Clinical commentary

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Progressive myoclonic epilepsy: myoclonic epilepsy and ataxia due to *KCNC1* mutation (MEAK): a case report and review of the literature

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ABSTRACT – Progressive myoclonic epilepsy (PME) is characterized by prominent myoclonus and generalized or focal seizures. A recently described novel *KCNC1* mutation is associated with a specific phenotype of progressive myoclonic epilepsy, which has been defined as myoclonic epilepsy and ataxia due to potassium channel mutation (MEAK). Our case illustrates a typical presentation of this disease and the potential for misdiagnosis as idiopathic generalized epilepsy during the early phase of the disease. Unique findings that may suggest an alternative diagnosis are a progressive myoclonus, prominent ataxia/dysmetria on examination, and abnormally high amplitude in the sensory evoked potential recording. We also report a brief review of the existing literature on MEAK. Early and accurate diagnosis with genetic testing may significantly help in counseling patients and families.

Key words: myoclonic epilepsy, PME, MEAK, *KCNC1*

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Progressive myoclonic epilepsy (PME) is a distinctive syndrome characterized by gradual neurological decline, myoclonus, and generalized or focal seizures. It is rare and comprises <1% of all types of epilepsy. There are several distinct entities of PME which includes Unverricht-Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF), neuronal ceroid lipofuscinosis (NCL), sialidosis, and dentato-rubro-pallido-luysian atrophy (DRPLA). These are distinguished based on various phenotypes. Recently, a new variant of PME has been described which has many similarities with ULD but is associated with a mutation in *KCNC1* (Magaudda *et al*., 2006; Muona *et al*., 2014). It is now considered a separate disease

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entity and described as myoclonic epilepsy and ataxia due to potassium channel mutation (MEAK) because of distinct underlying genetic and biologic mechanisms (Nascimento and Andrade, 2016). As there are limited cases reported in the literature, we present a case of MEAK, including data on scalp EEG along with somatosensory evoked potentials associated with this condition, with a summary of the current available literature.

Case study

The patient is an 18-year-old, left-handed, Caucasian male who had a first unprovoked generalized tonic-clonic seizure (GTCS) at age 11. He was evaluated by a pediatric neurologist, and his general/neurological examination was unremarkable except for slow rapid alternating movements. Reflexes and gait examination were normal. He was initially not started on an antiepileptic medication and had a second unprovoked GTCS five months later. After the second seizure, he was started on lamotrigine, 200 mg BID, and did not have another GTCS until age 17, within the setting of prescribed medication change.

At age 12, a year after the first seizure, he reported myoclonic jerks in his extremities, which gradually became a prominent symptom over the next several months. The school staff also noted difficulty with memory retention and fine motor skills. Zonisamide was added at age 13 for the myoclonic jerks and was initially successful. Myoclonus progressively worsened by age 15, thus lamotrigine was switched to levetiracetam, which controlled myoclonus until age 16. At age 17 years, his neurological examination was significantly worse. Cerebellar testing was abnormal with dysmetria on finger-to-nose and heel-to-shin testing. The examination also showed frequent multifocal action myoclonus. He had an ataxic gait and was unable to perform tandem steps. By age 18, the myoclonus became uncontrolled again, and valproate was added, which helped significantly. There is no family history of myoclonus, epilepsy, or clear genetic heritage from Baltic countries.

His MRI brain was normal except for a mildly prominent right retro-cerebellar cistern. Video-EEG monitoring upon admission as an inpatient at age 12 showed bilateral independent central-temporal spikes during wakefulness, and brief bursts of irregular generalized 3-Hz activity in short epochs of up to 2 seconds. In sleep, these discharges were frequent, generalized and had a polyspike morphology (*figure 1, 2*). Another evaluation at age 14 revealed bilateral central, parietal and temporal (C3/4, P3/4, T3/4) spikes in addition to previously noted irregular bursts of generalized spike and wave discharges, which were often associated with myoclonic jerks. A routine EEG at age 17 showed prior findings, as well as a photoparoxysmal response at frequencies of 9, 11 and 15 Hz.

