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Short communication

Paroxysmal kinesigenic dyskinesia: Cortical or non-cortical origin

Teun W. van Strien [a,b], Anne-Fleur van Rootselaar [c], Anthony A.J. Hilgevoord [a], Wim H.J.P. Linssen [a], Alexander J.A. Groffen [d], Marina A.J. Tijssen [c,e,*]

[a] Department of Neurology, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands
[b] Department of Neurology, Dr. Horacio E. Oduber Hospitaal, Oranjestad, Aruba
[c] Department of Neurology & Clinical Neurophysiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[d] Department of Functional Genomics & Clinical Genetics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VUMC, Amsterdam, The Netherlands
[e] Department of Neurology, University Medical Centre Groningen, The Netherlands

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ABSTRACT

Paroxysmal kinesigenic dyskinesia (PKD) is characterized by involuntary dystonia and/or chorea triggered by a sudden movement. Cases are usually familial with an autosomal dominant inheritance. Hypotheses regarding the pathogenesis of PKD focus on the controversy whether PKD has a cortical or non-cortical origin. A combined familial trait of PKD and benign familial infantile seizures has been reported as the infantile convulsions and paroxysmal choreoathetosis (ICCA) syndrome. Here, we report a family diagnosed with ICCA syndrome with an Arg217STOP mutation. The index patient showed interictal EEG focal changes compatible with paroxysmal dystonic movements of his contralateral leg. This might support cortical involvement in PKD.

1. Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is a rare disorder characterized by recurrent attacks of involuntary dystonia and/or chorea triggered by sudden movement. Most of the reported cases of PKD are familial and inherited in an autosomal dominant trait [1,2]. In a number of PKD pedigrees, patients and/or family members report infantile convulsions that fit the description of benign familial infantile seizures (BFIS) [3]. BFIS itself is also an autosomal dominant disorder characterized by nonfebrile seizures with an onset between 3 and 12 months of age, a good response to medication and no neurological sequelae [4,5]. A combined familial trait of PKD and BFIS has been reported as the infantile convulsions and paroxysmal choreoathetosis (ICCA) syndrome. It is typical for PKD, BFIS as well as ICCA syndrome that interictal EEG is normal. Recent genetic research led to the identification of PRRT2 on human chromosome 16p11.2 as the major causative gene [6,7]. Here, we report a patient from a family with ICCA syndrome, with interictal EEG focal changes that are compatible with his paroxysmal dystonic limb movements and enlighten the genetic findings in this pedigree.

2. Methods

Clinical and electrophysiological data and blood DNA samples from a three-generation family were collected after written informed consent and ethical approval by the Institutional Review Board. Linkage with chromosome 16 was confirmed using the microsatellite markers ((D16)S748, S499, S3046, S417, S420, S3068, S3131, S3100, S3145, S3120, S690, S3022, S3081, S685, S753, S409, S3080, S411, S3136, S3396, S3112, S514 and S397). FAM- and NED-labeled PCR products were separated in presence of a LIZ500 size marker on an ABI Prism 3137 apparatus and the results analyzed with GeneMarker v1.95 software (SoftGenetics LLC). Sequence analysis was performed using the BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems) with previously published primersets [7]. In view of previous studies showing linkage of PKD, ICCA and a form of BFIS to chromosome 16 [3,5,8], we hypothesized that each phenotype may reflect a different expression of a single trait with autosomal dominant inheritance.

3. Results

3.1. Index patient (pedigree III-4)

At the age of 16 years, the patient entered the consulting room, when his left leg suddenly made slow kicking movements almost causing him to fall. Fully conscious, he pretended to tie his shoelaces. The movements ceased after a few seconds. It turned out that these attacks happened approximately every other day, always

* Corresponding author. Movement Disorders, Department of Neurology AB 51, University medical Centre Groningen (UMCG), PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 3612400; fax: +31 50 3611707.
E-mail address: M.A.J.de.Koning-Tijssen@umcg.nl (M.A.J. Tijssen).

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involving his left leg. An attack typically lasted a few seconds and was provoked by a sudden initiation of movement. Occasionally a sensory warning preceded the attack, but he was unable to prevent the movements. During soccer games he suffered from several attacks per match. He had had these attacks for almost a year but had not mentioned it out of shame.

Neurological examination immediately after the attack was completely normal. An interictal EEG, recorded two weeks after the event, showed series of epileptic discharges over the right frontocentral area especially during drowsiness and hyperventilation, lasting up to 10 s (Fig. 1). During these discharges no abnormal movements were observed.

