ELSEVIER

Epileptic Negative Myoclonus As the Presenting Seizure Type in Rolandic Epilepsy

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Epileptic negative myoclonus is an uncommon seizure type characterized by a sudden, brief loss of muscle tone that may lead to falling. It has been associated largely with benign childhood epilepsy with centrotemporal spikes (rolandic epilepsy), although it may also be a feature of other epileptic syndromes. In patients with rolandic epilepsy, epileptic negative myoclonus usually appears during the course of the disease, well after a diagnosis of the epilepsy has been established. Described here are five patients with rolandic epilepsy in which the presenting seizure was falls due to epileptic negative myoclonus. Because developmental delay or neurocognitive problems were present in three of the children, it is possible that epileptic negative myoclonus may be misinterpreted as clumsiness-related falls in some children who actually have undiagnosed rolandic epilepsy.

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Introduction

Benign childhood epilepsy with centrotemporal spikes (BCECTS; also known as rolandic epilepsy), the most common epilepsy syndrome in childhood [1,2], usually presents with hemifacial motor seizures that frequently generalize. Somatosensory auras involving the face, mouth, and tongue may precede the motor seizures [3,4]. Most patients experience a benign clinical course characterized by few epileptic attacks, a self-limited period of seizure activity, preservation of normal cognitive abilities, and a good clinical response to antiepileptic drugs when treatment is necessary [5].

Atypical cases are common, however, and include patients with multiple and varied seizures, poor or no response to treatment, and cognitive deterioration, particularly in terms of the development of learning disabilities. Nevertheless, one of the most striking features of atypical BCECTS—albeit an uncommon one—is the brief atonic seizures known as epileptic negative myoclonus, leading to frequent falls [6,7]. These seizures usually appear after a period of months to years (median, 18 months) of typical rolandic events during antiepileptic drug therapy [8]. Epileptic negative myoclonus is defined as an interruption of tonic muscle activity, which is time-locked to an epileptic EEG abnormality, without evidence of an antecedent positive myoclonus in the agonist–antagonist muscles [9]. This negative myoclonus tends to appear in clusters lasting a few weeks each, with seizure-free intervals between clusters [6,7].

Described here are the cases of five patients with negative myoclonus as the presenting seizure type. Three patients were evaluated for falls, one had experienced mild motor delay, and another had both mild motor delay and attention deficit disorder. Of note, only one child experienced convulsions, and this occurred weeks after myoclonus onset (patient 1). In the remaining four cases, epileptic negative myoclonus was the only clinical expression of BCECTS. The main clinical characteristics are summarized in Table 1.

The objective here is to report on epileptic negative myoclonus as the initial manifestation of benign (rolandic) childhood epilepsy with centrotemporal spikes in children. This seizure type has usually been recognized only in patients with well-established rolandic epilepsy, not as the initial symptom leading to the diagnosis of epilepsy.

Methods

The clinical and electroencephalographic (EEG) characteristics of patients with epileptic negative myoclonus as the presenting seizure type were analyzed. Data gathered included demographic information, previous medical and family history, clinical presentation, interictal EEG findings,

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Table 1. Summary of clinical characteristics in five children with epileptic negative myoclonus as the presenting symptom of benign childhood epilepsy with centrotemporal spikes

Patient	Age at Dx, yr.mo/Sex	Previous neurodevelopmental history	Duration of epileptic negative myoclonus until recognition	EEG findings	Events captured on EEG	AED treatment	Clinical Response	Myoclonus Aggravation
1	5/F	Normal	Weeks	Typical rolandic spikes	Yes	CBZ, STM, VPA	Poor	Yes, with CBZ
2	6/M	Motor delay, ADHD	Probably years	Typical rolandic spikes	No	STM, VPA, CLBZ, LEV	Good to STM (stopped due to side effects); poor to VPA and CLBZ; LEV efficacious but intolerable. Currently OXCBZ.	No
3	9/F	ADHD	Days to weeks	Typical rolandic spikes	No	None	—	No
4	2.7/M	Mild motor and language delay	2-3 months	Rolandic spikes over right occipital region	No	VPA, TPM, STM	Excellent to STM	No
5	1.10</F	Normal	2 months	Typical rolandic spikes	No	VPA	Excellent (although only recently started)	No

