

## Case Report

# Ethosuximide completely suppressed epileptic negative myoclonus in childhood localization-related epilepsy

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## Summary

We report two cases of localization-related epilepsy manifesting frequent brief atonia. The patients were assumed to have epileptic negative myoclonus (ENM), and were successfully treated with ethosuximide (ESM). Both exhibited hemi-oro-facial twitches during sleep, and interictal electroencephalography (EEG) showed paroxysms over the contralateral posterior-temporal and centroparietal regions. Incessant atonia appeared at nine and 10 years of age accompanied by motor paresis. Ictal EEG showed irregular high-voltage spike-waves

predominantly over bilateral centroparietal regions. Carbamazepine and zonisamide were ineffective in controlling, or even aggravated ENM. The addition of ESM resulted in immediate and complete disappearance of ENM and partial motor seizures along with an improvement of motor paresis. The first case was assumed to have idiopathic etiology because of normal development before the onset of epilepsy, while the second case was considered to have cryptogenic etiology based on a pre-existing intellectual disability. Hence, we rec-

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commend that ESM should be considered for the treatment of ENM that develops during the course of localization-related epilepsy, regardless of the etiology. However, further studies are still needed to evaluate the effects of ESM in the treatment of ENM.

## Introduction

Epileptic negative myoclonus (ENM) is a characteristic seizure that occurs in various localization-related epilepsies (LREs). ENM represents a brief interruption of tonic muscle activity (<500 ms), time-locked to a spike on the electroencephalogram (EEG), without evidence of an antecedent myoclonus [1]. The clinical manifestations include sudden dropping of objects if the arm is involved, or falling to the floor if the leg is involved. Frequent ENM severely disrupt daily life activities and is often intractable. Here, we report two cases of LRE manifesting ENM that were successfully controlled by ethosuximide (ESM). ESM is thought to be effective for absence seizures but ineffective for partial seizures. While some case reports have discussed ESM efficacy for LRE manifesting several seizure types including ENM, our two cases support previous findings of successful treatment of ENM associated with LRE by ESM.

## Case reports

### Case 1

The patient was a nine-year-old girl with normal psychomotor development until the onset of epilepsy. Her family history was unremarkable and her past history included a

febrile seizure at one year. At seven years of age, she had her first epileptic attack, a generalized tonic seizure lasting several minutes. At that stage, an abnormality was detected by an electroencephalogram (EEG) and treatment with valproate (VPA) was initiated. Then, right or left facial twitches with licking and salivation were noted frequently during sleep. Sudden atonia on the right side of the body also occurred eventually. Treatment with carbamazepine (CBZ) and zonisamide (ZNS) aggravated brief atonia and were therefore replaced by clonazepam (CZP) after which some improvement was observed. At nine years of age, the occurrence of atonic attacks increased in frequency, along with an increased tendency to drop objects from the right hand and fall to the floor. One month later, she was referred to our hospital due to drowsiness and incessant atonia. Although she was right-handed, her grip was slightly weak on the right side. Brain magnetic resonance imaging (MRI) revealed no abnormality. An interictal EEG showed multifocal paroxysms predominantly over the left posterior-temporal and centroparietal (pT-C-P) areas during wakefulness (Fig. 1A) accompanied by generalized and almost continuous spike-waves during sleep (Fig. 1B). An ictal EEG revealed high-voltage irregular spike-waves predominantly over bilateral pT-C-P areas accompanied by simultaneous dropping of her right arm, and sudden, brief loss of right deltoid electromyogram (EMG) (Fig. 1C). Continuous intravenous midazolam (MDL) infused at 0.1 mg/kg/hour decreased the frequency of the atonia to less than half of that observed ini-

tially. However, atonia persisted even after a sufficient period of treatment with MDL; subsequently ESM was added to the treatment regimen. This resulted in total disappearance of atonia and drowsiness within 24 hours of initiating the treatment. The patient has been seizure-free for two years since then, while on maintenance treatment with 16 mg/kg/day VPA, 0.03 mg/kg/day CZP, and 10 mg/kg/day ESM. Her right hand grip became normal, although the Wechsler Intelligence Scale for Children-III (WISC-III) showed a borderline deficit at two months after the seizure-free period, with a verbal intelligence quotient (IQ) of 84, performance IQ of 64 and full scale IQ of 71.

