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Child Neurology: *PRRT2*-associated movement disorders and differential diagnoses

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Paroxysmal kinesigenic dyskinesia (PKD) (MIM 128200) is a rare paroxysmal movement disorder that occurs at an estimated prevalence of 1:150,000 individuals.[1] Onset is most commonly in childhood or adolescence, with sporadic and familial cases being reported.[2,3] PKD is characterized by short and frequent episodes of dystonic or choreiform movements that are precipitated by sudden voluntary movements or startle. Classic clinical criteria for PKD therefore include an identifiable kinesigenic trigger, short duration of attacks, no loss of consciousness or pain during attacks, normal interictal neurologic examination results, the exclusion of other organic diseases, onset between 1 and 20 years of age (if no family history), and a response to treatment with anticonvulsants (sodium channel blockers).[3] Genetically, most cases of PKD are caused by autosomal-dominant mutations in the *PRRT2* (proline-rich transmembrane protein 2; DYT10) gene,[4,5] making PKD part of an evolving spectrum of *PRRT2*-associated diseases that includes benign familial infantile seizures, infantile convulsions with choreoathetosis, episodic ataxia, hemiplegic migraine, and benign paroxysmal torticollis of infancy[6] (table 1 and table e-1 on the *Neurology*® Web site at Neurology.org). We briefly review the clinical presentation and genetics of movement disorders associated with *PRRT2* mutations and report an illustrative case that highlights typical and atypical features as well as important differential diagnoses in a family with *PRRT2*-associated PKD.

Clinical history. A 15-year-old, left-handed girl presented with a 3-day history of recurrent episodes of abnormal movements. She interpreted these episodes as sudden attacks of weakness. Her legs and trunk seemed predominantly affected, whereas her arms and face were relatively spared. She retained awareness during attacks and described an aura of nonspecific discomfort precipitating her abnormal movements.

Medical history was significant for recurrent episodes of migraine with aura. The patient was born at full term after an uneventful pregnancy, reached all developmental milestones appropriately, and is currently a high school student with good grades.

On neurologic examination, the movement disorder was found to fluctuate with voluntary motor activity but was not entirely paroxysmal in nature (video 1). At rest, tone in both legs seemed to be intermittently increased, a finding that was not clearly distinguishable from intermittent voluntary movements. When attempting to walk, increased tone was observed in her limbs and trunk, without overt torsion or dystonic posturing of fingers. The patient showed a slow, unsteady, narrow-based staggering gait with a tendency to fall, and felt unable to walk without support. Her trunk showed shaking movements, possibly consistent with intermittent dyskinesias or hyperkinetic or jerky dystonia. With ongoing motor activity in tasks such as walking or climbing stairs, abnormal movements of her legs and trunk increased to an extent that prevented her from moving forward. The remainder of the neurologic examination revealed mild cerebellar-like tremor on finger-to-nose testing only. Notably, no deficit in strength was appreciable.

Laboratory studies, CSF analysis (including levels of biogenic amines, 5-10-methylenetetrahydrofolate, and pterins), and MRI scans of the patient's brain and spine revealed no abnormalities.

Family history. The patient's mother had paroxysmal dyskinesias since childhood with a frequency from multiple per day to 1 every few months. Attacks were stereotypical, with the trigger always being a sudden movement, although tiredness, anxiety, and stress would increase the likelihood. After a sudden movement, she experienced brief unilateral dystonic posturing of her arm and leg, most commonly of her right side. She was diagnosed with epilepsy and treated with phenytoin and carbamazepine, which led to a reduction in the frequency of attacks. The diagnosis of PKD, however, was only made when her son presented with similar symptoms. By then, she had few attacks despite having discontinued anticonvulsants for years. Interestingly, she reports frequent migraines with aura. The patient's brother became symptomatic at age 12 years,

Supplemental data at Neurology.org

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Table 1 *PRRT2*-associated movement disorders