Abbreviations:
ADHD = Attention deficit hyperactivity disorder
AED = Antiepileptic drug
CBZ = Carbamazepine
CLBZ = Clobazam
Dx = Diagnosis
EEG = Electroencephalography
F = Female
LEV = Levetiracetam
M = Male
OXCBZ = Oxcarbazepine
STM = Sulthiame
TPM = Topiramate
VPA = Valproate

ictal EEG findings if available, the presence or absence of other seizure types, and the response to any antiepileptic drug therapy prescribed.

Case Reports

Patient 1

A previously healthy girl began experiencing frequent falls at age 4 years 6 months. The falls were attributed to a sudden loss of motor control over her left lower leg. Myoclonic jerks were not reported. Two brief generalized clonic seizures during the initial stages of sleep occurred within weeks of the falls onset. Perinatal, medical, and family history was unremarkable. Physical and neurologic findings were unremarkable, as was cranial magnetic resonance imaging. The initial awake EEG at age 4 years and 8 months revealed epileptiform activity consistent with rolandic spikes over the left centrotemporal area. A repeat awake and asleep record 3 months later showed similarly located spikes, with occasional bursts of generalized spike-and-wave activity. Finally, another study performed 6 weeks later captured a typical loss of tone event, which correlated with a 2-second cluster of bilateral rolandic spikes. Initial treatment with carbamazepine was accompanied by aggravation of the falls. Sulthiame was substituted for carbamazepine with no improvement. Recently, valproic acid replaced sulthiame.

Patient 2

A 7-year-old boy with mild motor delay and attention deficit disorder had a history of frequent falls since reaching independent gait at 18 months. Although initially these events appeared to be true accidental falls, eventually an apparent sudden loss of motor control of the right lower leg preceding the falls became evident. The neurologic examination was unremarkable. At 6 years of age, EEG revealed bilateral rolandic spikes over the centrotemporal areas, most predominant on the left side. Enhancement of the epileptiform activity was noted during the early sleep stages, covering up to 20% of the sleep record. After sulthiame was prescribed, the falls ceased; however, this medication was discontinued because of hyperventilation episodes. Valproic acid and clobazam were introduced, but had to be discontinued because of behavioral side effects before an effect on the falls could be assessed. Introduction of levetiracetam therapy was followed by total cessation of falls. As of writing, however, this medication was being discontinued because of emotional symptoms, including apparent suicidal ideation, and oxcarbazepine was being introduced.