Past medical history revealed that his birth and psychomotor development had been unremarkable. At the age of four months he had had nonfebrile generalized seizures treated with rectal benzodiazepines, intravenous phenobarbital and phenytoin. Routine blood tests and cerebrospinal fluid examination were normal. An interictal EEG showed epileptic activity. At the age of 16 months, within a few days after discontinuation of the anticonvulsive therapy a cluster of tonic-clonic seizures occurred. Valproic acid (200 mg dd) was restarted preventing further seizures and was discontinued at the age of two years (normal EEG). He was diagnosed with benign familial infantile seizures (BFIS) because of the family history (see below). He had had no further seizures up to the age of 13 years when he suffered from a single generalized tonic-clonic seizure. An interictal EEG showed right-sided frontotemporal epileptic discharges. Valproic acid (1000 mg dd) was restarted. An MRI of the brain was normal. At the age of 14 years he had two generalized tonic-clonic seizures after cessation of the valproic acid (normal EEG beforehand). Valproic acid was restarted (1000 mg dd).

After the current attack with involuntary leg movements and taking in account BFIS in the medical history, the diagnosis ICCA was made. Treatment with carbamazipine (400 mg dd) was initiated and valproic acid was stopped. During three years follow-up no involuntarily movements nor epileptic seizures occurred unless he incidentally forgot his medication.

Haplotype analysis of 23 markers providing coverage of the critical regions revealed the presence of a single allele on chromosome 16, also present in other affected family members, that was absent in non-affected individuals. Mutation analysis revealed a novel Arg217STOP mutation in the PRRT2 gene at a position where frameshift mutations were also found to cause familial PKD [6,7].

3.2. Family history

The youngest uncle (II-4; Fig. 2, pedigree) of the index patient, suffered from dystonic posturing of the left side of his body triggered by sudden movements and lasting 10–15 s from the age of

