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Epileptic Negative Myoclonus as the First and Only Symptom in a Challenging Diagnosis of Benign Epilepsy With Centrotemporal Spikes

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Abstract

Objective: To investigate the clinical and neurophysiological characteristics of epileptic negative myoclonus as the first and only ictal symptom of benign epilepsy with centrotemporal spikes. **Methods:** Electrophysiological evaluations included polygraphic recordings with simultaneous video electroencephalogram monitoring and tests performed with patient's upper limb outstretched in standing posture. Epileptic negative myoclonus manifestations, electrophysiological features, and responses to antiepileptic drugs were analyzed. **Results:** The authors report 2 patients with benign epilepsy with centrotemporal spikes, who had epileptic negative myoclonus as the first and only seizure type. Video electroencephalogram monitoring results showed that their negative myoclonus seizures were emanating from the contralateral central and the parietal regions. Epileptic negative myoclonus was controlled by administration of valproate and levetiracetam. **Conclusion:** Epileptic negative myoclonus can be the first and only seizure type of benign epilepsy with centrotemporal spikes, and long-term follow-up monitoring should be the care for the recurrence and/or presence of other types of seizures.

Keywords

epileptic negative myoclonus, benign epilepsy with centrotemporal spikes, VEEG, surface EEG

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Epileptic negative myoclonus is an epileptic attack characterized by brief (50-400 milliseconds) muscle inhibitions with focal, multifocal, or bilateral distribution and time-locked to sharp wave or spike-and-wave discharges on the contralateral central areas, without apparent preceding myoclonic events.[1,2] Epileptic negative myoclonus is a rare epileptic condition whose exact physiopathology remains unresolved.

As an unspecific motor disorder, epileptic negative myoclonus can be observed in a wide etiological spectrum ranging from idiopathic, such as benign epilepsy with centrotemporal spikes, to symptomatic forms due to cortical dysplastic lesions,[1,3,4] an adverse reaction to antiepileptic drugs,[5-9] or more recently, autoimmune encephalitis.[10,11] In the idiopathic group, it can be detected in children suffering from partial epilepsy, including benign epilepsy with centrotemporal spikes.[8,12]

Benign epilepsy with centrotemporal spikes, or rolandic epilepsy, is the most common benign focal epilepsy of childhood. It is characterized by an excellent prognosis with the spontaneous normalization of the electroencephalography (EEG) on reaching puberty.[13] It is an idiopathic, age-specific epileptic syndrome with a high level of genetic predisposition and a benign course. Seizures are focal and involve unilateral sensorimotor functions of the face causing speech arrest and hypersalivation. Seizures frequently spread either to an upper arm ipsilateral to the facial side involved or to both arms.[14,15]

Epileptic negative myoclonus may be the presenting symptom in some children with benign epilepsy with centrotemporal

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spikes. However, epileptic negative myoclonus has rarely been reported as the first symptom in these clinical situations. In this article, the authors describe the clinical and EEG findings from 2 boys diagnosed with benign epilepsy with centrotemporal spikes who suffered from frequent epileptic negative myoclonus as the first and only ictal symptom. The authors report a detailed clinical and video EEG characteristics of their seizures and discuss the electrophysiological implications.

Material and Methods

The clinical and EEG characteristics of patients with epileptic negative myoclonus as the presenting seizure type were analyzed. Data gathered included demographic information, medical and family history, clinical presentation, interictal EEG findings, ictal EEG findings if available, the presence or absence of other seizure types, and the response to any antiepileptic drug therapy prescribed.