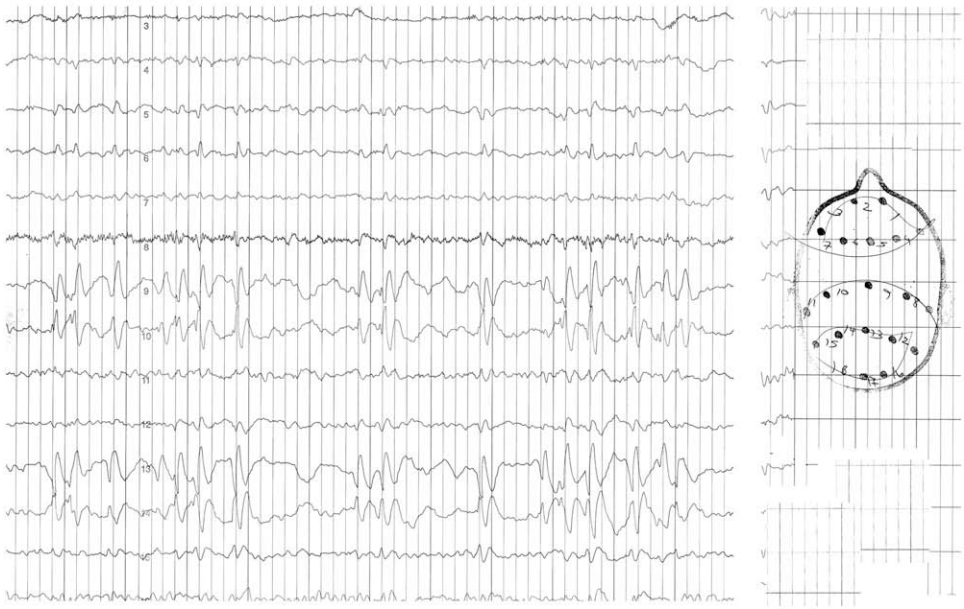

Figure 1. Awake electroencephalographic recording, patient 3. Note typical rolandic spikes over the right parasagittal region.

Patient 3

A 9-year-old girl who had been initially evaluated 1 year before for attention deficit disorder and mild learning disabilities began experiencing intermittent episodes of numbness in both legs, followed by an abrupt muscle tone loss in either the right leg or both lower legs. Physical and neurologic examinations were unremarkable. Two EEG records, including sleep, demonstrated typical bilateral, independent rolandic spikes in the right parasagittal and the left centrotemporal regions (Fig 1). Cranial magnetic resonance imaging was unremarkable. A diagnosis of epilepsy negative myoclonus was given. No medication has been prescribed, because the patient has not experienced any other seizure type and the negative myoclonus events are uncommon.

Patient 4

A boy, 2 years 7 months old, with a previous history of mild motor and language delay was evaluated for a subacute onset of falls, some sudden and some gradual, reportedly following an abrupt loss of muscle tone in his legs. The neurologic examination was unremarkable. A sleep EEG demonstrated occipital epileptiform activity, although the side of origin could not be discerned. A subsequent sleep-deprived EEG 3 weeks later depicted frequent right occipital spikes of rolandic-like morphology. Cranial magnetic resonance imaging was unremarkable. Metabolic screening was unremarkable, including blood lactate, ammonia, arterial blood gases, carnitine, and very long chain fatty acids. Treatment with valproate was rapidly discontinued because frequent skin flushing appeared. Topiramate was introduced, but was also stopped shortly after, because of restlessness and oligohidrosis. Finally, sulthiame therapy was accompanied by disappearance of the falls.

Patient 5

A 22-month-old previously healthy girl presented with a several weeks history of falls, occurring in different fashions, including gradual falls, sudden events apparently not related to muscle tone changes, and sudden loss of muscle tone in the legs. She was evaluated not long before the present report. Her EEG during wakefulness revealed a very active rolandic focus on the left side, with occasional spreading to the right. A sleep record showed similar findings. Valproate was initiated followed by disappearance of falls within a few weeks.

Results

Five children, aged 22 months to 9 years, were identified with epileptic negative myoclonus as the presenting seizure type leading to the diagnosis of BCECTS. Only one child (patient 1) eventually sustained convulsions more usually associated with this epilepsy type. The remaining four children manifested only epileptic negative myoclonus. Interictal EEG 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 [10]. The myoclonus was captured on video EEG in patient 1.

The clinical response to antiepileptic drug therapy was inconsistent. One child did not respond at all, three attained seizure control with either valproate or sulthiame and oxcarbazepine, and in one case treatment was not prescribed. The only patient who received carbamazepine experienced seizure (myoclonus) aggravation, which was not seen in the remaining children who were treated at different stages of the disease with either valproate, sulthiame, topiramate, clobazam, or levetiracetam. Patient 2 had a history of motor delay and ADHD, patient 3 had ADHD, and patient 4 exhibited mild motor and language delay.