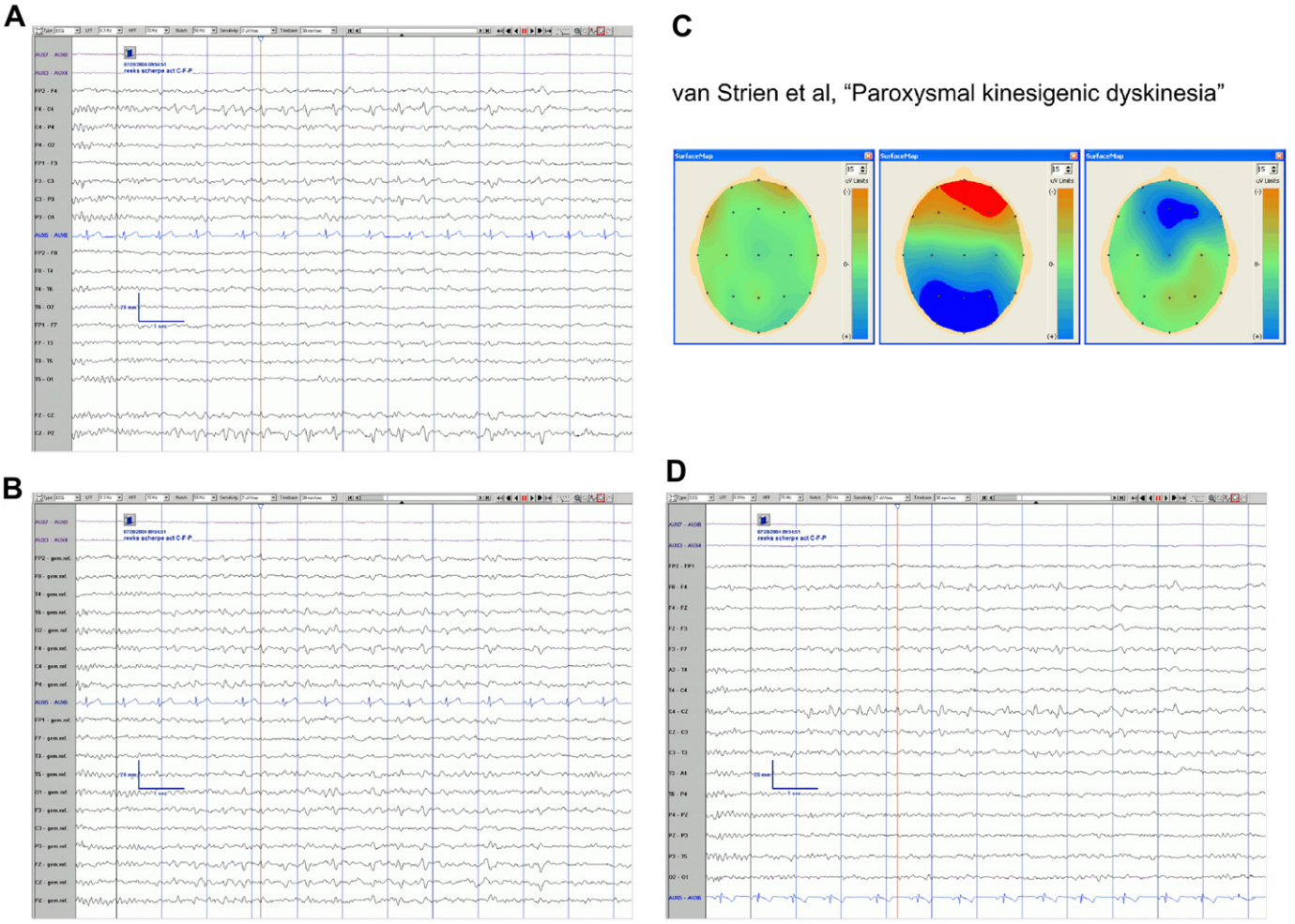

Fig. 1. Interictal EEG recording of the index patient showing focal discharges lasting up to 10 s, maximal over the right frontocentral area. A: bipolar longitudinal derivation; B: average reference; C: amplitude maps at *T*peak minus 75 m s, at *T*peak (vertical marker line) and *T*peak plus 75 m s; D: transverse derivation. (Low frequency filter 0.3 Hz, High frequency filter 70 Hz, original sensitivity 7 μV/mm, time base 30 mm/s; aux5–aux6: electrocardiography, aux3–4 and 7–8: eye movements).

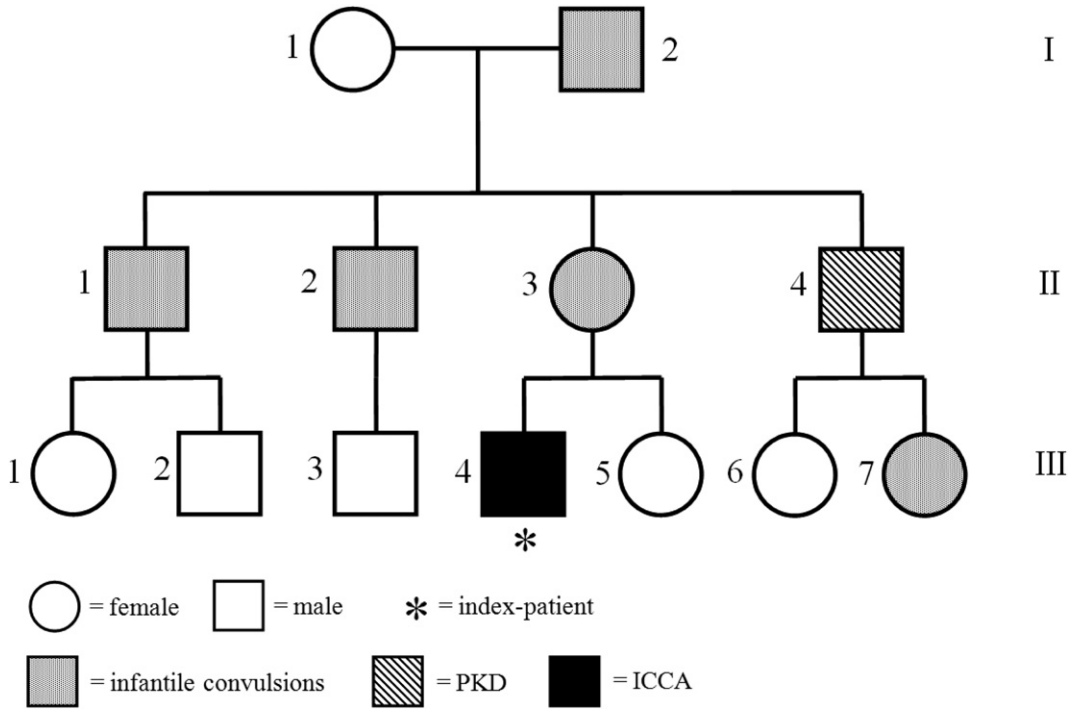

Fig. 2. Pedigree showing the autosomal dominant inheritance of infantile convulsions, PKA or ICCA in three generations. Linkage analysis of 23 markers in the region D16S748-D16S397 demonstrated that the phenotypes co-segregated with chromosome 16. As an exception, subject II-1 reported infantile convulsions but did not carry the disease allele. No recombinations were detected. No DNA samples were available for subjects III-1, 2, 3, 5, 6 and 7.

