MYOCLONIC EPILEPSY, ATAXIA AND KCNC1 GENE MUTATION (MEAK): DESCRIPTION OF A FAMILY

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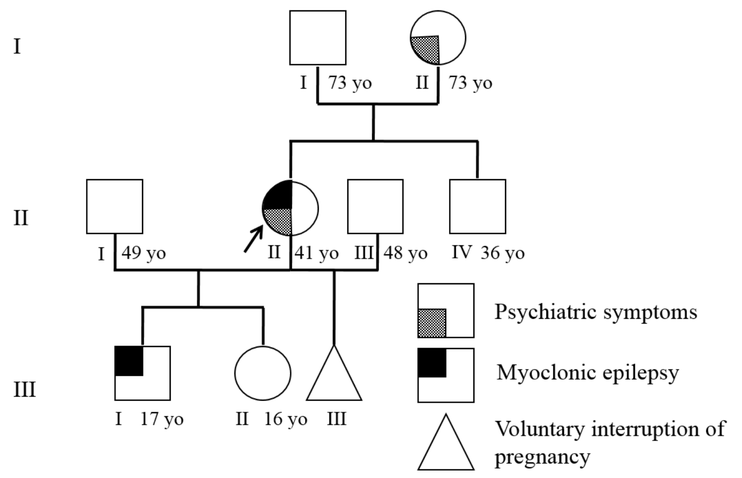
Introduction

Progressive myoclonus epilepsies (PMEs) are a group of rare, inherited disorders manifesting with action myoclonus, tonic-clonic seizures and ataxia. Recently, whole exome sequencing of patients with PMEs of unknown cause has allowed the identification of a de novo mutation, c.959G>A (p.Arg320His), in KCNC1, a novel major cause for this group of diseases (1). Epilepsy syndrome with this mutation was designated as MEAK: Myoclonus Epilepsy and Ataxia due to Potassium channel mutation.

Methods

We describe a small pedigree with two affected members, mother and son. They underwent full clinical evaluation and neuroradiological, neurophysiological and neuropsychological testing. We performed investigations focusing on the research of the most common causes of myoclonic epilepsies. Both patients underwent Sanger sequencing for the mutation recently described on the KCNC1 gene.



Results

II:II: 41-year-old female

Physiologic anamnesis: dystocic delivery, learning difficulties required assistance since primary school

Neurological examination: 30 years old	Neurological examination: 40 years old
➢ Hypotonia	➢ Diffuse hypotonia
➢ Reflex and spontaneous myoclonus	➢ Myoclonus +++
➢ Mild dysmetria	➢ Dysarthria, dysmetria
➢ Hyperreflexia of lower limbs	➢ Ataxic gait

Epileptic anamnesis:

➢15 years:

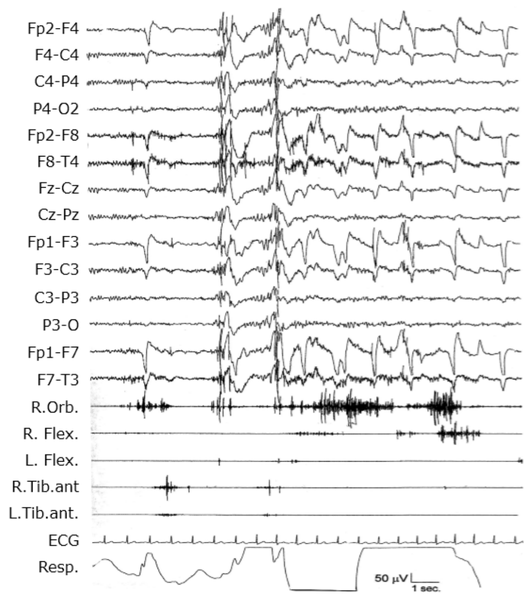
-sensory left leg aura evolving into bilateral tonic-clonic seizure

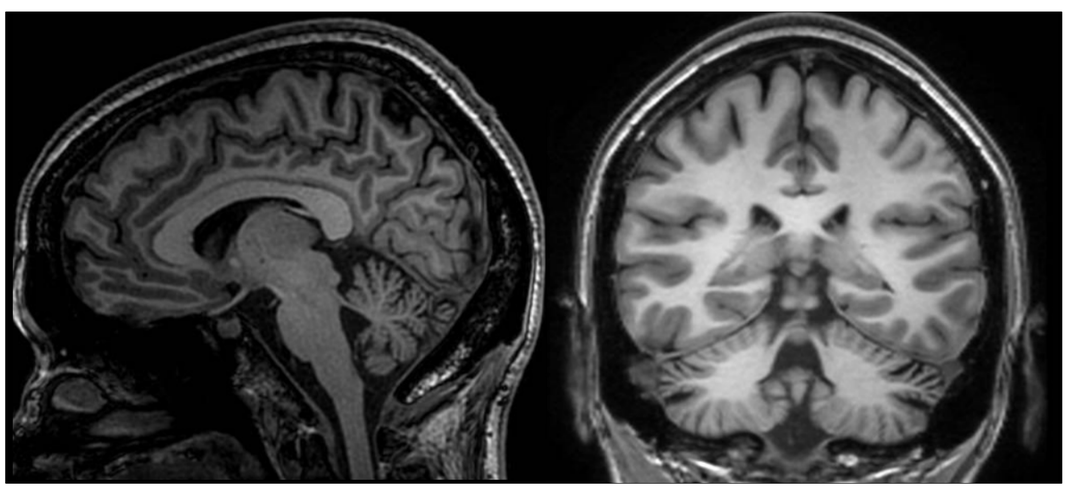
-massive myoclonic jerks, awareness preserved; 3-5 min, several/week.