### **Case 2**

The patient was a ten-year-old girl with an unremarkable family history. She was delayed in speech, was hyperactive and excitable, with a full scale IQ of 49 by WISC-III at eight years of age. A blood examination and brain MRI revealed no abnormality. At six years of age, the first seizure occurred during sleep as a secondary generalized tonic-clonic convulsion. An abnormality was detected by EEG and VPA was started. Since the age of eight, seizures increased progressively and usually occurred soon after falling asleep. Seizures presented as twitching on the right side of the mouth with salivation and tonic contraction of the right upper limb. She was treated with antiepileptic drugs such as CBZ and ZNS for the partial seizures, but with little clinical effect. An interictal EEG revealed right occipital paroxysms during wakefulness (Fig. 2A) and

very frequent paroxysms over the left pT-C-P area during sleep (Fig. 2B). At 10 years of age, incessant brief atonia appeared in the trunk and the right arm, causing severe disruption of daily life activities. She was right-handed, but voluntary movement of the right arm was diminished because of the focal postural dystonia (restricted to the right arm) that had not been noticed previously. An ictal EEG revealed irregular high-voltage spike-waves predominantly over bilateral centroparietal areas simultaneous with repetitive atonic falls to the knee from a sitting position along with eyelid twitches, salivation, and decreased consciousness (Fig. 2C). Atonia disappeared completely within one week of adding ESM to the treatment regimen. Since then, she has been seizure-free for one year while on maintenance treatment with 20mg/kg/day VPA and 10 mg/kg/day ESM. While dystonia has diminished, she requires risperidone for hyperactivity and excitability that worsened since the occurrence of incessant atonia.

### **Discussion**

In both cases, the atonia was confirmed to be ENM, which is brief interruption of tonic muscular activity corresponding to the spike-wave burst on EEG, by simultaneous recording of an ictal EEG and surface EMG in *Case 1*, and by direct observation of atonia with an EEG recording in *Case 2*.

ENM can be observed in a wide variety of idiopathic epilepsies such as benign childhood epilepsy with centrotemporal spikes (BCECT); symptomatic epilepsies such as

mitochondrial diseases, birth anoxia and neuronal migration disorders; and cryptogenic conditions [2]. In this report, *Case 1* was considered to have idiopathic etiology because normal development was observed before the onset of epilepsy, while *Case 2* had a cryptogenic etiology because of the preexisting intellectual disability.

A literature search identified a few reports of patients with LRE and ENM who had been successfully treated by ESM [3–7] (Table). The common features among our cases and the reported cases are as follows: 1) ENM occurs between five and 10 years of age, i.e., the same period with the most frequent occurrence of absence seizures; 2) hemi-facial twitches are observed during sleep; 3) interictal paroxysms appear mainly over the contralateral centroparietal and temporal regions, or rolandic area, and are activated during sleep; and 4) an ictal EEG shows irregular high-voltage spike-waves, predominantly over the contralateral or bilateral centroparietal regions.