Electrophysiological Investigation

Electrophysiological evaluation included at least 1 cycle of awake and asleep EEG with hyperventilation and photic stimulation in accordance with the international 10/20 system for electrode placement. All video EEG recordings were obtained on a digital Micromed EEG machine (Nihon Kohden digital 100 K, Japan) with a high-frequency filter at 70 Hz and time constant at 0.3 seconds. Tests for awake and asleep status (eyes open or closed) and for hyperventilation were included in the EEG examination. To examine the paroxysmal limb movements and to capture typical seizures, the patients were instructed to stand and raise both upper limbs and keep them outstretched in front of the body. They were also instructed to write, to read by holding a book in their hands, or to grasp a toy during the video EEG monitoring. The authors included video EEG recording with surface silver disk electrodes from the right deltoid and quadriceps. These EEG tracings were examined and interpreted by 2 certified neurophysiologists.

Clinical Case

Patient 1. This patient was a 3-year 7-month-old right-handed boy with a history of mild motor control and language delays. He was admitted to our pediatric outpatient clinic experiencing frequent rapid falls to the ground for the past 13 days. The falls were attributed to a sudden loss of motor control over his left lower leg. Myoclonic jerks, however, were not reported. He was born after an uneventful pregnancy and delivery and had normal development. Physical and neurologic findings were unremarkable, as was cranial magnetic resonance imaging (MRI). There was no family history of epilepsy or neurological diseases. He reported some weakness in the left upper and lower limbs. Consciousness was fully preserved and he was able to speak intelligibility during the attacks. However, it is unknown whether there was somatosensory aura preceding the seizures. The initial awake EEG performed after partial sleep deprivation revealed frequent bilateral centrotemporal spikes and sharp slow-wave complexes predominantly on the right side. Enhancement of the epileptiform activity was noted during the early sleep stages, covering up to 60% to 70% of the sleep record (Figure 1). Metabolic screening was remarkable, including blood lactate, ammonia, arterial blood gases, camitine, and very-long-chain fatty acids. The patient was discharged with a normal neurological examination and a treatment with valproic acid (20 mg/kg/d). Four months later, he was presented with sudden episodes of brief loss of tone in the left leg that occasionally caused him to fall to the ground. These events occurred several times daily. He did not have partial motor or generalized seizures. In view of this symptomatology, a video EEG study was indicated.

Patient 2. This patient was a 9-year 4-month-old right-handed previously healthy boy but presented with episodes of sudden drops of his left arm for a month without impairment of consciousness. The frequency of drop attacks was unaccounted for due to the difficulty of being monitored or observed. He was born after an uneventful pregnancy and delivery and had normal development. There was no family history of epilepsy or neurological diseases. His EEG during wakefulness revealed a very active rolandic focus on the right side, with spreading to the left, compatible with the diagnosis of rolandic epilepsy. A sleep record showed similar findings. Valproate was initiated and falls disappeared within a few weeks. Cranial MRI was normal. He was discharged with a normal neurological examination and valproate was initiated (22 mg/kg/d), leading to disappearance of seizures within a few weeks.

Results

Video EEG Evaluation

During wakefulness, the EEG showed frequent bilateral centrotemporal discharges predominantly maximal over the right central area and occasionally generalized and diffuse spike-and-wave paroxysms. The background activity was normal.

Subsequently, the 2 children were asked to stand and extend arms and remain in that posture while the authors recorded any atonic seizures. The authors captured frequent atonic seizures involving the left extremities of both boys. During these attacks, boys suffered from repeated episodes of brief and unexpected loss of postural tone in the left leg (patient 1) and in the left arm (Figure 2; patient 2). The intensity of the symptomatology was remarkably variable from slight sensation of weakness or instability to severe loss of equilibrium. The duration of the seizures, which sometimes occurred in clusters, was variable ranging from 250 to 400 milliseconds. These focal inhibitory events were immediately followed by an intense recuperation of the tone and corporal position which were unaccompanied by jerks. Focal atonic seizures did not precipitated by sensory stimuli, such as touch, sound, or startle. Interictal EEG data

