BMC Neurology

CASE REPORT

Open Access

Myoclonus improvement after seizures in progressive myoclonic epilepsy type 7: a case report

Pedro Lucas G S B Lima[1†], Paulo R Nobrega[2,3†], Fernando Freua[4], Pedro Braga-Neto[2], Anderson R B Paiva[4], Thiago Gonçalves Guimarães[5*] and Fernando Kok[4]

Abstract

Background Progressive Myoclonic Epilepsy (PME) is a group of rare diseases that are difficult to differentiate from one another based on phenotypical characteristics.

Case report We report a case of PME type 7 due to a pathogenic variant in *KCNC1* with myoclonus improvement after epileptic seizures.

Discussion Myoclonus improvement after seizures may be a clue to the diagnosis of Progressive Myoclonic Epilepsy type 7.

Keywords Myoclonus, Epilepsy, *KCNC1*, Movement disorders, Case report

Background

Progressive Myoclonic Epilepsies (PMEs) are a group of rare and severe conditions characterized by action myoclonus, refractory epilepsy, ataxia and dementia. Most diseases in this group have an autosomal recessive pattern of inheritance [1, 2]. PMEs usually present in late childhood or adolescence. Patients commonly become wheelchair-bound and have a reduced life expectancy.

Progressive Myoclonic Epilepsy type 7, also known as myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK), is associated with the recurrent c.959G>A (p.Arg320His) variant in *KCNC1* and stands out for , relatively easily treatable epilepsy without severe cognitive impairment and autosomal dominant inheritance associated with *de novo* variants [1, 2]. Other variants in EPM7 have been reported to cause epileptic encephalopathy [3].

Case Report

A 29-year-old woman presented at the age of 10 with upper limb abnormal jerky movements. These movements were triggered by action and worsened in the morning. After two months, she started focal epileptic seizures with left limb tonic postures that progressed to generalized tonic-clonic seizures in most occurrences. Her mean seizure frequency was around 2 to 5 seizures a month and tonic-clonic seizures lasted up to 5 min at most, followed by 30 to 60 min of somnolence.

†Pedro Lucas G S B Lima and Paulo R Nobrega contributed equally to this work.

*Correspondence:
Thiago Gonçalves Guimarães
thiagogguimaraesneurologia@gmail.com
[1]Faculty of Medicine, Federal University of Ceara, Fortaleza, Ceara, Brazil
[2]Division of Neurology, Federal University of Ceara, Fortaleza, Ceara, Brazil
[3]Centro Universitário Christus, Fortaleza, Ceara, Brazil
[4]Neurogenetics Center, Department of Neurology, University of Sao Paulo, Sao Paulo, Brazil
[5]Movement Disorders Center, Department of Neurology, University of Sao Paulo, Av. Dr. Eneas de Carvalho Aguiar, 255, 5th Floor, Room 5084, Cerqueira Cesar, Sao Paulo, Sao Paulo 05403-900, Brazil

Interestingly, involuntary movements worsened during the menstrual period and improved after each generalized tonic-clonic seizure (Video). The improvement lasted from 5 to 7 days after each seizure. Improvement in myoclonus was not seen with fever and the patient did not consume alcohol.

Following the myoclonus and seizures onset in early adolescence, progressive impairment in gait and balance was observed. By the age of 21, the patient was wheelchair-bound.

Seizures were controlled with valproate. The patient has been seizure-free since the age of 15. Before presenting at our outpatient clinic, she was on carbamazepine which wasn't effective. No other anti-seizure drugs had been used before valproate and piracetam (which we discontinued posteriorly due to somnolence).

The patient's early development was marked by a delay in walking and language (she walked without support at the age of three and spoke more elaborated phrases around four years of age). Her medical history was remarkable only for insulin-dependent diabetes mellitus. Her family history was unremarkable.

By the age of 29, the patient achieved a highschool degree. She recently scored 25/30 on Mini Mental State Examination. Neurological examination revealed severe generalized action myoclonus, global ataxia, and dysarthria (Video). Brain MRI showed mild cerebellar atrophy (Fig. 1). Electroencephalogram disclosed generalized spike and spike-wave paroxysms. Whole exome sequencing identified a previously described missense variant c.959G>A (p.Arg320His) in *KCNC1* [4, 5]. This variant is classified as pathogenic according to ACMG criteria [6] and was reported to cause Myoclonic Epilepsy Type 7 (OMIM#616,187). Unfortunately, parental testing could not be performed for segregation analysis.

