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Tremor and Other Hyperkinetic Movements

Case Reports

Paroxysmal Kinesigenic Dyskinesia: First Molecularly Confirmed Case from Africa

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Abstract

Background: Paroxysmal kinesigenic dyskinesia (PKD) is a movement disorder, with an excellent response to carbamazepine treatment. It has been described in various populations, but not yet in an African population.

Case report: In a patient who reported to clinic with side effects of carbamazepine, *PRRT2* gene screening was performed based on a clinical history compatible with PKD. A common PRRT2 mutation was identified in this patient, hereby the first genetically confirmed PRRT2-associated PKD in Africa.

Discussion: Reporting genetic confirmation of an unusual movement disorder from an equally unusual location shows the wide geographical distribution of PRRT2-associated disease. It also illustrates recognizability of this treatable disorder where the easiest accessible diagnostic tool is neurological history and examination.

Keywords: Paroxysmal Kinesigenic Dyskinesia, Africa, *PRRT2*, carbamazepine

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Background

First reported in 1892 in Japan by Kure,[1,2] paroxysmal kinesigenic dyskinesia (PKD; OMIM # 128200) is a rare movement disorder, with a prevalence of about 1:150,000 individuals.[2] It has an autosomal dominant inheritance, and with its variable expression and incomplete penetrance, the above figure may underestimate the true prevalence.[2,3] The main clinical features are brief dyskinesias upon initiation of movement (Table 1).[2–4] There is a conspicuous response to carbamazepine and phenytoin, in dosages much lower than required for seizure disorders.[2–4]

The *PRRT2* gene is located on chromosome 16, was first identified in the Chinese population and codes for a member of a central nervous system transmembrane protein family.[5,6] *PRRT2* gene mutations have also been implicated in other paroxysmal movement disorders such as infantile convulsions, benign familial infantile epilepsy, and infantile convulsions with choreoathetosis syndrome.[2,3] PKD has been described all over the world including African-American patients,[7,8] but not in Africa itself. This first genetically confirmed PKD from Africa adds to the ubiquitous nature of the predominant *PRRT2* frameshift mutation,[3] which was also found in this patient. Knowledge of its salient clinical features (Table 1) lends itself to recognition regardless of a low-resource setting.

Case report

A 12-year-old male reported to Kilimanjaro Christian Medical Centre in Moshi, Northern Tanzania, with complaints of abdominal fullness

Table **1. Clinical Aides to Diagnose PKD**

Onset between 1 and 20 years unless there is a family history of PKD
Suddenly occurring and short-lived (less than a minute) dyskinesias
High frequency of up to hundred times a day
Triggered by movement or being startled
Combinations of dystonia, chorea, ballism, and athetosis are possible
Painless with preserved level of consciousness
Excellent response to low dosages of carbamazepine or phenytoin
Normal interictal neurological examination and no other organic cause

Adapted and summarized from Ebrahimi-Fakhari et al.[3]
Abbreviation: PKD, Paroxysmal Kinesigenic Dyskinesia.

after his daily medication intake. He was the second out of three children from nonconsanguineous parents. An elder teenage sister and baby brother had no symptoms at the time of this study. There was no medical history or family history of neurological disorders except for persistent mild stuttering in the father. The patient had been using low-dosage carbamazepine (100 mg twice daily) since 2 years before presenting to our hospital. Side effects were abdominal fullness, nausea, and occasional chest pain. At the age of 6 years, he received the diagnosis of a functional movement disorder, followed by the diagnosis of complex partial epilepsy, for which carbamazepine was prescribed. This caused symptoms to disappear.

The symptoms consisted of sudden, painless twisting movement of arms, trunk, face, tongue, and, to lesser extent, legs. It would occur almost every time he initiated movement, lasting 10–20 seconds. His tongue twisted within his mouth so that he could not talk or swallow, and his involuntary leg movements made him fall. Loss of consciousness never occurred. Symptoms completely resolved with carbamazepine use, but when his medication ran out all would recur within 2 days. A proton pump inhibitor had relieved the carbamazepine-related abdominal complaints so that carbamazepine benefits still outweighed the burden of side effects.

Physical examination revealed no dysmorphisms. Skin, muscle bulk, joints, and chest auscultation was normal. Neurological examination in the patient, father, and sister was also normal, with no features of myotonia or provocation by exercise or sudden movement. Magnetic resonance imaging of the brain, electrocardiogram, and blood and cerebrospinal fluid analysis (CSF) were unremarkable, with normal blood glucose of 6.0 mmol/L and CSF glucose of 3.6 mmol/L. Based on history, dramatic medication response, and the normal interictal physical examination (Table 1), the clinical diagnosis was PKD. The *PRRT2* gene was most likely to explain this clinical phenotype.[3]

Written informed consent in English and kiSwahili was obtained from the patient himself, and from the next-of-kin, his accompanying father. Venous blood was sampled and sent to the Genome Diagnostics Nijmegen of Radboud University Medical Center, Nijmegen, The Netherlands, for *PRRT2* mutation analysis. Genetic counseling before and after test results was done in the presence of patient and his father, in English and kiSwahili, and information was provided in written form.

DNA sequence analysis of the *PRRT2* gene revealed a heterozygous pathogenic frameshift mutation c.649dup (p.(Arg217fs)) (NM_145239.2), confirming the diagnosis of PKD. This frameshift mutation at a mutational hotspot gives rise to a premature stop codon. It has been reported to make up 78.5% of all PKD-associated *PRRT2* mutations.[2]

Discussion

A first genetic confirmation from a certain geographical region is not a scientific novelty, and the same *PRRT2* frameshift mutation was already described in an African-American family in the United States.[8] Furthermore, this patient's serendipitous treatment with carbamazepine is not exceptional because it is a locally available and affordable drug, used for various epilepsy and mental health symptoms and signs. The diagnostic delay in this case did not lead to treatment delay. However, neurology and genetics facilities are still unavailable in most of Africa,[9,10] and this observation stresses the value of movement disorders education in low-resource areas.

There is variation in genetic and phenotypic expression. *PRRT2* is implicated in PKD and other paroxysmal movement disorders, seizure disorders, and intellectual impairment,[2,3] and other genes are involved in non-*PRRT2* PKD. As penetrance is incomplete[2,3] and parents have declined further testing, it is not known whether the *PRRT2* mutation in our patient is *de novo*. The patient's father had a mild, yet persistent stutter. It remains speculative whether this could be a mild phenotype with kinesigenic dysfunction of the oropharyngeal musculature alone. Screening for *PRRT2* mutation in a cohort of stammer patients has not been performed, although other genetic associations with stammering are there.[11]

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Authors' contribution

M. Dekker and R. Chengo performed clinical investigations and diagnostic work-up. M. Dekker, R. Chengo, H. Kumburu, and B. Hamel conceived the study and drafted the manuscript. H. Kumburu was responsible for storage of the blood and cerebrospinal fluid samples, and E.-J. Kamsteeg and B. Hamel were responsible for genetic analysis.

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