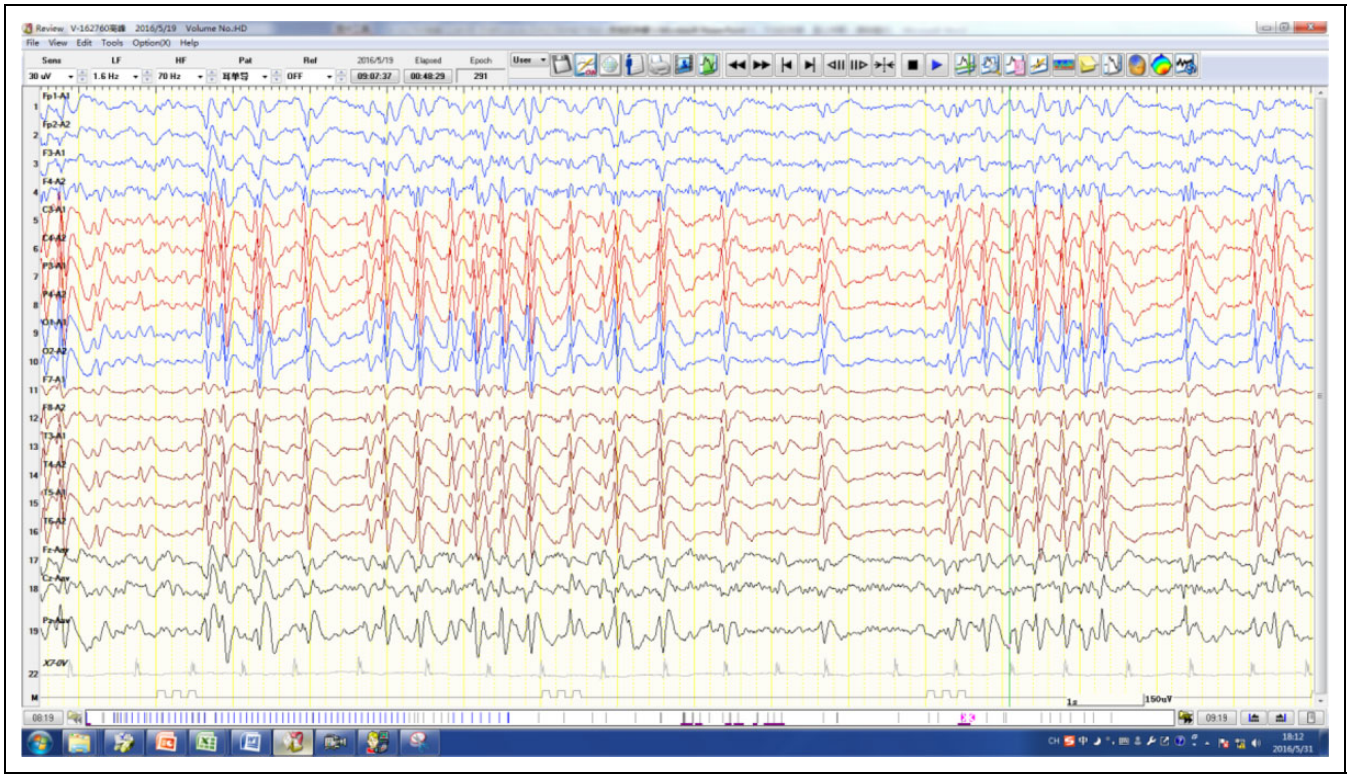

Figure 1. Enhancement of the epileptiform activity was noted during the early sleep stages, covering up to 60% to 70% of the sleep record.