Genetic testing was obtained at age 17, and a total of 21 genes were tested, which included *ATP13A2*, *CLN3*, *CLN5*, *CLN6*, *CLN8*, *CSTD*, *CSTB*, *CSTF*, *DNAJC5*, *EPM2A*, *FOLR1*, *GOSR2*, *GRN*, *KCNC1*, *KCTD7*, *MFSD8*, *NHLRC1*, *PPT1*, *PRICLKE1*, *SCARB2*, and *TPP*. Testing revealed the heterozygous mutation, p.R320H, a known pathogenic variant in the *KCNC1* gene confirming the diagnosis of MEAK. This was a presumed *de novo* mutation as his healthy parents did not undergo genetic testing. Also, he was heterozygous for p.P93L (c.278C>T) variant, of unknown significance, in the *EPM2* gene. *EPM2* gene mutation is associated with Lafora disease, but the clinical symptoms and signs were not consistent with Lafora disease, suggesting that it was an incidental non-pathogenic finding. SSEP findings showed normal bilateral upper extremities and left lower extremity evoked potentials. However, for the right lower extremity, P38 to N47 amplitude was abnormally high (22 μV), which has been reported in other diseases causing progressive myoclonic epilepsy (*figure 3*) (Avanzini *et al*., 2016; Shibasaki *et al*., 1985). Based on the genetic testing and other data, as described above, his diagnosis is consistent with the recently described entity of myoclonic epilepsy and ataxia due to potassium channel mutation (MEAK).

Discussion

Neurophysiology

Voltage-gated potassium ion channels (Kv) are present in all cells and are responsible for a variety of cellular functions. The subfamily of Kv3 has four subunits: Kv3.1, Kv3.2, Kv3.3, and Kv3.4. Kv3.1 is a fast-activating/deactivating, high-threshold, voltage-gated potassium channel which plays an integral part in the olivocerebellar system, affecting the control and modulation of motor activity (McMahon *et al*., 2004). It is encoded by the *KCNC1* gene, which is located on chromosome 11, at 11p15.1. A common mutation causes substitution of histidine for arginine at codon 320 of the Kv3.1 protein, resulting in a decrease in channel current (Ried *et al*., 1993) and results in a phenotype of myoclonic epilepsy and ataxia with potassium channel mutation (MEAK) as described above. In the pivotal paper, out of 84 clinically confirmed PME cases without clear genetic etiology, 16 who had MEAK were found to have a heterozygous missense mutation, c.959G>A (p.Arg320His), in *KCNC1*, 13 of whom were unrelated. Many other types of mutations have been described in *KCNC1*, resulting in different phenotypic

