



Clinical letter

Migrating focal seizures in Autosomal Dominant Sleep-related Hypermotor Epilepsy with KCNT1 mutation

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1. Introduction

Mutations in the sodium-gated potassium channel subunit gene KCNT1 are associated to different phenotypes such as Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE), previously named Nocturnal Frontal Lobe Epilepsy (ADNFLE), and other forms of focal epilepsies, epileptic encephalopathies and intellectual disabilities [1].

Here we describe a family with an ADSHE spectrum disorder in which the proband showed, during his disease course, both sleep-related hypermotor seizures and migrating focal seizures during wake.

2. Case report

The proband is a five year old boy, born from non-consanguineous parents.

His mother and the older maternal uncle suffered from SHE from seven-eight to seventeen-eighteen years; both were treated with carbamazepine with good control of seizures. The younger maternal uncle suffered from a severe form of SHE since the age of nine. He was treated

with several antiepileptic drugs with poor effect and developed a psychiatric disability leading to institutionalization [2].

Moreover, a positive family history for psychiatric disorders was present both in his maternal grandfather (personality disorder) and in his maternal grandmother (depression); in both, seizures never occurred (Fig. 1) [2].

The proband, at the age of two, was admitted in our Hospital because of nocturnal awakenings followed by groaning, crying, drooling and tachycardia, lasting a few minutes in absence of responsiveness. Initially, these episodes were interpreted as sleep terrors. After a few weeks, clear epileptic attacks appeared with mouth and arms automatisms, followed by hypertonus of limbs and dystonic posturing with fencing position.

A first video-polysomnographic investigation documented focal seizures in nocturnal sleep with bilateral independent fronto-temporal onset.

ADSHE was diagnosed because of family history and carbamazepine was started.

The MRI showed multiple very small cerebral cavernomas with no sign of previous bleedings.

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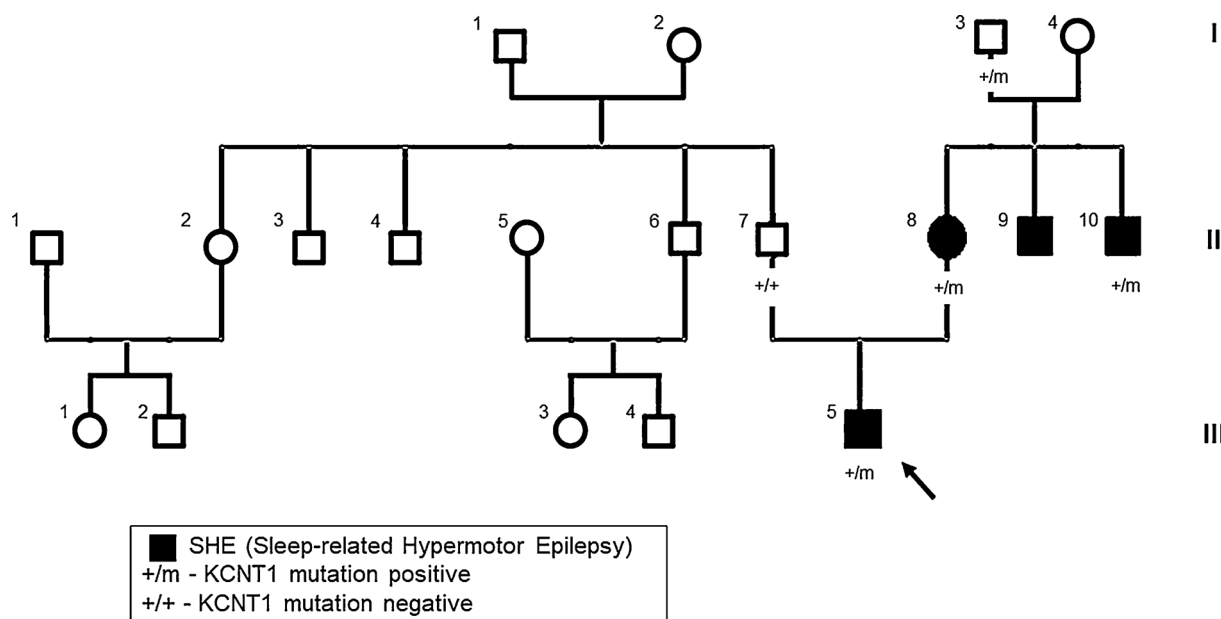


Fig. 1. Family Pedigree.

Family Pedigree: the proband (III-5), proband's mother (II-8), younger uncle (II-10), older uncle (II-9), maternal grandfather (I-3), maternal grandmother (I-4).

After three months from seizure onset the clinical picture worsened with more than 50 episodes per night; clobazam, midazolam, levetiracetam and phenytoin were added in different combinations without any effect on seizure frequency. In the same period he became at first hyperkinetic and aggressive, after a few days hypotonic and obtunded, with catatonic appearance. The EEG during this “dyscognitive status” showed focal electric discharges, mostly arising from the temporal areas, migrating from one hemisphere to the other. Electrographically the discharges were characterized by an onset with a rhythmic activity in the alpha frequency band, progressively slowing into a theta/delta high amplitude rhythm (Fig. 2).