Discussion

Benign childhood epilepsy with centrotemporal spikes, or rolandic epilepsy, is the most common epilepsy syndrome in childhood, affecting up to 24% of all children with pediatric epilepsy [1,2]. It is an idiopathic, age-specific

epileptic syndrome with a high genetic predisposition and a benign course. Typically, patients experience hemifacial motor seizures that may be preceded by somatosensory symptoms involving the inner cheek, tongue, and lips [4,11], frequently spreading to either the upper arm or to both arms ipsilateral to the facial side involved [3,4]. A notorious predisposition for attacks to occur during early sleep or slightly before awakening is a hallmark of this syndrome [5]. Secondary generalization of seizures is common, especially among younger patients [4,12].

The EEG pattern is quite specific, with normal background activity and epileptiform activity consisting of wide, biphasic or triphasic spikes of relatively high amplitude located over the descending (centrotemporal) areas of the rolandic strip, represented in the record on leads T3-C5 or T4-C6 [3,13]. When viewed on monopolar montages, a dipole depicting positive frontal polarity and negative polarity in the inferior rolandic area may be noted, which is considered pathognomonic of benign rolandic epilepsy [14].

Although most cases of BCECTS follow a self-limited, benign course including preserved cognitive function, atypical forms of the syndrome are often encountered. Despite a growing body of information on these unusual cases, there is no consensus on what ''atypical'' means for BCECTS. Reports on atypical cases include patients with seizures other than the classic ones (mostly atypical absences and negative myoclonus), poor response to antiepileptic drugs, cognitive impairment, and marked exacerbation of epileptiform activity during sleep consistent with continuous, diffuse slow-spike-and-wave activity [6]. Focal atonic seizures occur in 9% of atypical cases [15]. Indeed, atypical clinical features have been reported in up to 50% of BCECTS patients [16]. This subgroup of patients includes those not fulfilling the classic criteria for BCECTS (i.e., nocturnal simple partial seizures with or without secondary generalization, normal neurodevelopmental history, typical EEG findings, and normal neuroimaging studies). In fact, atypical forms of the syndrome appear to be quite common, although the outcome is similar for both typical and atypical cases [17].

One of the most notorious features of atypical BCECTS, albeit uncommon, are the brief, atonic seizures leading to frequent falls also known as epileptic negative myoclonus [6,7]. These events consist of a transient muscular (atonic) inhibition correlating with simultaneous epileptiform EEG activity in the contralateral rolandic area [9]. They usually appear after a period of months to years of typical rolandic events (median, 18 months). Negative myoclonus tends to appear in clusters lasting few weeks each, with seizure-free periods intervals.

Negative myoclonus may occur in association with a variety of epileptic and nonepileptic neurologic conditions. The broad range of clinical features and etiologies of negative myoclonus includes asterixis during toxic-metabolic encephalopathies [9]; new seizure types induced by certain antiepileptic drugs such as carbamazepine [18], oxcarbazepine [19], and lamotrigine [20]; brain malformations [21,22]; and even a photosensitivity phenomenon [23].

Epileptic negative myoclonus has also been described in symptomatic epilepsies related to mitochondrial cytopathies, neonatal hypoxic–ischemic encephalopathy, brain vascular malformations, and progressive myoclonus epilepsies. [1]. However, this negative myoclonus is most frequently encountered as epileptic negative myoclonus in various types of epilepsy, BCECTS being the most common [9]. In particular, epileptic negative myoclonus occurs rather frequently (9%) in an atypical form of benign partial epilepsy of childhood known as pseudo-Lennox–Gastaut syndrome, characterized by generalized minor seizures and interictal epileptiform activity similar to that seen in BCECTS but in more than half of the cases with marked exacerbation of this activity in sleep, consistent with the definition of electrical status epilepticus in sleep [12].