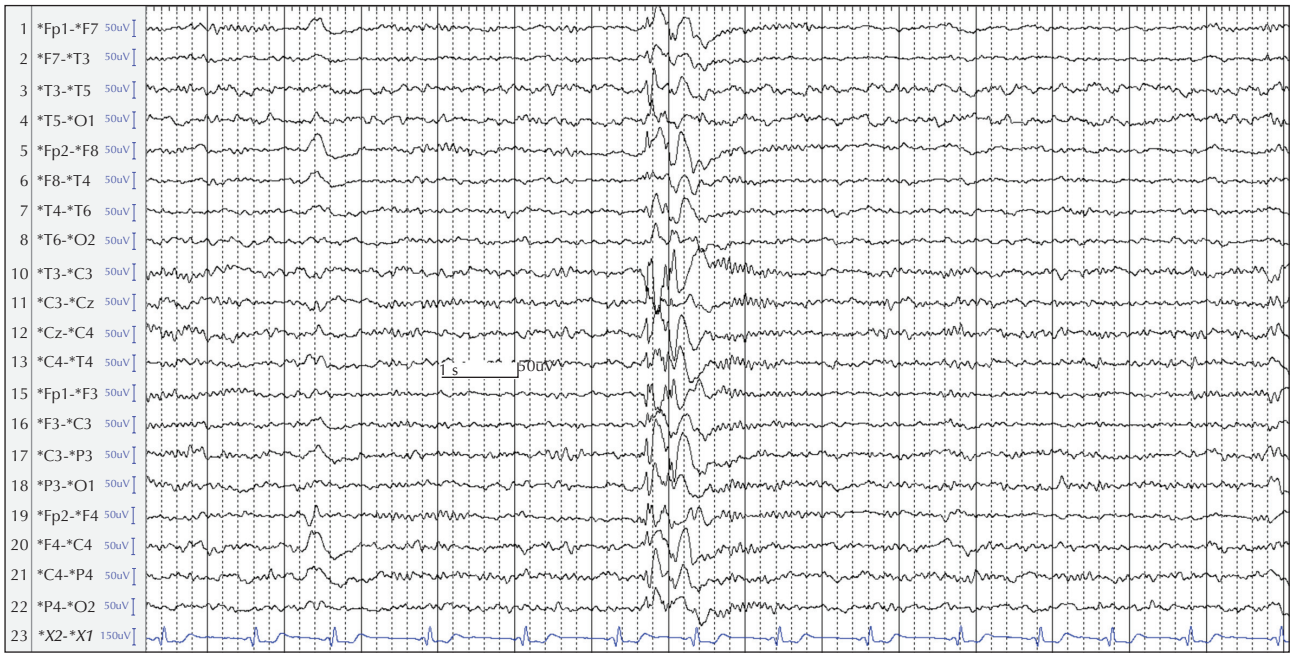

Figure 1. Generalized spike-and-wave discharge.