Discussion

Next-Generation Sequencing (NGS) technology has uncovered rare genetic causes in unsolved PME cases, including established and novel PME-related genes, with a diagnostic yield of over 80% in PME, underlining its status as one of the best genetically defined epilepsy syndromes [7].

The potassium channel subfamily Kv3 consists of four subunits which are encoded by *KCNC1, KCNC2, KCNC3*, and *KCNC4*. Pathogenic variants in *KCNC3* are associated with spinocerebellar ataxia type 13, whereas *KCNC2* and *KCNC4* have not been associated with human disease up to this moment [8]. Regarding *KCNC1*, a study conducted in 2016 found that 16 out of 84 clinically confirmed Progressive Myoclonic Epilepsy (PME) cases without clear genetic etiology had a monoallelic missense variant in the *KCNC1* gene, c.959G>A (p.Arg320His), 13 of whom were unrelated [9]. The authors suggested the name MEAK (Myoclonus Epilepsy and Ataxia due to

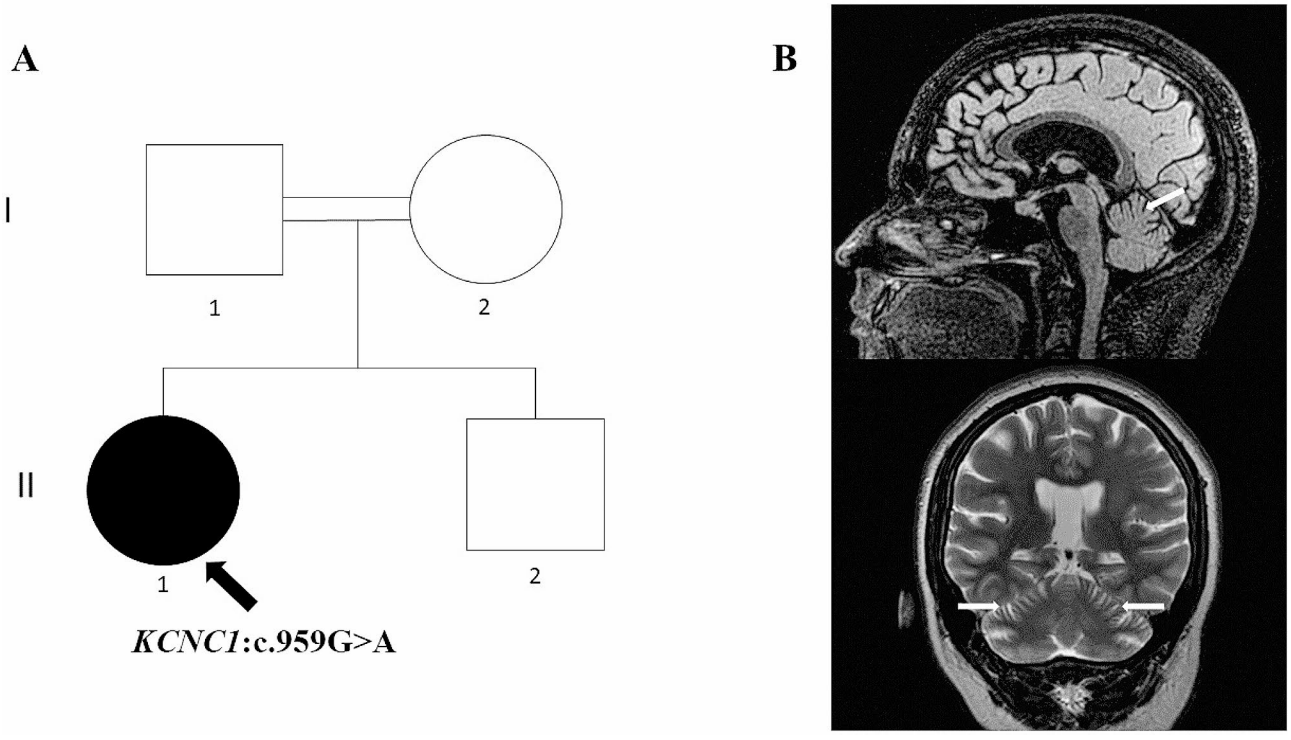

Fig. 1 Family pedigree (**A**): the patient's parents were unaffected first-degree cousins. Brain MRI (**B**) showed mild cerebellar atrophy

potassium channel mutation) for the condition, corresponding to the PME type 7.