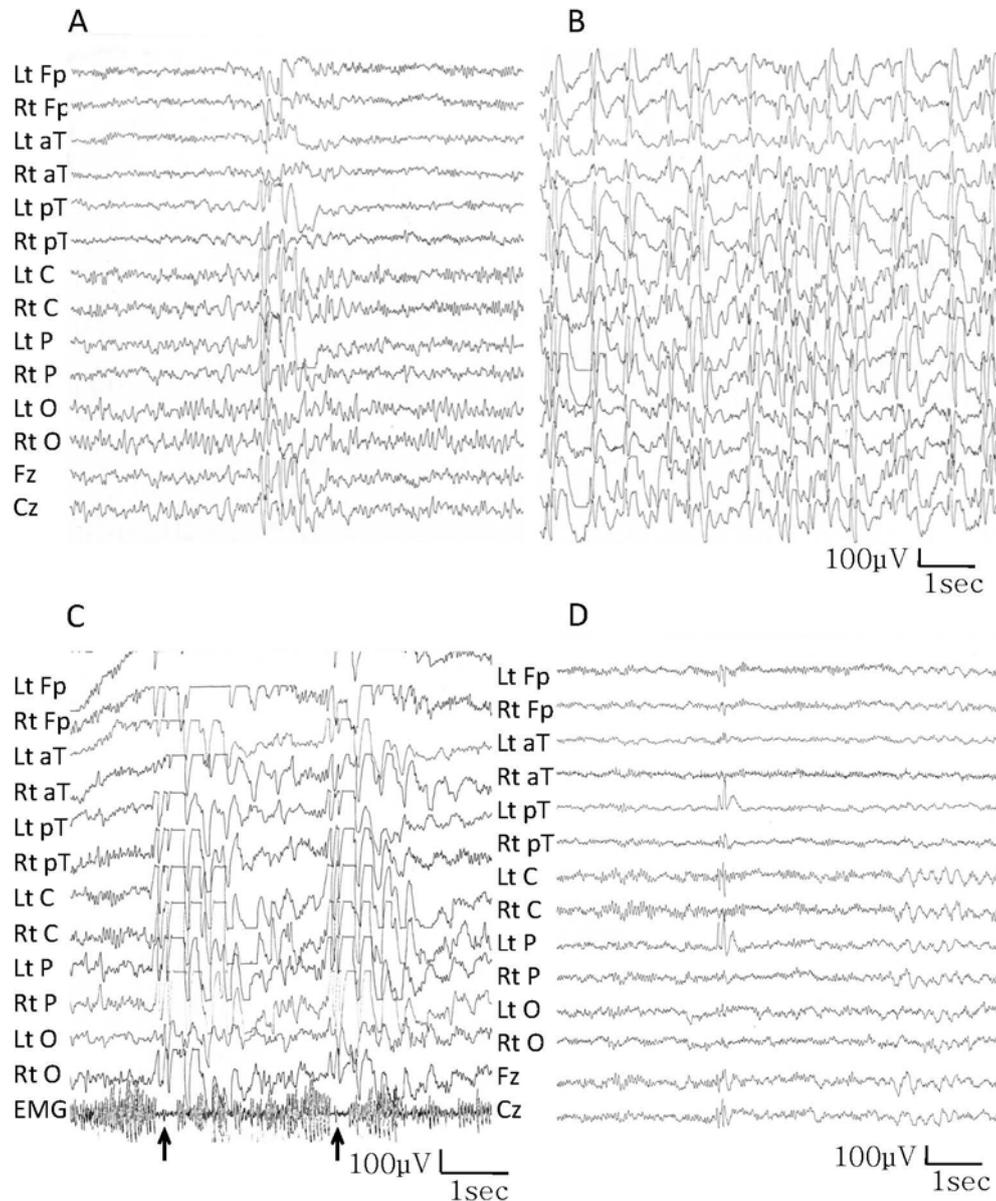
Aicardi et al. [8] distinguished an epileptic syndrome called “atypical benign partial epilepsy (ABPE)”, which is similar to BCECT. ABPE manifests as generalized minor seizures such as absence and atonic falls, and markedly activated paroxysms during sleep. “LRE with ENM” as described above has some overlapping features with ABPE, but differ in some aspects such as having cryptogenic and symptomatic etiologies, and partial atonia instead of generalized minor seizures. *Case 2* in this report, and most cases reported by Capovilla et al. [6], were treated with ESM

and showed excellent improvement regardless of cryptogenic and symptomatic etiologies.

It is possible that ENM and absence seizure originate from the same brain region. Absence seizure was previously thought to originate from the subcortical or thalamic region and spread subsequently to the entire cortex, but a focal cortical origin has recently been suggested. In a study using rat model [9], spike-wave discharges originated consistently from the perioral region of the somatosensory cortex and propagated to the adjacent cortex and thalamus. In this regard, Oguni et al. [10] used the term “atonic absence seizures” for extensive ENM with loss of consciousness resulting from expansion of epileptic discharges, which implies that ENM and absence seizure are part of the same continuum. In this report, *Case 2* had repetitive atonia that involved the trunk and was accompanied by loss of consciousness, which would correspond to “atonic absence seizures.”

No partial motor seizures were observed after ESM was added to the treatment regimen in our cases. Two explanations can be proposed: 1) ESM is effective for the treatment of partial motor seizures as well as ENM; and 2) ESM is only directly effective for ENM that has replaced partial motor seizure. The latter explanation seems to be more appropriate because partial motor seizure was rarely seen during incessant ENM in both our cases. However, we also speculate that both cases may harbor a focal etiology; therefore, ESM also might counteract the pathway associated with the partial motor seizures.