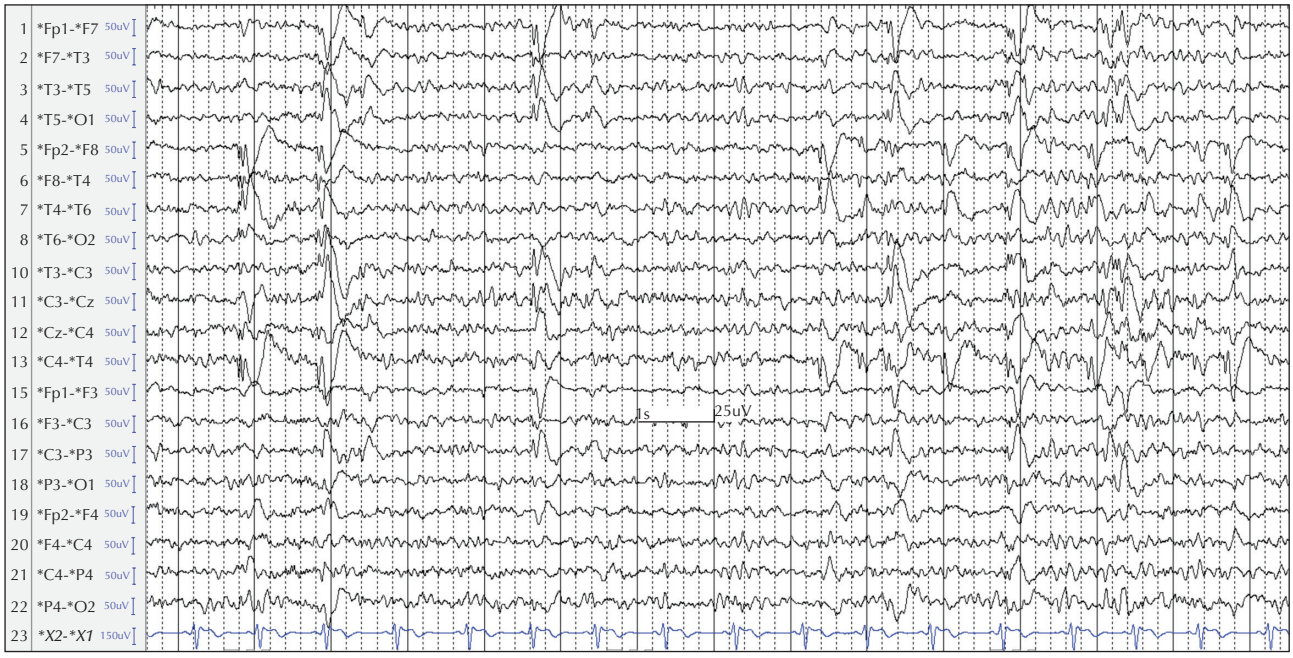

Figure 2. Independent, focal right and left temporal polyspikes and spikes.

expression, such as infantile-onset developmental epileptic encephalopathy (DEE) and dysmorphic features without epilepsy (Cameron *et al*., 2019; Poirier *et al*., 2017). A recent study found that a small molecular activator of Kv3 channel (RE01) can reverse the neurophysiologic changes from mutation and may guide us towards developing a therapeutic agent for MEAK (Munch *et al*., 2018).

Clinical features

Typically, the disease onset is around a mean age of 10 which is similar to our patient (Oliver *et al*., 2017). However, the symptoms at disease onset vary significantly. Myoclonus is a first symptom for the majority of patients, and few patients report GTCS as an early manifestation, similar to our patient. In general, GTCS