The phenotype described in PME type 7 consists of normal early development with myoclonus as the first symptom (onset at 6 to 14 years), which becomes progressively worse affecting the gait and resulting in patients being wheelchair-bound by adolescence or early adulthood in most cases. Tonic-clonic seizures may be present but are not frequent. Mild cognitive decline occurs in some cases after seizure onset. Magnetic resonance may be normal or show cerebellar atrophy [9, 10]. Exacerbation during menses was reported [5]. High fever is reported to transiently (from hours to days) improve gait and myoclonus in PME type 7 patients [5]. Our patient, however, did not report improvement with fever. Alcohol and pregnancy were also reported to improve the condition of these patients [5]. The patient in this report did not consume alcohol.

Compared to other types of PME, the type 7 has a somewhat similar presentation to Unverricht-Lundborg disease (PME type 1), but with more severe disease progression [2, 10]. To the best of our knowledge, there are no reports describing improvement of myoclonus after seizures in this condition.

Seizures may reduce post-ictal neuronal activity by several mechanisms. Increased calcium entry during depolarization activates a calcium-dependent membrane potassium conductance that allows potassium efflux and membrane hyperpolarization [11, 12]. Extracellular calcium levels also change markedly after paroxysmal neuronal firing. Seizures result in a decline in extracellular calcium activity of approximately 50% [13]. This decrease may impair synaptic transmission because synaptic vesicle fusion and neurotransmitter release are dependent on the entrance of extracellular calcium [14, 15]. Seizure discharges also produce recurrent GABAergic synaptic inhibition via inhibitory interneurons [16, 17], thus reducing excitatory output. Neuromodulators, such as endocannabinoids, adenosine, and neuropeptide Y (NPY) are synthesized and released from neurons following membrane depolarization and inhibit neuronal activity. We hypothesize that the post-seizure inhibition of neuronal activity caused by the aforementioned factors may result in myoclonus improvement in the patient reported here. The deficiency in potassium channel activity may lead to an increase in other compensatory mechanisms responsible for the termination of seizures, but further studies are needed to confirm this hypothesis.

The current therapeutic approach to PMEs remains palliative, to control seizures and myoclonus, and improve patients' quality of life and independence. Literature is scarce concerning pharmacological options in PMEs, mostly composed of reports and small observational studies [18]. Valproic acid (VPA) is the most reported drug in PMEs. It is described as the drug of choice, alone or in combination with clonazepam, due to its high effectiveness on myoclonus, seizures, and photosensitivity [18].

The PMEs, despite having similar phenotypic features overall, form a very heterogeneous group of conditions, each having a different genetic background and disease-causing mechanism. This makes a single therapeutic approach to all forms unlikely, but also opens up the possibility for personalized therapeutic approaches. Currently, there are several experimental studies in animal and cellular models that aim to correct the main disease-causing mechanism, such as enzyme replacement therapies for Sialidosis and Gaucher's disease type III, and gene replacement therapy for Lafora disease [2].

This case describes a patient with PME type 7 and illustrates a novel interesting clinical phenomenon myoclonus improvement after seizures in a rare form of progressive myoclonic epilepsy. This adds to the literature as a possible clinical phenomenon that may help clinicians to raise suspicion of Progressive Myoclonic Epilepsy type 7.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03625-z.

Supplementary Material 1

Supplementary Material 2

Author contributions

PLGSBL, TGG and PRN were responsible for the conceptualization of this report. All authors were engaged in data collection, literature review and early manuscript draft. PBN, ARBP, FF and FK were responsible for manuscript revision. The final version of the article was written by TGG, PRN and PLGSBL.

Funding

No external funding was provided for this research.