When this focal status with catatonic behaviour appeared, nocturnal seizures stopped completely.

The administration of phenobarbital bolus during EEG lead to the cessation of seizures with progressive improvement of reactivity over days reaching the return to baseline after two months. The overall acute phase lasted for five months and the patient is still seizure free.

Griffiths Mental Development Scales assessed (GMDS) psychomotor development during follow-up. Scales revealed a global stable mild development delay (General developmental Quotient (GQ) = 65, aged three years and seven months; GQ = 68, aged four years and nine months), with worse performance in “Sub-scale C: Language: Receptive and expressive language”.

A Next Generation Sequencing (NGS) Epileptic Encephalopathies panel of 38 genes was performed with mutation confirmation by Sanger sequencing (list of the 38 genes included in the panel: ALDH7A1, ALG13, BRAT1, CDKL5, CHD2, DNM1, GABRA1, GABRB3, GNAO1, GRIN2A, HCN1, IQSEC2, KCNA2, KCNB1, KCNQ2, KCNQ3, KCNT1, MEF2C, PCDH19, PIGA, PNKP, PNPO, PRRT2, QARS, SCN1A, SCN2A, SCN2A, SCN8A, SLC25A22, SLC2A1, SLC35A2, SLC6A1, SPTAN1, ST3GAL3, STXB1, SYNGAP1, TBC1D24, WWOX).

The panel detected a heterozygous missense variant in KCNT1 at chromosome 9q34.3 disrupting a highly conserved alanine residue in the intracellular C-terminal domain (NM_020822:c.G2896A:p.A966T).

The same mutation was found in the mother, in the maternal grandfather and in the previously mentioned severely affected maternal uncle.

We got the clinical history from the latter (now 33 year-old), reporting a highly refractory focal epilepsy, started at the age of nine with hypermotor episodes during sleep, firstly characterized by fear and

wandering [2] and later by tonic-dystonic seizures, resembling the one observed in our patient. At the age of 24, before the genetic diagnosis and the marked worsening of a pre-existing psychiatric disorder, he underwent stereo-EEG recordings, showing a left insular onset of seizures (patient 8 in ref [3].).

3. Discussion

There are few reports of the same mutation in individual with EIMFS or SHE both sporadic or among the same family. The association of different phenotypes with the same mutation may be the result of either genetic modifiers or environmental factors [1,4].

To our knowledge, this is the first reported case of a mutation in the KCNT1 gene manifesting with clinical features partially compatible with both ADSHE and EIMFS phenotypes. Indeed, although initially the clinical manifestations of our patient could fit the SHE definition criteria, he rapidly developed a dyscognitive status related to continuous migrating seizures.

On the other hand, a diagnosis of EIMFS is not applicable because of the age of onset and the clinical course, including response to treatment, atypical for EIMFS.

The complete and persistent response to PB add-on and the mild neurodevelopmental impairment observed at follow-up are rather unusual both for EIMFS and ADSHE related to KCNT1 mutation.

The presence of very small cerebral cavernomas with no signs of previous bleeding was considered an incidental finding.

The c.G2896A:p.A966T KCNT1 mutation detected in heterozygosity in our patient has been previously reported in a child with a severe early-onset epilepsy and suppression-burst consistent with Ohtahara Syndrome. Differently by our patient, the reported case showed a homozygous pattern of mutation related to concomitant paternal isodisomy for chromosome 9 at single nucleotide polymorphism (SNP) array; the mutation was inherited from the father who had a positive family history for childhood idiopathic epilepsy [4].

The identification of KCNT1 mutations in both ADSHE and EIMFS suggests that the two phenotypes may be part of a larger spectrum [1].

In this view our patient appears to be the link between the two forms with some characteristics of each one.