Both cases had facial twitches during sleep



**Figure 1.** EEG recordings of Case 1.

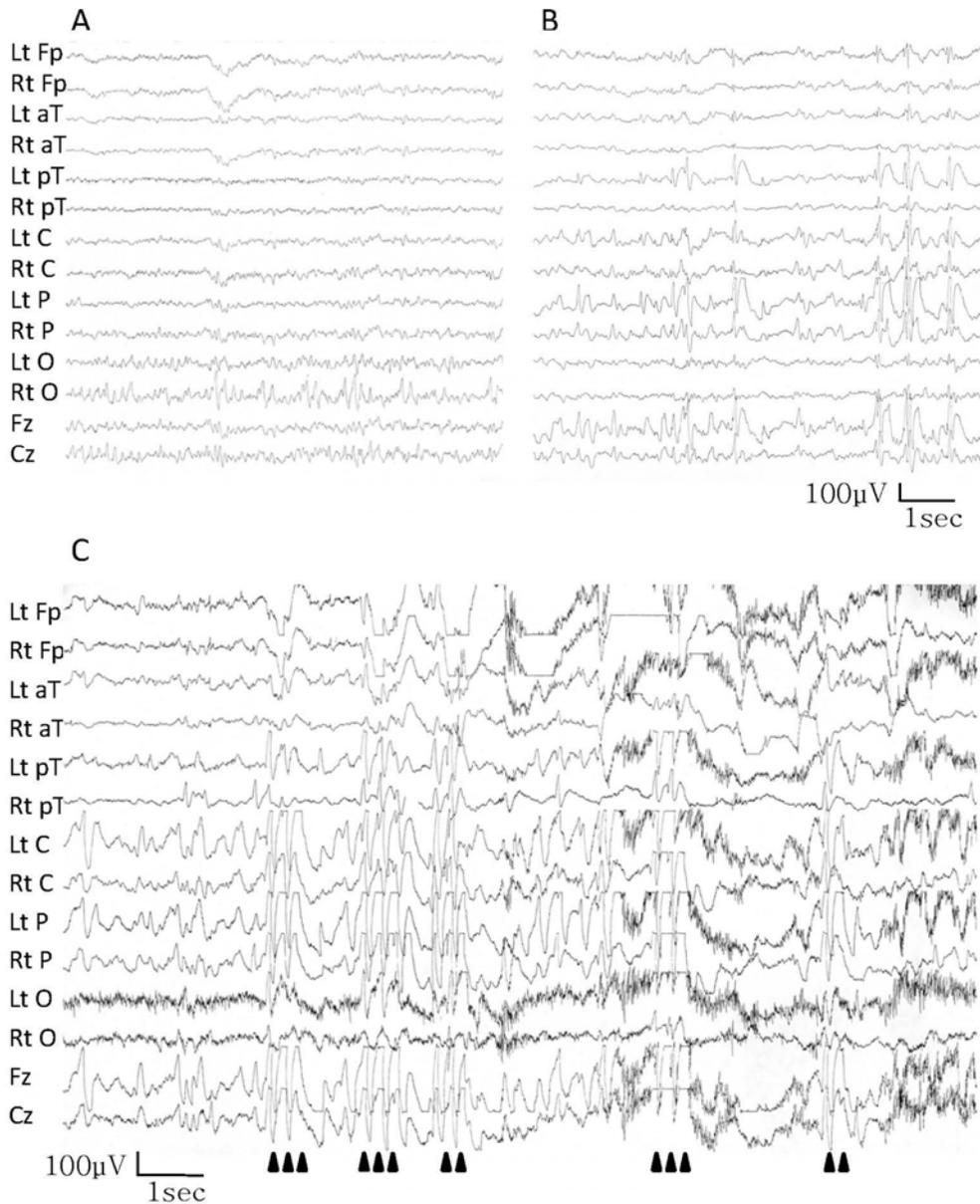
**A and B:** Interictal recordings at nine years of age when increased episodes of brief atonia were observed.

Paroxysms mainly seen in the left pT-C-P area during wakefulness (**A**) are markedly activated during sleep (**B**).

**C:** Ictal recording before ESM was prescribed during admission to our hospital at the age of nine. EEG was recorded together with surface EMG on the right deltoid, in the standing position with arms actively raised to horizontal position. Arrows indicate ENM: abrupt dropping of the right arm accompanied by simultaneous paroxysms predominantly at bilateral pT-C-P areas.

**D:** Sleep recording after six months of treatment by ESM, when seizures were completely suppressed. Note the marked reduction of paroxysmal discharge.

EEG electrodes were placed according to a modification of 10-20 montage; C and P are the points divided in three between Fp and O on the vertex, whereas aT and pT are on the side of the head. Abbreviation: Lt, left, Rt, right.



**Figure 2.** EEG recordings of Case 2.

**A and B:** Interictal recordings at the age of eight, before appearance of brief atonia. Paroxysms are mainly seen in the right occipital area during wakefulness (**A**) and in the left pT-C-P area during sleep (**B**).

**C:** Ictal recording at 10 years of age, while in the sitting position. Repetitive episodes of atonia (arrowheads) with loss of consciousness followed by “atonic absence seizures” are seen.