➢20 years: episodes in which she suddenly dropped things from hands, possible traumatic falls preceded by massive myoclonic jerks, no impairment of consciousness; mainly catamenial

Drug resistant: PB, VGV, CNZ, LTG, VPA, LEV, CLB, ZNS

Substantial improvement of seizure frequency during pregnancy.





Neuropsychological assessment:

- MMSEc: 28.62 (cut off 23.8)
- BBDM: +0,43 (cut off > 0)
- WAIS-R: tot IQ 63; verbal 70, non verbal 61

Genetic testing: MERRF, DPRLA, CSTB, SCN1A negative

Muscular biopsy: negative

III:I: 18-year-old boy

Physiologic anamnesis: 9 years → brain injury → EEG showing epileptiform abnormalities

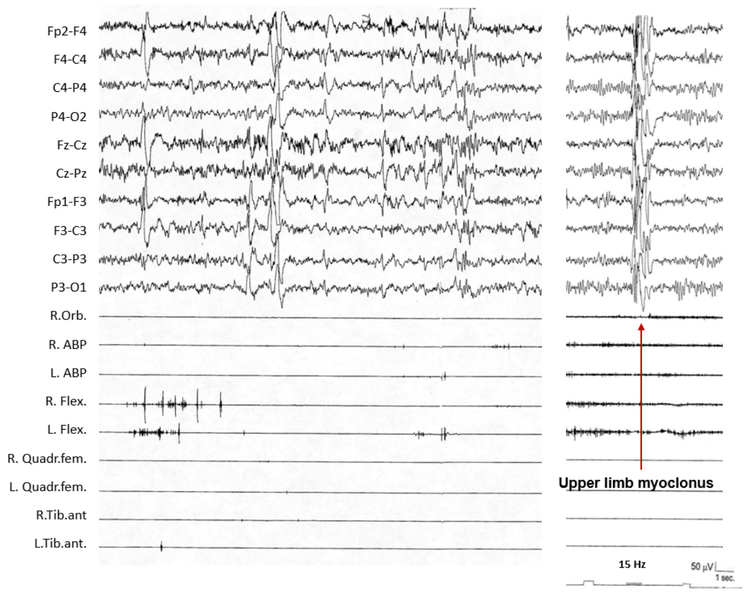
Neurological examination: 12 years old	Neurological examination: 16 years old
➢ Mild diffuse hypotonia	➢ Dysarthria
➢ Lower limb dysmetria	➢ Action myoclonus
➢ Sporadic myoclonus > upper limbs	➢ Ataxic gait → wheelchair
➢ Normal IQ	➢ IQ: 62

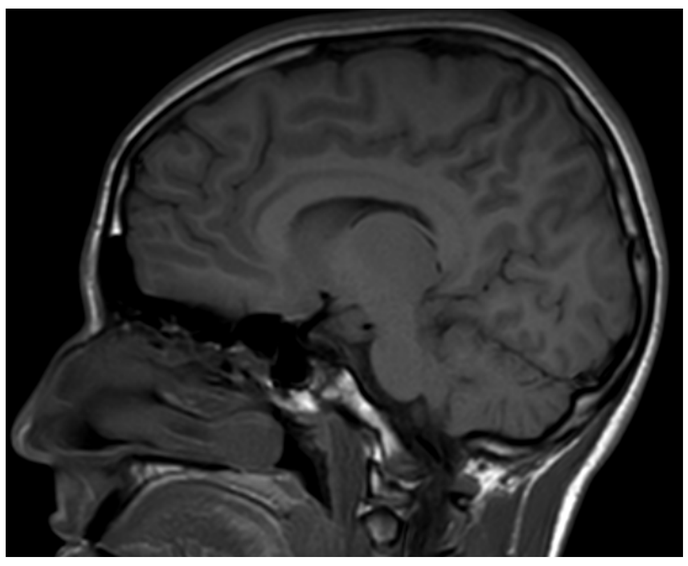
Epileptic anamnesis:

➢12 years: generalized tonic-clonic videogame-induced seizures

➢ 14 years: spontaneous and reflex myoclonic jerks

Drug resistant: VPA, LEV





Sanger sequencing performed on both patients revealed a **heterozygous mutation of KCNC1 gene c.959G>A (p.Arg320His)**.

Conclusions

We describe a family with progressive myoclonic epilepsy associated with a mutation in *KCNC1*. Recently, mutations in this gene have been identified as a novel major cause for this syndrome (1). In this paper, only one family with this mutation has been reported, whereas the remaining cases are sporadic.

Our patients (mother and son) are particularly interesting because they show a considerable phenotypic variability with a clinical picture that is more severe in the son, even if they carry the same mutation.

KCNC1 encodes $K_V3.1$, functioning as a highly conserved K+ channel subunit. A possibility for pharmacological treatment for patients with this mutation could be represented by modulation of K_V3 channel, but at the moment there are no drugs available with activating effects on this particular potassium channel.

The improvement during pregnancy reported by our patient could also suggest targeted hormonal therapies, however, more studies in larger groups of patients are required.

Bibliography

1. Muona M, Berkovic SF, Dibbens LM et al. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. Nat Genet 2015;47(1):39-46.