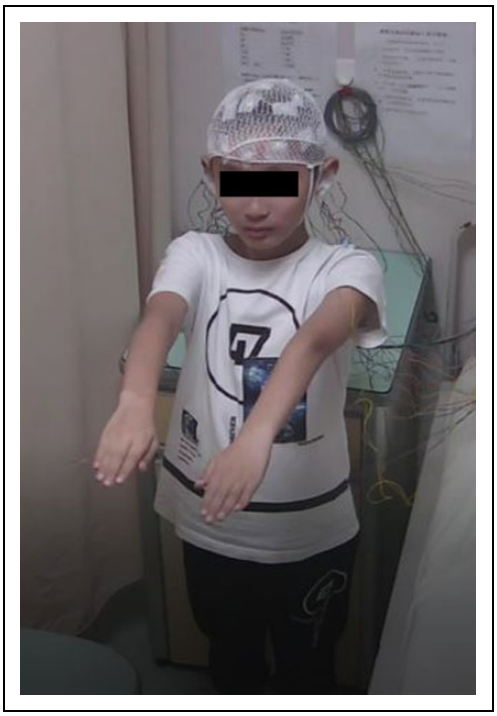

Figure 2. Brief and unexpected loss of postural tone in the left arm (patient 2).

showed typical rolandic spikes, consisting of a focal negative diphasic slow spike of medium to high voltage followed by a slow wave located in the centrotemporal areas.

Subsequently, the 2 boys were asked to sleep for EEG data acquisition. The data showed continuous or almost continuous diffuse spike-and-wave discharges that occupied more than the 60% to 70% of the recordings.

Detailed Analysis of EEG Recordings During Focal Epileptic Negative Myoclonus

The episodes of sudden loss of postural tone in the left upper and/or lower limb were time-locked to the right side centrotemporal spikes and sharp slow-wave complexes and epileptiform discharges (Figure 3). These paroxysms were slightly asymmetrical that were maximum over the left hemisphere. The duration of the focal inhibitory seizures was brief, and consciousness was fully preserved. Neither of the patients experienced myoclonic jerks.

Treatment and EEG Evolution

After the video EEG–polygraphic recording analyses, the patients were diagnosed with rolandic epilepsy. Both were treated with valproate (20 mg/kg/d). These 2 children experienced a marked clinical and EEG improvement after treatment. After 4 months, patient 1 was presented with sudden episodes of brief loss of tone in the left leg that occasionally caused his falls to the ground. However, atonic seizures leading to the falls recurred in patient 1 prompting an increase in valproate dosage to 24 mg/kg/d. After half a year of follow-up, patient 2 appears