Note that motion artifacts increase as the patient falls down after the repetitive ENM. EEG electrodes were placed as described in Figure 1.

**Table:** A literature review of case reports describing localization-related epilepsy with epileptic negative myoclonus successfully treated by ethosuximide

Past report	Etiology	Age at epilepsy onset	Age at ENM onset	Seizures besides ENM	Body part affected by ENM	Interictal paroxysms	Ictal paroxysms of ENM	Drugs besides ESM (→effect for ENM)	Effect on epilepsy
Kubota et al [3]. 1 case	Idiopathic	6 years	4 months after onset of epilepsy	Nocturnal left facial twitching, occasionally generalized	Both arms to head	Right C-T rolandic discharges	Bilateral C-P SWs	VPA, CBZ (→induce), CLB (→partly effective)	Completely free of ENM
Oguni et al [4]. 6 cases	Idiopathic	2-8 years	5-8 years of age	Nocturnal focal (hemifacial to arm) motor seizures	One arm to both arms, head, trunk	SWs over C-P (-T) regions during awake, marked increasing during sleep	Contralateral - bilateral C-P(-T) SWs	CBZ (→effective for none), VPA, ZNS, PB etc.	Seizure-free in all cases
Shirasaka et al [5]. 1 case	Idiopathic	9 years	6 months after onset of epilepsy	Generalized seizures during sleep	Right arm	SWs over right and left rolandic area, spreading during sleep	SWs over left F-P region	VPA, ZNS (→aggravate), CBZ (→aggravate)	Seizure-free for 2 years under ESM monotherapy
Capovilla et al [6]. 9 cases	Idiopathic, cryptogenic, symptomatic	8 months-4 years	3-12 years of age	Partial seizures with secondary generalization, spasms, atypical absences	One limb to several parts of the body	(Multi) Focal abnormalities with bilateral synchronization and continuous SWs during sleep	Contralateral focal – diffuse (C-P dominant) SWs	VPA, CBZ, PB, VGB, BZPs.	Seizure-free in 5 cases, decreased more than 75% in 4 cases
Capovilla et al [7]. 2 cases	Idiopathic	3, 8 years	3, 9 years of age	Brief simple motor seizures at one leg or generalized seizures	Unilateral leg and arm (with fecal incontinence)	Paroxysms over contralateral vertex regions increasing during sleep	Spike(SW)s over contralateral F-C or Cz region	VPA, CBZ, CLB	Seizure-free for 1 year and 27 months, respectively

ENM; epileptic negative myoclonus, ESM; ethosuximide, SW; spike and wave, VPA; valproate, CBZ; carbamazepine, CLB; clobazam, ZNS; zonisamide, PB; phenobarbital, VGB; vigabatrin, BZP; benzodiazepine

but ENM occurred almost exclusively during posturing against gravity in the waking state. Hence, we propose that partial motor seizure and ENM originate from the same region closely related to the motor executive area in the cerebral cortex, and that the same abnormal electrical discharge results in either positive or negative motor phenomenon determined by the degree of tonic muscular activity. Negative myoclonus can be evoked by electrical stimulation of the premotor cortex, primary motor cortex, and supplementary motor area necessary for the generation of proper motions [11]. Using magnetoencephalography, one study [3] showed that ENM originated from the neck and orofacial region of the primary motor cortex. In our cases, motor paresis at the ENM-affected parts progressed transiently, highlighting a close relationship between ENM pathophysiology and motor execution.

In both cases described here, the intellectual and behavioral problem appeared or worsened correlating with the occurrence of ENM, and persisted even after remission of seizures. This outcome may be associated with the prolonged phase of epileptic activity. Hence early remission is advisable not only to lessen the seizure discomfort but also to reduce the likelihood of a long-lasting negative psychological impact.

In the cases presented in this report, CBZ and ZNS, which are often used for LRE, were ineffective for the treatment of ENM or even aggravated it. Benzodiazepines such as CZP and MDL were partially effective. Similar therapeutic responses have been reported

[4–6, 12]. ESM is effective in the pentylene-tetrazol model, and specifically acts as a T-type calcium channel blocker on thalamic neurons and related cortical assemblies [13–15]. On the other hand, CBZ and ZNS are effective in the maximal electroshock model, and act on the sodium channel [14, 15]. Therefore, different electrical pathophysiology would cause different seizure types and invoke different drug responses.

It is uncertain whether ESM is able to prevent ENM before its onset; therefore, initiating treatment with ESM and discontinuing CBZ or ZNS soon after the appearance of ENM during the course of LRE is recommended.

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