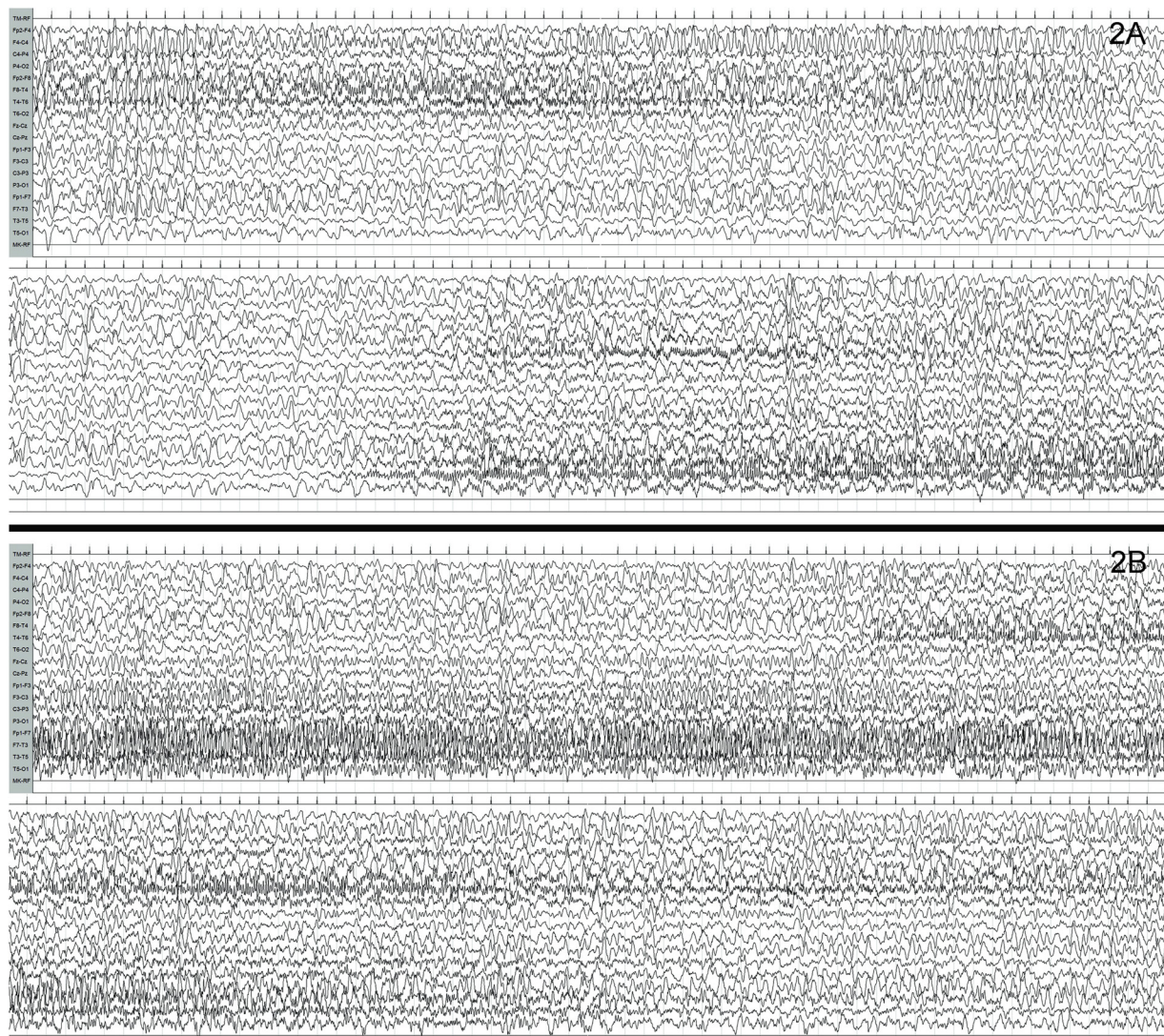


Fig. 2. Migrating Focal Seizures. Wake EEG recorded during the “dyscognitive status”, three months after nocturnal focal seizures onset. Monomorphic slow high amplitude background activity. Focal seizures mostly involving the temporal areas shifting from the right hemisphere to the left (first two rows) (Fig. 2A) and then from the left to the right (last two rows) (Fig. 2B) (migrating focal seizures). The child showed a catatonic behaviour during the exam, with no response to external stimuli and obtundation. The electrical status resolved with PB bolus (50 mg), clinical improvement was slow but persisted over weeks, leading to *quo ante* status. SI 10–20, 30 s/page (60 s each row), Sens 14 Uv/mm, HF 30 Hz, LF 0.1 s.

Author’s list and their individual contributions to the manuscript

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.seizure.2019.02.019>.

References

- [1] Lim CX, Ricos MG, Dibbens LM, Heron SE. KCNT1 mutations in seizure disorders: the phenotypic spectrum and functional effects. *J Med Genet* 2016;53:217–25. <https://doi.org/10.1136/jmedgenet-2015-103508>.
- [2] Gaggero R, Devescovi R, Nobili L, Baglietto MG, Zucconi M, Schinardi A. Benign parasomnias and nocturnal frontal epilepsy: differential diagnosis in a case report. *J Child Neurol* 2001;16:628–31. <https://doi.org/10.1177/088307380101600823>.
- [3] Proserpio P, Cossu M, Francione S, Tassi L, Mai R, Didato G, et al. Insular-opercular seizures manifesting with sleep-related paroxysmal motor behaviors: a stereo-EEG study. *Epilepsia* 2011;52:1781–91. <https://doi.org/10.1111/j.1528-1167.2011.03254.x>.
- [4] Martin HC, Kim GE, Pagnamenta AT, Murakami Y, Carvill GL, Meyer E, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. *Hum Mol Genet* 2014;23:3200–11. <https://doi.org/10.1093/hmg/ddu030>.