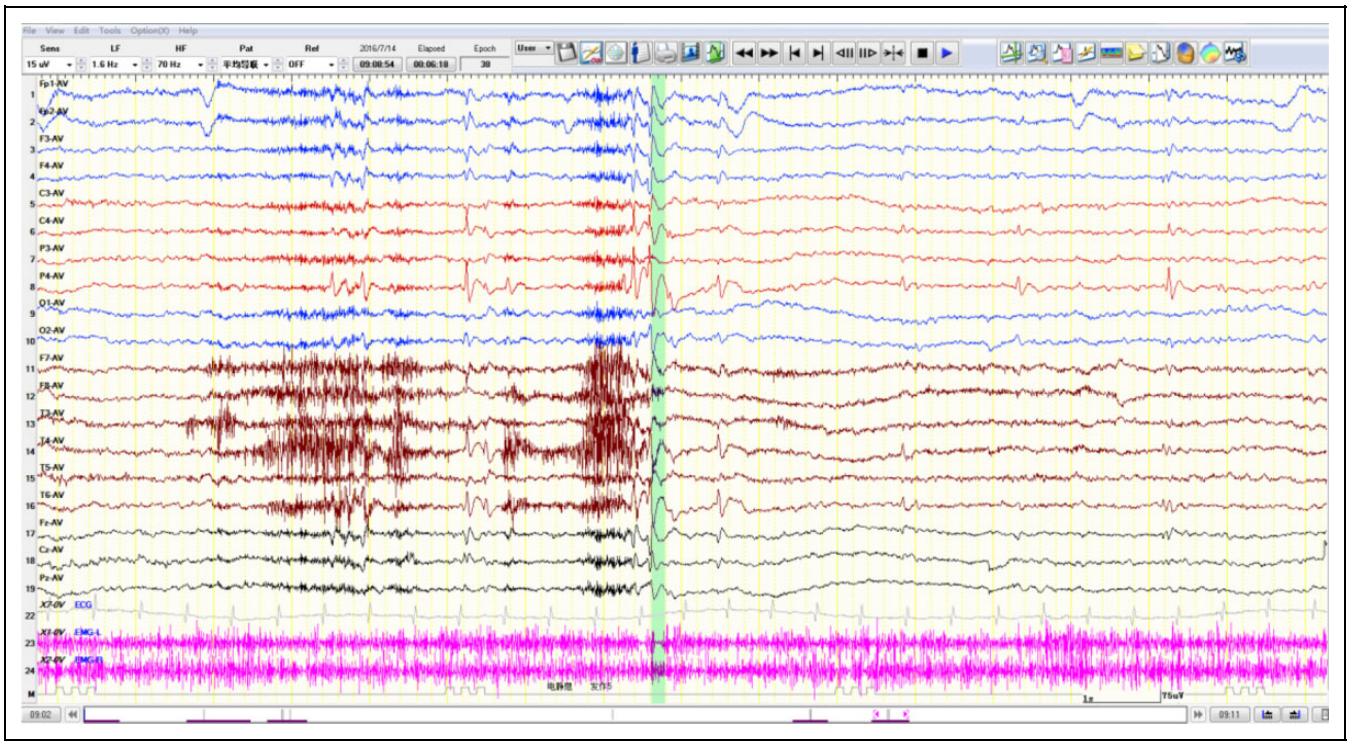

Figure 3. A focal negative diphasic slow spike of medium to high voltage followed by a slow wave located in the centrotemporal areas.

to be seizure-free. No intellectual decline was observed in this patient and the scholarly progress is fair.

Discussion

Both patients in this study had typical electroencephalographic findings, but none of them had typical rolandic seizures or any other seizure type preceding epileptic negative myoclonus attack. During video EEG monitoring, epileptic negative myoclonus was detected when patients stood with their arms outstretched to maintain a tonic posture. Simultaneous electromyography (EMG) monitoring provided valuable information regarding the time relationship between a spike and an epileptic negative myoclonus attack.[16] Thus, the brief lapse of postural tone due to the inhibition of muscular activity was easy to observe. To explain possible neurophysiological mechanisms, some reports indicate that epileptic negative myoclonus is produced by an inhibitory action on the primary sensorimotor cortex corresponding to the body segment on which it occurs.[17] Other investigations, however, indicate a significant association between the contralateral centroparietal spike component and epileptic negative myoclonus,[18,19] suggesting a cortical excitatory mechanism.

In the 2 cases presented in this study, contralateral localization of the epileptogenic zone with unilateral atonia and the EMG silent period were correlated with the slow-wave component of the contralateral rolandic spike-and-wave discharges. This observation is in accordance with other investigations in which the slow-wave component of the spike-and-wave complexes was narrowly associated with the inhibitory focal seizures. Similarly, other investigators have also reported that patients with epileptic negative myoclonus associated with contralateral rolandic spikes, a rough coincidence between the interruption of the EMG activity and the slow component of the spike-and-wave discharges.[17,20-22] It was observed that high-amplitude spikes followed by a large slow wave in the lateral motor regions with a tendency to generalize and accompanied by dropping of the outstretched contralateral arm was often related to epileptic negative myoclonus.[6] Furthermore, the amplitude, range, and frequency of the discharges were also related to the intensity of the clinical manifestations variably oscillating from slight focal atonia to severe gait disturbances, originating pseudoataxia.[23,24] High-amplitude but diffused and frequent discharges could markedly influence the function of the cortex and could potentially lead to epileptic negative myoclonus attack. These might be potential targets for intervention. Although detailed studies have analyzed the pathophysiological basis of this condition, the conclusions have varied. Some reports suggest that the onset of the EMG silent period was related to a negative component of the spike on the EEG, occurring before the slow wave.[21]