fifteen years. Incidentally, a sensory prodrome occurred enabling him to sit down and preventing him from falling during the attack. The frequency of the attacks was about 3 times a week and they became less over the years. He never consulted a doctor for it. His past medical history was unremarkable; he had not suffered from any seizures. Neurological examination and an interictal EEG showed no abnormalities. He choose not be treated as the involuntary movements did not interfere with his daily life. Genetic studies showed he also had the mutation.

The grandparents, of West-African ethnic origin, immigrated from Suriname to Holland. Several family members are known with infantile seizures (Fig. 2). Some details, including EEGs, are lacking. His granddad (I-2) had a seizure at the age of 1½ years. The mother of the index patient (II-3) had one or two seizures when aged six month old. She was found to carry the affected allele. His uncle (II-1), who did not carry the allele, reported seizures at the age of 13 months and at age 6 and 14 years. Another uncle (II-2) had one seizure when five months old. He did have the mutation. They were all successfully treated with phenobarbital. His cousin (III-7) had one seizure when 18 months old. No DNA was available for genetic studies from this family member.

4. Discussion

Here, we describe a patient, diagnosed with ICCA and a proven Arg217STOP mutation, with paroxysmal dystonic posturing in his left leg and focal interictal EEG changes over the right frontocentral area. This might indicate cortical involvement in the abnormal posturing. These EEG abnormalities, and also the persistence of seizures into adulthood observed in this pedigree are in fact atypical for the ICCA syndrome. The occurrence of EEG changes in PKD is also rare. Clinical criteria for PKD proposed in 2004 include the presence of a kinesigenic trigger, short duration of the attacks, preserving of consciousness and response to phenytoin or carbamazepine [9]. No clear statement was formulated with respect to EEG abnormalities. A number of patients fulfilling the clinical criteria for PKD have been reported with ictal and/or interictal EEG abnormalities, including focal slowing. These abnormalities did not correspond in particular with the dystonic posturing limb. The persistence of generalized tonic-clonic seizures during adulthood in ICCA has also been reported before. Lee et al. described 3 out of 8 pedigrees with generalized tonic-clonic seizures beyond childhood [10]. It appears that, although rare, both the persistence of seizures beyond childhood and EEG abnormalities do not rule out the diagnosis of PKD [11,12].

Whether PKD has a cortical or subcortical origin is controversial. In the 60's different authors considered PKD as a variety of (reflex) epilepsy because of the paroxysmal nature of the attacks and the excellent response to anticonvulsants. On the other hand PKD was argued to be a disorder of the basal ganglia due to the in general normal (inter)ictal EEG's, the preservation of consciousness and the subcortical nature of the attacks with dystonic posturing and choreatic movements .The focal interictal abnormalities in relation to PKD, in our patient contralateral to the symptomatic side, and the persistence of epileptic generalized seizures during adulthood might suggest cortical involvement in the dystonic posturing in our patients.

Over the past 15 years the etiologic discussion of PKD turned into a discussion about the pathogenesis [13]. In 1997 Szepetowski and colleagues defined the new syndrome ICCA in four French families with a dominant inheritance trait of benign infantile familial convulsions and variably expressed paroxysmal dyskinesia [3]. Different paroxysmal central nervous system disorders were linked to mutations in ion-channel-related genes, for example episodic ataxia type 1 and 2, different idiopathic epilepsies and familial hemiplegic migraine. With the recent identification of PRRT2 as the major PKD gene [7], it appears as if the paroxysmal attacks of PKD in the ICCA syndrome do not represent

a channelopathy as expected [14–16]. The function of PRRT2 is however not yet established and thus, an indirect effect on ion-channel functions is conceivable.

All affected individuals shared a single allele on chromosome 16 that was absent in non-affected individuals, however with the exception of individual II-1, a possible phenocopy, who reported seizures but did not share the same allele. The possibility that ICCA, PKD and BFIS2 are genetically homogeneous has been proposed after the identification of overlapping critical regions on chromosome 16 [3,5,8]. In this study, a single PRRT2 mutation was identified in affected members of a single family who exhibited infantile convulsions, ICCA and PKD, thus demonstrating the genetic homogeneity of these phenotypes unequivocally.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.parkreldis.2012.03.006.

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