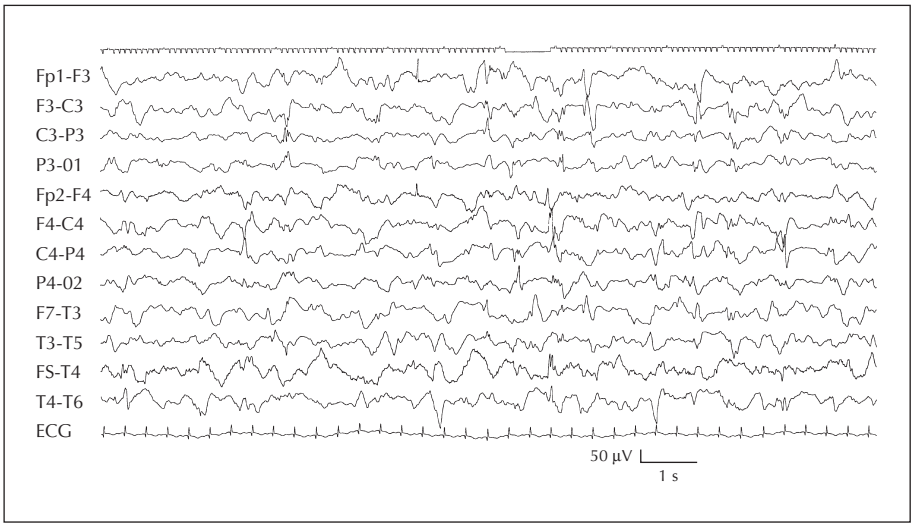

Figure 4. Interictal EEG during the administration of intravenous lidocaine in Patient 2.
The EEG recorded six days after the start of intravenous lidocaine shows multifocal spikes but no suppression-burst pattern during sleep.

Table 1. Summary of clinical findings and treatment.

Patient	1	2
Seizure type	Myoclonus, focal seizures	Myoclonus, focal seizures
EEG findings	Suppression-burst during sleep	Suppression-burst during sleep
Brain MRI findings	No abnormality	No abnormality
Examination of metabolic disorders (Fatty acids, organic acids, amino acids)	No abnormality (examined at 4 days of age)	No abnormality (examined at 4 days of age)
Dose of intravenous lidocaine	0.5 mg/kg/hour	0.5 mg/kg/hour
Blood lidocaine level	<1.0 μg/mL	<1.0 μg/mL
Concomitant drugs at the start of lidocaine infusion	PB, ZNS	PB, vitamin B6
Duration of intravenous lidocaine	50 days	35 days
Final antiepileptic drugs	VPA, CBZ	CBZ
Development (age at follow-up)	Severe delay (5 years 2 months)	Severe delay (2 years 7 months)

PB: phenobarbital; ZNS: zonisamide; VPA: sodium valproate; CBA: carbamazepine.

epilepsies with early-infantile onset, focal seizures are common even in the absence of structural brain abnormalities (Akiyama *et al*., 2010).

The two infants in our study exhibited typical clinical and EEG characteristics of EME. Their focal seizures were initially resistant to treatment but responded to lidocaine and CBZ. It is important to note that lidocaine exerted an effect even at a low dosage. We did not observe any adverse effects in either of these patients. Lidocaine, originally used as a local anaesthetic and anti-arrhythmic agent, also has an antiepileptic effect (Bernhard *et al*., 1955). It is useful for status epilepticus, clusters of seizures, and neonatal seizures, although it may occasionally induce seizures (Mesulam, 1987). Lidocaine can be administered by continuous drip infusion (Hattori *et al*., 2008) or tape, and is particularly beneficial since it does not induce an impairment of consciousness.

In the cases presented, although treatment with lidocaine and CBZ carried a potential risk of aggravation of spasms and myoclonus, it was our intention to explore every possible treatment option, including these drugs, because the patients' seizures were truly uncontrollable. Since the patients were hospitalised, we felt that we would be able to respond to any possible adverse reactions without delay. Epileptic spasms were observed in Patient 1 during treatment with lidocaine, but her spasms were transient and she did not suffer from epileptic spasms or myoclonus when treated with CBZ. Since lidocaine and CBZ proved to be effective in the two cases and both drugs function as sodium channel blockers (Stone and Javid, 1988), we speculate that a cause of seizures, in at least a proportion of patients with EME, may be related to a mechanism associated with the sodium channel. Unfortunately, we were unable to perform a detailed genetic analysis of our patients in order to uncover the presence or absence of a channelopathy, and the aetiologies of the present patients remain unclear. Further study is therefore required to elucidate the cause of the seizures. In conclusion, we feel it is worthwhile to attempt to treat intractable focal seizures in patients with EME with lidocaine and/or CBZ. □

Disclosures.

All authors declare that they have no conflicts of interests to disclose.

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