Surprisingly, the patients reported here had benign epilepsy with centrotemporal spikes with negative myoclonus as the first and only seizure manifestation. Epileptic negative myoclonus is typically associated with different seizure types and not likely to be a marker of any special epileptic syndrome. It has been increasingly recognized in either partial or generalized epilepsies.[16,25,26] Watemberg et al[27] published 5 cases of benign epilepsy with centrotemporal spikes and epileptic negative myoclonus as the presenting seizure type. Thus, it was

uncertain whether our patients with epileptic negative myoclonus belong to the "pure" benign epilepsy with centrotemporal spikes or an atypical benign partial epilepsy.[28] In these patients, in spite of the clinical severity with numerous falls, there was no intellectual decline and the brain MRI was normal. The seizures disappeared progressively after valproate monotherapy. Thus, the overall prognosis of the 2 patients was benign, confirmed by following up for a year, in keeping with the diagnosis of benign epilepsy with centrotemporal spikes. However, epileptic negative myoclonus can be found in the syndrome of continuous spike-and-wave discharges during slow sleep. Even if epileptic discharges increased dramatically in sleeping stage in the present cases, it is thought to be unlikely given the lack of cognitive regression and atypical absences of other seizures. The peculiar electroclinical presentation seen in the 2 patients differed from those of atypical benign childhood epilepsy with centrotemporal spikes not only because of the lack of typical rolandic attacks and atypical absence events but also because of the lack of electrical status epilepticus in sleep.

One of the 2 patients in this study had a history of mild motor and language delays, preceding the onset of epileptic negative myoclonus and the diagnosis of benign childhood epilepsy with centrotemporal spikes. This fact raises the question of whether epileptic negative myoclonus is more likely to occur in children with rolandic epilepsy, clinically evident or not, who are neurologically abnormal prior to the diagnosis of benign childhood epilepsy with centrotemporal spikes. Indeed, Hahn et al[29] reported a relatively high incidence (9%) of atonic seizures among 43 benign childhood epilepsy with centrotemporal spikes children with a clinical course consistent with atypical benign childhood epilepsy with centrotemporal spikes. Although no studies with large cohorts of patients has been published, the reported cases[30,31] have no abnormal development. Thus, epileptic negative myoclonus as the initial manifestation of benign childhood epilepsy with centrotemporal spikes may not be associated with the developmental status of the patients. The patient with developmental delays in our study had a missense mutation of the next-generation sequencing technology *DIAPH3* (c3038C>T; p.pro1013leu Heterozygous mutation) gene, which was confirmed as having a de novo origin by analysis of family members. This gene mutation can contribute to the risk of autism spectrum disorders[32] and auditory neuropathy.[33] Based on this observation, the authors cautiously speculate the cause of language delay in one of the patients is this gene mutation. Further investigations are needed to reveal the nature of relationship between them.

The response of epileptic negative myoclonus to antiepileptic drugs depends on the etiology of the disease. The normal cranial MRI and no intellectual decline in the patients described here suggested that their epileptic negative myoclonus were idiopathic. The antiepileptic medication reduced the number of seizures and decreased the epileptiform activity on the EEG in the immediate period. But during the later follow-up, one of the patients with *DIAPH3* gene mutation relapsed after being seizure-free for 4 months. As a result, his valproate dosage was increased and he remains seizure-free (approximately 6 months at present). After initial treatment, the other patient also remained seizure-free for 6 months. Afterward, he presented frequent episodes of sudden drop of the right arm during EEG monitoring, but they were overlooked by his parents. Another antiepileptic drug, levetiracetam was prescribed and the patient remains seizure-free (1 month at present). These patients remain in our care and exhibited no symptoms of any other type of seizure. These observations are in keeping with the proposal that the treatment response remains uncertain when ictal epileptiform discharges form part of the natural history of the underlying condition as in the case of atypical benign partial epilepsy.

In summary, although well recognized in benign childhood epilepsy with centrotemporal spikes, a short-lasting epileptic negative myoclonus might be the only manifestation of the rolandic epilepsy in some children. Detailed video EEG evaluation is necessary for making an accurate diagnosis. Long-term follow-up is necessary to immediately detect any recurrence of epileptic negative myoclonus and the possible presence of any other type of seizure.