Type	Predominant age at onset	Cardinal clinical features
Paroxysmal kinesigenic dyskinesia	Childhood/adolescence	Paroxysmal attacks of dystonic, choreiform, or ballistic movements of short duration (<1 min)
		Precipitated by a kinesigenic trigger, e.g., sudden voluntary movements, with emotional stress or anxiety often lowering the threshold
		Frequent attacks (up to hundreds per day), sometimes improvement with age
		A premonitory sensation or aura is frequently reported
		No loss of consciousness
		Normal interictal neurologic examination and exclusion of other causes
		Responsive to low doses of anticonvulsants (sodium channel blockers)
Paroxysmal kinesigenic dyskinesia with infantile convulsions	Infancy/childhood/ adolescence	Benign infantile convulsions that usually start after age 3 months and subside before age 3 years
		Paroxysmal attacks of dystonic movements triggered by sudden voluntary movements, anxiety, or exercise, usually present in late childhood or adolescence
Familial hemiplegic migraine	Infancy/childhood/ adolescence	Rare variant of migraine with aura that involves paroxysmal attacks of hemiparesis
		Often headaches with gradually progressing visual, sensory, motor, or basilar-type symptoms at onset
		Rarely severe variants with recurrent blindness or coma or even prolonged hemiparesis, cerebellar ataxia, epilepsy, and mental retardation
Benign paroxysmal torticollis	Infancy	Paroxysmal head rotation or tilting, usually alternating from side to side
		Often associated with irritability, agitation, vomiting, pallor, abnormal truncal posture and gait
		Episodes of variable duration (minutes to days)
		Remission usually by age 2 years
Episodic ataxia	Infancy/childhood/ adolescence	Brief intermittent episodes of ataxia of variable duration
		Often triggered by sudden movements, startle, physical or emotional stress
Other paroxysmal dyskinesias		
Paroxysmal nonkinesigenic dyskinesia	Infancy/childhood	Paroxysmal attacks of dystonic or choreiform movements of long duration (usually minutes to several hours)
		Few attacks per day, sometimes improvement with age
		Occur at rest or are precipitated by caffeine and alcohol consumption
		Normal neurologic examination between attacks and exclusion of other causes
		Positive family history
Paroxysmal exercise-induced dyskinesia	Childhood/adolescence	Paroxysmal attacks of mostly dystonic movements triggered by prolonged exercise (usually minutes to hours)
		No response to anticonvulsants in most cases
		Responsive to ketogenic diet in GLUT-1 deficiency syndrome

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when he presented with paroxysmal repetitive, unilateral dystonic posturing of his right arm and leg that occurred exclusively after attempting to quickly rise to stand or walk. His dystonia was mostly limited to his right hemibody and was sometimes accompanied by twisting movements of his head and neck to his right. His interictal neurologic examination revealed no deficits and MRI including time-of-flight angiography scans was unremarkable. Attacks completely subsided with low-dosage oxcarbazepine and only returned

temporarily when his weight-adapted dosage fell below 6 mg/kg/day (300 mg/day).

Genetic analysis. PCR-based Sanger sequencing was used to analyze coding exons and flanking introns of the *PRRT2* gene. The patient, her brother, and her mother were found to carry a heterozygous c.649dupC, p.Arg217Profs*8 mutation in exon 2.

Clinical course and differential diagnoses. In view of the family history of classic PKD and the autosomal dominant inheritance of this disease, an atypical presentation of PKD was initially considered. A trial of low-dosage oxcarbazepine (8 mg/kg/day) was given with complete resolution of symptoms within days (video 2). Genetic testing revealed a pathogenic *PRRT2* mutation in all 3 affected family members. In order to further evaluate the possibility of an atypical presentation within the growing spectrum of paroxysmal disorders associated with *PRRT2* mutations vs a functional disorder (and to be able to provide proper treatment for the latter), we suggested a trial of discontinuation of therapy after 16 months of remission on oxcarbazepine. This was discussed with the family. Oxcarbazepine was discontinued and episodes did not return after a 10-month follow-up, supporting a functional movement disorder as the most likely diagnosis, although a spontaneous remission of PKD[3] cannot be ruled out definitively.

DISCUSSION This case illustrates the diagnostic challenge when faced with distinguishing an atypical phenotype within the spectrum of *PRRT2*-associated movement disorders from an unrelated differential diagnosis in a family with genetically confirmed *PRRT2*-associated PKD. Our report highlights the need to carefully evaluate differential diagnoses including functional movement disorders. This is particularly important and challenging given the remarkable interfamilial and intrafamilial pleiotropy seen in patients with *PRRT2*-associated movement disorders and considerable clinical overlap between subtypes of paroxysmal dyskinesias[7] (table 1 and table e-1). Key clinical characteristics of PKD are recurrent unilateral or bilateral episodes of dystonia, choreiform movements, or ballism that are triggered by sudden voluntary movements such as initiation of walking, standing up, or being startled (table 1). Episodes are usually brief, stereotypical, and do not involve loss of consciousness. They vary in frequency and a precipitating aura is frequently reported, sometimes allowing the patient to partially control arising episodes.[2,3] The disease is paroxysmal with the interictal examination being unremarkable. Often, a dramatic improvement is seen with anticonvulsant treatment (sodium channel blockers) (particularly in *PRRT2* mutation carriers[8]), making this a possible way to confirm the diagnosis.[3] The overall prognosis of PKD is good as the frequency of attacks tends to decline with age and spontaneous remission occurs in a subset of patients.[3]

Important differential diagnoses for primary PKD include secondary causes such as demyelinating disease, stroke, trauma, encephalitis, hypoparathyroidism, or pseudohypoparathyroidism with basal ganglia calcification, and rarely perinatal hypoxic encephalopathy or moyamoya disease. PKD must be distinguished from diseases that might mimic its phenotype, most importantly exercise-induced dystonia (particularly GLUT1 deficiency syndrome), seizures, pseudoseizures, tics, and functional movement disorders.