Data availability

The dataset generated during the current study is available from the corresponding author on reasonable request. The detailed information regarding the identified variant is available in the ClinVar repository under the Variation ID 162519.

Declarations

Ethics approval and consent to participate

Patient provided verbal and written consent for this work but because this article is a case report no Institutional Review Board (IRB) approval was necessary.

Consent for publication

Patient provided verbal and written informed consent for this publication.

Competing interests

The authors declare no competing interests.

Received: 26 December 2023 / Accepted: 5 April 2024
Published online: 23 May 2024

References

1. Malek N, Stewart W, Greene J. The progressive myoclonic epilepsies. Pract Neurol. 2015;15(3):164–71.
2. Orsini A, Valetto A, Bertini V, Esposito M, Carli N, Minassian BA, et al. The best evidence for progressive myoclonic epilepsy: a pathway to precision therapy. Seizure. 2019;71:247–57.
3. Cameron JM, Maljevic S, Nair U, Aung YH, Cogné B, Bézieau S, et al. Encephalopathies with KCNC1 variants: genotype-phenotype-functional correlations. Ann Clin Transl Neurol. 2019;6(7):1263–72.
4. Barot N, Margiotta M, Nei M, Skidmore C. Progressive myoclonic epilepsy: myoclonic epilepsy and ataxia due to KCNC1 mutation (MEAK): a case report and review of the literature. Epileptic Disord. 2020;22(5):654–8.
5. Oliver KL, Franceschetti S, Milligan CJ, Muona M, Mandelstam SA, Canafoglia L, et al. Myoclonus epilepsy and ataxia due to KCNC1 mutation: analysis of 20 cases and K+channel properties. Ann Neurol. 2017;81(5):677–89.
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a Joint Consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405.
7. Canafoglia L, Franceschetti S, Gambardella A, Striano P, Giallonardo AT, Tinuper P et al. Progressive Myoclonus epilepsies: Diagnostic Yield with Next-Generation sequencing in previously Unsolved cases. Neurol Genet. 2021;7(6).
8. Park J, Koko M, Hedrich UBS, Hermann A, Cremer K, Haberlandt E, et al. KCNC1-related disorders: new de novo variants expand the phenotypic spectrum. Ann Clin Transl Neurol. 2019;6(7):1319–26.
9. Nascimento FA, Andrade DM. Myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK) is caused by heterozygous KCNC1 mutations. Epileptic Disord. 2016;18(S2):S135–8.
10. Muona M, Berkovic SF, Dibbens LM, Oliver KL, Maljevic S, Bayly MA, et al. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. Nat Genet. 2015;47(1):39–46.
11. Timofeev I, Grenier F, Steriade M. Contribution of intrinsic neuronal factors in the generation of cortically driven electrographic seizures. J Neurophysiol. 2004;92(2):1133–43.
12. Alger BE, Nicoll RA. Epileptiform burst afterhyperolarization: calcium-dependent potassium potential in hippocampal CA1 pyramidal cells. Science. 1980;210(4474):1122–4.
13. Heinemann U, Lux HD, Gutnick MJ. Extracellular free calcium and potassium during paroxsmal activity in the cerebral cortex of the cat. Exp Brain Res. 1977;27(3–4):237–43.
14. Cohen JE, Fields RD. Extracellular calcium depletion in synaptic transmission. Neuroscientist. 2004;10(1):12.
15. King RD, Wiest MC, Montague PR. Extracellular calcium depletion as a mechanism of short-term synaptic depression. J Neurophysiol. 2001;85(5):1952–9.
16. Dorn T, Witte OW. Refractory periods following interictal spikes in acute experimentally induced epileptic foci. Electroencephalogr Clin Neurophysiol. 1995;94(1):80–5.
17. Kostopoulos G, Avoli M, Gloor P. Participation of cortical recurrent inhibition in the genesis of spike and wave discharges in feline generalized penicillin epilepsy. Brain Res. 1983;267(1):101–12.
18. Ferlazzo E, Trenite DKN, de Haan GJ, Felix Nitschke F, Ahonen S, Gasparini S, et al. Update on Pharmacological Treatment of Progressive Myoclonus Epilepsies. Curr Pharm Des. 2017;23(37):5662–6.

Publisher's Note