Author Contributions

JC and GZ contributed to conception and design and contributed to acquisition, analysis, and interpretation. HG contributed to conception and contributed to acquisition and analysis. XPL and WT contributed to conception and contributed to analysis. CFW and XYW contributed to conception. All authors drafted the manuscript, critically the revised manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The patients gave their informed consent prior to inclusion in the study. Details that might disclose the identity of the patient under study were omitted.

References

1. Apartis E, Vercueil L. To jerk or not to jerk: a clinical pathophysiology of myoclonus. *Rev Neurol (Paris)*. 2016;172(8-9): 465-476.
2. Qian P, Li H, Xue J, Yang Z. Scalp-recorded high-frequency oscillations in atypical benign partial epilepsy. *Clin Neurophysiol*. 2016;127(10):3306-3313.
3. Guerrini R, Bonanni P, Rothwell J, et al. Myoclonus and epilepsy. In: Guerrini R, Aicardi J, Andermann F, et al, eds. *Epilepsy and Movement Disorders*. Cambridge, CA: Cambridge University Press; 2002:165-210.

4. Shibata T, Yoshinaga H, Oka M, Kobayashi K. West syndrome associated with epileptic negative myoclonus. *No To Hattatsu Brain Dev*. 2014;46(5):354-358.
5. Cerminara C, Montanaro ML, Curatolo P, Seri S. Lamotrigine-induced seizure aggravation and negative myoclonus in idiopathic rolandic epilepsy. *Neurology*. 2004;63(2):373-375.
6. Parmeggiani L, Seri S, Bonanni P, Guerrini R. Electrophysiological characterization of spontaneous and carbamazepine-induced epileptic negative myoclonus in benign childhood epilepsy with centro-temporal spikes. *Clin Neurophysiol*. 2004;115(1):50-58.
7. Belcastro V, Arnaboldi M, Taborelli A, Prontera P. Induction of epileptic negative myoclonus by addition of lacosamide to carbamazepine. *Epilepsy Behav*. 2011;20(3):589-590.
8. Gélisse P, Genton P, Velizarova R, Serafini A, Crespel A. Worsening of negative myoclonus by lamotrigine in a case of idiopathic focal epilepsy of children with long-term follow-up. *Brain Dev*. 2012;34(3):248-250.
9. Fanella M, Egeo G, Fattouch J, et al. Oxcarbazepine-induced myoclonic status epilepticus in juvenile myoclonic epilepsy. *Epileptic Disord*. 2013;15(2):181-187.
10. Li X, Wu D, Fernández IS, et al. Negative myoclonus in a child with anti-NMDA receptor encephalitis. *J Neurol Sci*. 2015;358(1-2):532-534.
11. Gündüz A, Kiziltan ME, Coşkun T, Delil Ş, Yeni N, Özkara Ç. Electrophysiological findings in Rasmussen's syndrome. *Epileptic Disord*. 2016;18(1):73-76.
12. Capovilla G, Rubboli G, Beccaria F, et al. Intermittent falls and fecal incontinence as a manifestation of epileptic negative myoclonus in idiopathic partial epilepsy of childhood. *Neuropediatrics*. 2000;31(5):273-275.
13. Swaiman KF, Ashwal S, Ferriero DM, Schor NF. *Neurophysiology of Seizures and Epilepsy Swaiman's Paediatric Neurology: Principles and Practice*. 5th ed. US: Elsevier/Saunders; 2012:731-732.
14. Luo C, Zhang Y, Cao W, et al. Altered structural and functional feature of striato-cortical circuit in benign epilepsy with centro-temporal spikes. *Int J Neural Syst*. 2015;25(6):1550027.
