JICNA® | Journal of the International Child Neurology Association
A peer reviewed open access e-journal in Child Neurology

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ORIGINAL RESEARCH

PRRT2 related Paroxysmal Kinesigenic Dyskinesia (PKD): The Therapeutic Challenges

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https://doi.org/10.17724/jicna.202.259

Received: 7 November 2022
Accepted: 7 March 2024

Abstract

Paroxysmal dyskinesia (PxD) is a group of disorders that is rare. In this group of primary PxD, paroxysmal kinesigenic dyskinesia (PKD) is the most common subtype. This disorder is characterized by classical features of multiple episodes of brief dyskinesia precipitated by a "kinesigenic trigger." We present a case of a 10-year-old boy with genetically proven PRRT2-related PKD. This child had self-limited infantile epilepsy and PxD undiagnosed for the last 5 years. The child showed a dramatic response to carbamazepine. However, the drug was discontinued due to extensive cutaneous rash. The child was given a trial of valproate but with no response. Later, the child responded to topiramate and remained symptom-free for a follow-up of 3 months thereafter.

Keywords: Paroxysmal kinesigenic dyskinesia (PKD), proline-rich transmembrane protein 2 (PRRT2), carbamazepine, oxcarbazepine, topiramate, valproate, levetiracetam.

Background

Paroxysmal kinesigenic dyskinesia (PKD) is a most common subtype of the primary paroxysmal dyskinesia (PxD), which is a rare disorder. Proline-rich transmembrane protein 2 (PRRT2) is the most frequently implicated gene in patients with PKD. PKD is characterized by brief episodic dystonia or choreoathetosis, usually either triggered by a voluntary movement described as a kinesigenic trigger or precipitated by an emotional outburst or sudden startle [1]. PKD can be misdiagnosed as seizures, benign myoclonus, tics, or functional movement disorders. It is important to consider secondary causes like metabolic disorders and cerebrovascular pathologies as well. When PKD is suspected, genetic testing for PRRT2 gene mutation and/or therapeutic trials of sodium channel blockers are recommended. However, if the patient does not tolerate the first-line pharmacotherapeutic medications there is no standard guideline available for the choice of therapeutic options. Here, we present a case of a child with PRRT2 gene mutation presenting as PKD who developed extensive rashes when started on carbamazepine. We also present a review of currently available data regarding the effectiveness of other medicines when sodium channel blockers are contraindicated.

Case Report

A 10-year-old boy presented with paroxysmal movements for the past 5 years. His mother described these episodes as abnormal twisting of arms and legs lasting for 5–10 s. Initially, it was noticed that the child could not walk immediately after getting up from a chair. These symptoms were at first thought to be insignificant. However, as the child grew older, the symptoms worsened to the extent that they limited his independent ambulation. On most occasions, sudden changes in posture and getting down from the school bus or bikes precipitated these events. There were a few episodes that occurred at rest. The child described tingling of both arms preceding the twisting of limbs. For the past 2 years, with the progressive involvement of the legs, the child had few episodes of fall. Hence, his parents never left him alone. The child had 20–25 episodes per day.

The child was born to a non-consanguineous couple. There were no concerns regarding his development. He was a student in class IV with an average scholastic performance. He was a shy boy with a few friends. He had two episodes of febrile seizures between 18 and 24 months. His father had an unprovoked seizure at 3 years of age and has been asymptomatic since then. No other family members had similar complaints.

During the examination, the child was alert, oriented and cooperative child. His head circumference was measured at 51 cm, and he did not display any focal deficits or abnormal limb or ocular movements. It was noted that activities such as walking, running, or getting up from a chair did not precipitate the events in the clinic. Based on these observations, the syndromic diagnosis was paroxysmal dystonia in a child with a history of febrile seizures. The etiological differentials considered were genetic causes of PxD due to mutations in various genes like PRRT2, SLC2A1, and PNKD, as well as metabolic disorders and cerebrovascular disorders. The child's intelligence quotient

was determined to be 97 on Malin's Intelligence Scale for Indian Children. Both plain and contrast MRI brain scans, as well as electroencephalography studies, were normal. Laboratory investigations showed normal random blood glucose (88 g/dL), arterial lactate (0.9 mmol/L), and fasting ammonia (47 μmol/L) levels. Considering PKD as the most likely differential diagnosis, carbamazepine was started for the child at 2.5 mg/kg/day and a sample for clinical exome sequencing (CES) was sent. The child became asymptomatic in 10 days. After 4 weeks, he came for follow-up. A heterozygous single base pair duplication in exon 2 of the *PRRT2* gene (c649dup) was detected on CES leading to frameshift and premature truncation of the protein 8 amino acids downstream to codon 217 (p. Arg217ProfsTer8; ENST00000567659.3). Thus, the clinical possibility of PKD was confirmed genetically with a complete response to carbamazepine. Segregation analysis could not be done due to financial constraints.