The neurophysiologic mechanisms leading to this seizure type are not fully understood. It has been shown to arise from both subcortical and cortical sources [24,25]. Intracerebral recordings and electrical stimulation procedures in epileptic patients suggest the involvement of premotor, primary motor, primary sensory, and supplementary motor areas in the genesis of epileptic negative myoclonus [9], particularly through cortical stimulation. A recent report on carbamazepine-related epileptic negative myoclonus suggests, however, that increased cortical inhibition could be the electrophysiologic correlate in these cases. Moreover, the presence of spike-wave rather than sharp waves seems to be more associated with seizure worsening by carbamazepine [18].

Epileptic negative myoclonus as an isolated clinical event has not been previously reported [9]. During the last 2 years the authors encountered five children aged 22 months to 9 years who presented with frequent falls. Four of these patients had EEG features of BCECTS and one (patient 4) exhibited right occipital rolandic spikes, probably suggestive of Panayiotopoulos syndrome [26]. Recent reports have raised the possibility of BCECTS and Panayiotopoulos syndrome as part of a clinical continuum [27]. A recent study by Caraballo et al. [28] indicated that 12.5% of children with Panayiotopoulos syndrome may sustain rolandic seizures and up to one third of these patients eventually develop classical BCECTS. Patient 4 may thus represent a case of early Panayiotopoulos syndrome with later progress to BCECTS.

In spite of the EEG findings, none of the present patients had typical rolandic seizures or any other seizures preceding the epileptic negative myoclonus events, and only one child (patient 1) eventually developed convulsive seizures. The parents and children described the falls as a result of sudden loss of tone in one of the legs, although at times a more gradual onset was reported. The brief lapse of postural tone is the result of inhibition of muscular activity [29]. In accord with anecdotal reports [30], carbamazepine triggered epileptic negative myoclonus aggravation in the one patient who was prescribed with this drug.

Notably, three of the five patients had a history of mild motor delay or attention deficit disorder preceding the onset of the negative myoclonus and the diagnosis of BCECTS. These facts raise the question of whether epileptic negative myoclonus is more likely to occur in children with rolandic epilepsy, clinically evident or not, who are not neurologically intact prior to the diagnosis of BCECTS. Indeed, Hahn et al. [15] reported a relatively high incidence (9%) of atonic seizures among a 43 BCECTS children with a clinical course consistent with atypical BCECTS. Although no large series of patients has been published, the reported cases [18,20,27] have pertained to children with normal development. Thus, epileptic negative myoclonus as the initial manifestation of BCECTS may not be related to the developmental status of the patient.

The peculiar electroclinical presentation seen in these children differed from that of atypical BCECTS not only because of the lack of typical rolandic attacks and atypical absence events, but also for the lack of electrical status epilepticus in sleep. Moreover, only one of the five children presented with clusters of typical falls lasting several weeks each. The negative myoclonus in the remaining four patients did not follow any particular course.

The combination of minor developmental and neuropsychiatric symptoms and occasional falls likely provokes a delay in the diagnosis of epileptic negative myoclonus in some children. Moreover, the fact that epileptic negative myoclonus has not been reported as the initial symptom of BCECTS raises the intriguing possibility that some patients with epileptic negative myoclonus as the sole manifestation of BCECTS, particularly those with some degree of motor impairment, may go unrecognized as the disease gradually subsides.

In summary, epileptic negative myoclonus may be the presenting symptom in some children with BCECTS. This phenomenon, although well recognized in BCECTS, has previously been reported only in patients with a well-established diagnosis, often as a complication of antiepileptic drug treatment, particularly carbamazepine. Two of the five patients described here had some degree of motor developmental impairment (one also had ADHD) and one had been diagnosed with ADHD prior to the appearance or recognition of the negative myoclonus events. Because epileptic negative myoclonus tends to appear in clusters during a brief period in BCECTS patients, a short-lasting epileptic negative myoclonus might be the only manifestation of BCECTS in some children; if misinterpreted as a clumsiness-related event, it could therefore be overlooked as an initial symptom of epilepsy in some children with developmental delay or ADHD.

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