15. Dörtcan N, Guveli BT, Dervent A. Long-term clinical and electroencephalography (EEG) consequences of idiopathic partial epilepsies. *Med Sci Monit*. 2016;22:1480-1485.
16. Yang Z, Liu X, Qin J, et al. A study on epileptic negative myoclonus in atypical benign partial epilepsy of childhood. *Brain Dev*. 2009;31(4):274-281.
17. Yoshimura M, Zhang S, Ueda Y, et al. An analysis of epileptic negative myoclonus by magnetoencephalography. *Epilepsy Res*. 2015;110:139-145.
18. Rubboli G, Mai R, Meletti S, et al. Negative myoclonus induced by cortical electrical stimulation in epileptic patients. *Brain*. 2006;129(pt 1):65-81.
19. Usui K, Matsuda K, Terada K, et al. Epileptic negative myoclonus: a combined study of EEG and [123I]iomazenil (123I-IMZ) single photon emission computed tomography indicating involvement of medial frontal area. *Epilepsy Res*. 2010;89(2-3):220-226.
20. Oguni H, Sato F, Hayashi K, Wang PJ, Fukuyama Y. A study of unilateral brief focal atonia in childhood partial epilepsy. *Epilepsia*. 1992;33(1):75-83.
21. Yu HY, Kwan SY, Lirng JF, Liao KK, Chu YK, Liao SQ. Epileptic negative myoclonus: SPECT, PET, and video/EEG studies and the dramatic effects of levetiracetam. *Epilepsy Behav*. 2009;14(4):687-690.
22. Battaglia G, Casazza M. Epilepsy and myoclonus. In: Sghirlanzoni A, et al. eds. *Prognosis of Neurological Diseases*. Milan, Italy: Springer; 2015.
23. Fejerman N, Caraballo R, Tenembaum SN. Atypical evolutions of benign localization-related epilepsies in children: are they predictable? *Epilepsia*. 2000;41(4):380-390.
24. Panayiotopoulos CP.Benign childhood focal seizures and related epileptic syndromes. In: Panayiotopoulos CP, eds. *A Clinical Guide to Epileptic Syndromes and their Treatment*. London, United Kingdom: Springer; 2010:339-375.
25. Tassinari CA, Rubboli G, Parmeggiani L, et al. Epileptic negative myoclonus. In: Fahn S, Hallert M, Luders HO, et al, eds. *Negative Motor Phenomena*. Philadelphia, PA: Lippincott-Raven; 1995:181-97. (*Advances in Neurology*; vol. 67.)
26. Guerrini R, Takahashi T. Myoclonus and epilepsy. *Handb Clin Neurol*. 2013;111(111):667-679.
27. Watemberg N, Leitner Y, Fattal-Valevski A, Kramer U. Epileptic negative myoclonus as the presenting seizure type in rolandic epilepsy. *Pediatr Neurol*. 2009;41(1):59-64.
28. Eeg-Olofsson O. Rolandic epilepsy. *Pediatr Neurol*. 2010;42(3):237.
29. Hahn A, Pistohl J, Neubauer BA, Stephani U. Atypical "benign" partial epilepsy or pseudo-Lennox syndrome. Part I: symptomatology and long-term prognosis. *Neuropediatrics*. 2001;32(1):1-8.
30. Noachtar S, Holthausen H, Lüders HO. Epileptic negative myoclonus. Subdural EEG recordings indicate a postcentral generator. *Neurology*. 1997;49(6):1534-1537.
31. Hirano Y, Oguni H, Osawa M. Epileptic negative drop attacks in atypical benign partial epilepsy: a neurophysiological study. *Epileptic Disord*. 2009;11(1):37-41.
32. Xie J, Li H, Zhu H, et al. Analysis of DIAPH3 gene mutation in a boy with autism spectrum disorder. *Zhonghua yi xue yi chuan xue za zhi*. 2016;33(4):484-484.
33. Carvalho GM, Ramos PZ, Castilho AM, Guimarães AC, Sartorato EL. Molecular study of patients with auditory neuropathy. *Mol Med Rep*. 2016;14(1):481-490.