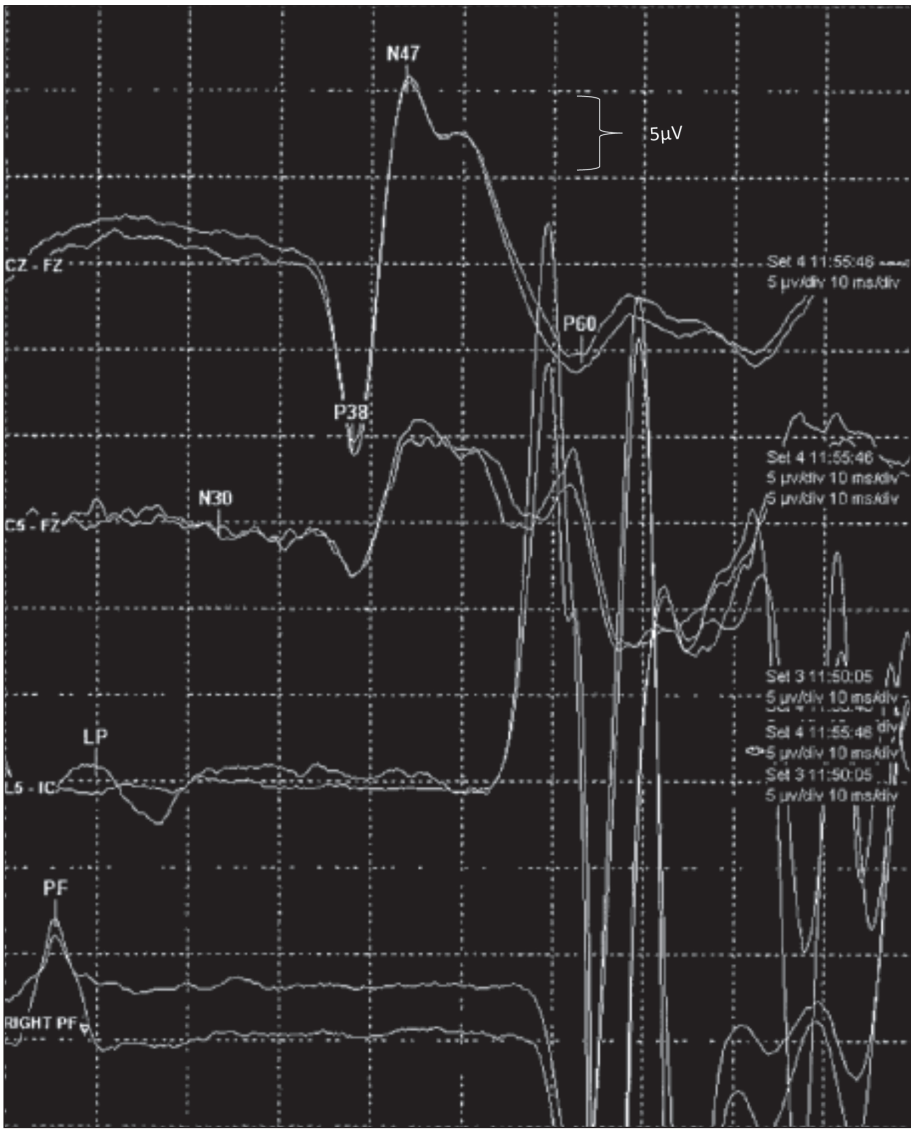

Figure 3. Right posterior tibial somatosensory evoked potential (giant SSEP amplitude P38-N47 = 22µV).

are rare, as in our case, however, myoclonus becomes progressively worse and often exacerbated by stress and startle. Ataxia was also commonly noted in 19 out of 20 patients in a large series of MEAK patients by Oliver et al. (2017) Importantly, symptoms commonly noted with other causes of progressive myoclonic epilepsy, such as hearing loss, retinal abnormalities, and sensory impairment, have not been reported. Formal neuropsychological testing typically shows a low normal range of verbal performance and overall mild cognitive decline. No cases with severe dementia have been reported. From a nosological point of view, the absence of overt cognitive impairment in patients with MEAK makes it similar to the Unverricht-Lundborg group of PMEs. Commonly, the EEG shows preservation of background rhythms with generalized polyspikes and polyspike waves, but focal spikes can be seen also, as reported in our patient. Brain MRI typically shows global symmetrical cerebellar atrophy which was not evident in this case. A recent case report of two male siblings with *KCNC1* mutation due to parental mosaicism also revealed a similar clinical profile of near normal early development, myoclonus starting at 10 years of age, rare GTCS, minimal cognitive impairment, and generalized epileptiform discharges on EEG (Kim *et al*., 2018). Our finding of giant high-amplitude somatosensory evoked potentials has been reported in the prior MEAK case series, and other progressive myoclonic epilepsy diseases (Shibasaki *et al*., 1985; Avanzini *et al*., 2016; Oliver *et al*., 2017). Valproate

and zonisamide are noted to be the most successful medications, while some success was also reported with levetiracetam, topiramate, and acetazolamide. A case series of patients with ULD, which included one patient with *de novo KCNC1* mutation, revealed that perampanel was effective in reducing myoclonus and the patient was able to regain his ability to transfer and walk with support (Crespel *et al*., 2017). Another study has also noted effectiveness of perampanel in progressive myoclonic epilepsy patients (Canafoglia *et al*., 2019). Lamotrigine caused worsening of myoclonus, which was also noted in our case (Oliver *et al*., 2017). There are insufficient data available to evaluate the efficacy of dietary treatment in this condition.

KCNC1 mutation results in a specific phenotype of progressive myoclonic epilepsy, which was recently described as myoclonic epilepsy and ataxia due to potassium channel mutation (MEAK). Our case illustrates a typical presentation of this disease as well as the potential for misdiagnosis during the early phase of the disease as idiopathic generalized epilepsy. Important findings that may suggest an alternative diagnosis are progressive myoclonus, prominent ataxia/dysmetria on examination and abnormal high-amplitude somatosensory evoked potentials. Early and accurate diagnosis with genetic testing may significantly help in counseling patients and families. □

Disclosures.
The authors have no conflict of interest to declare.

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