Although sporadic cases are reported, primary PKD is mainly a familial disease with autosomal dominant inheritance and incomplete penetrance (~60%–90%).[9] Whereas our patient's mother and brother show the classic clinical picture of PKD, several findings in our patient are considered atypical and might point to other etiologies. Importantly, abnormal movements were not clearly paroxysmal, had no kinesigenic trigger, and were of unusual long duration. She showed a mixture of different movement disorders that did not appear to follow established patterns and fluctuated considerably. Features suggestive of a functional etiology[10] (summarized in table e-2) included a rapid onset and increment of symptom intensity and an unusually high degree of impairment, contrasting her low level of emotional involvement. Similar to the well-known coexistence of both epileptic seizures and psychogenic nonepileptic seizures within the same family or even the same patient, prior exposure to family members with a genetically determined movement disorder is a risk factor for a functional etiology in this case. On the other hand, her abnormal movements, albeit fluctuating within individual episodes, could not be subjected to distraction or exhaustion. Common features of functional movement disorders such as associated symptoms (pain, sensory deficits, or weakness), an underlying psychosocial trigger or secondary gain, a history of somatization in the past, or psychiatric illness were not discernible.

Interestingly, migraines are commonly reported in *PRRT2* mutation carriers (table e-1) and hence migraines with aura in this family could be part of a *PRRT2*-associated phenotype. The low frequency of migraine episodes, however, did not allow us to assess a potential response to oxcarbazepine.

In conclusion, the identification of *PRRT2* as a major genetic cause for a spectrum of paroxysmal neurologic diseases has allowed better disease classification and enables genetic confirmation of a clinical diagnosis in many cases (table 1 and table e-1). However, as our report highlights, the presence of a

mutation or family history does not exclude other causes such as a functional movement disorder. The diagnostic challenge is even greater, as it is almost certain that the spectrum of *PRRT2*-associated movement disorders is broader than we currently recognize. Our report emphasizes the need to combine a thorough clinical evaluation with the growing understanding of genetics behind complex monogenic movement disorders.

AUTHOR CONTRIBUTIONS

All authors were involved in the care of the patients reported in this manuscript. Dr. Ebrahimi-Fakhari: acquisition and interpretation of clinical and genetic data, drafting the manuscript, video editing, screening and reviewing the relevant literature, revising the manuscript critically. Dr. Kang: reviewing the literature, revising the manuscript. Dr. Kotzaeridou: reviewing the literature, revising the manuscript. Dr. Kohlhase: genetic testing, analysis, data interpretation. Dr. Klein: interpretation of genetic and clinical data, revising the manuscript. Dr. Assmann: attending physician of record for this patient, continues to see the family in her movement disorders clinic, acquisition and interpretation of clinical and genetic data, drafting the manuscript, revising the manuscript critically. All authors have read and approved the final manuscript being submitted.

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DISCLOSURE

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INFLUENZA VACCINATION AND CARDIOVASCULAR RISK IN PATIENTS WITH RECENT TIA AND STROKE

Bayzidur Rahman, Anita Heywood, Aye Moa, C. Raina MacIntyre, Sydney, Australia: Lavallée et al.[1] found no effect of influenza vaccination on risk of cardiovascular disease in recent TIA or stroke patients. Vaccination status was determined by baseline self-report, which has poor validity and is subject to recall bias.[2] This can result in misclassification of vaccination status and bias of the reported effect.

Vaccination timing was not presented in the 3 component studies. Survival analysis was conducted on a baseline vaccination status for any cardiovascular event occurring during the 2-year follow-up. Without annual vaccination data, it is unknown whether participants were protected by vaccination at the time of subsequent cardiovascular events.

The pooling of data from 3 separate studies for the main analyses is not ideal. The analyses should appropriately consider between-study variation (e.g., individual patient data meta-analysis).[3] Two of the component studies (OPTIC and PERFORM) were multicentered (clustered), which also warrants consideration. This study failed to show an unbiased effect of vaccination on cardiovascular events, which conflicts with data showing such an effect.[4,5]

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CORRECTIONS

MRI measurement of brain iron in patients with restless legs syndrome

In the article "MRI measurement of brain iron in patients with restless legs syndrome" by R.P. Allen et al. (*Neurology*® 2001;56:263–265), there is an error in the author byline. The third author's name should read "F.W. Wehrli, PhD."

Child Neurology: *PRRT2*-associated movement disorders and differential diagnoses

In the article "Child Neurology: *PRRT2*-associated movement disorders and differential diagnoses" by D. Ebrahimi-Fakhari et al. (*Neurology*® 2014;83:1680–1683), there is an error in the footnote under table 1. Table 1 is not reproduced from Gupta and Lang but was created by the authors. Supplemental table e-2 was modified from Gupta and Lang (Gupta A, Lang AE. Psychogenic movement disorders. Curr Opin Neurol 2009;22:430–436), with permission. The authors regret the error.

CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS

In the article "CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS" by V. Limmroth et al. (*Neurology*® 2014;83:1780–1788), there is an error in the Acknowledgment section: "Prof. Krzysztof" should read "Prof. Selmaj" and "Dr. Strangel" should read "Dr. Stangel." In addition, the first sentence in the Methods under "Safety data" should read: "Safety was evaluated by an independent data safety monitoring board on the basis of adverse events, laboratory data, vital signs, MRI assessment for PML, physical examination, 12-lead ECG, and local tolerance." The authors regret the errors.

Author disclosures are available upon request (journal@neurology.org).