A week later, the boy attended the pediatric emergency unit with extensive, itchy, and slightly painful erythematous cutaneous papular rash and a temperature of 100°F. He had no cough, coryza, or history of any other drug intake. He was given oral paracetamol and intravenous pheniramine maleate (Avil) observed for 4 h. Carbamazepine was discontinued because of his rash, afterwhich his lesions reduced significantly. The boy was negative for HLA-B*15:02. The child remained symptom-free for a month before experiencing a recurrence of PxDs, which progressively worsened and became more frequent. This time, sodium valproate was started at 5 mg/kg/day and increased to 30 mg/kg/day over a period of 3 weeks, but the episodes showed no improvement. Topiramate was started at 1 mg/kg/day and increased to 3 mg/kg/day. Bouts of paroxysmal dystonia ceased at this dosage of topiramate. Hence, it was continued, while sodium valproate use was discontinued. At his last follow-up, the child was symptom-free for 3 months and was attending school regularly.

Points highlighted in this case

1. One should be careful when initiating carbamazepine even when the patient is negative for the HLA-B*15:02 genotype. The risk of rash should be explained to the family.
2. Topiramate was effective at a low dose, while valproate was ineffective even when administered in the usual anti-seizure dosage range.

Discussion

Paroxysmal dyskinesia is a rare group of disorders. Under this category, PKD is the most common subtype, with a frequency of 1: 150,000 [2]. The PRRT2 gene is most commonly implicated in the causation of PKD. Mutations in the PRRT2 gene mutation can lead to a spectrum of disorders with different signs and symptoms affecting patients across different age groups. These disorders may include benign familial epilepsy, PKD or a combination of both. Other syndromes linked with PRRT2 gene mutation, though less common, include absence epilepsy, frontal lobe epilepsy, hemiplegic migraine, and episodic ataxia [1].

A characteristic finding in all patients with PRRT2 mutation is a dramatic response to anti-seizure medications (ASMs). Initially, PKD was considered a channelopathy before the causal gene was identified. However, with the increased insight into the pathophysiology of the PRRT2 spectrum of disorders, it is now categorized as a "synaptopathy" rather than the previously considered category of "channelopathy" [3]. PRRT2 is localized in the presynaptic membrane and directly interacts with various synaptic proteins like Synaptosomal-Associated Protein (SNAP25) and Vesicle Associated Membrane Protein 2 and the synaptotagmins Syt1 and 2, regulating the voltage-gated ion channels by altering the calcium (Ca^{2+})-sensing mechanism [4, 5].

Diagnosis of PRRT2-related PKD may be delayed due to similar conditions such as tics, seizures, and functional movement disorders, among others. PRRT2-related PKD is generally considered a benign disorder with resolution expected by adulthood. Therefore, the decision to initiate pharmacotherapy is guided by the frequency and severity of the episodes and is usually reserved for cases where the disease significantly limits daily activities. Sodium channel blockers are the drugs of choice, with carbamazepine and oxcarbazepine being the preferred medications. A complete or partial response is achieved in 97% of the patients once they are initiated on carbamazepine or oxcarbazepine. Carbamazepine is initiated at 1 mg/kg/day and titrated to achieve optimal response. The usual dose is as low as 1.5–2.5 mg/kg/day but higher doses can be used [6, 7]. The dose of oxcarbazepine needed to achieve a similar response may be higher than carbamazepine. The dose is higher in those with self-limited infantile epilepsy than the ones with PKD in isolation. It usually ranges between 8 and 12 mg/kg/day [8, 9]. Newer studies suggest that oxcarbazepine is equally effective as carbamazepine in patients with PKD. Considering a better side effect profile, oxcarbazepine is the drug of choice [10]. To further reduce the side effects, it is recommended to administer the medication once daily at bedtime. If a patient develops skin rashes, the medication should be stopped immediately as it can progress into life-threatening Steven Johnson syndrome, especially in those with the HLA-B*15:02 genotype. It is advisable to avoid both oxcarbazepine and phenytoin in those who develop skin rash secondary to carbamazepine. In such cases, other sodium channel blockers like topiramate, lamotrigine, and other ASMs like valproate can be considered.

The role of topiramate as a monotherapy in patients with PKD has been explored [11, 12]. The dose is started at a minimal dose of 12.5 mg/day and titrated weekly to achieve a response, which is usually noted at a mean dose of 3 mg/kg/day. Sodium channel blockade is one of the many mechanisms by which topiramate exerts its action. Weight loss is a common side effect encountered in those receiving topiramate. The efficacy of lamotrigine is documented in a few case reports, especially in young women and those with coexisting epilepsy [13, 14].

Other medications like valproate and levetiracetam have been tried with variable effects. Levetiracetam has been found to be least efficacious, with valproate having a relatively better profile in patients with PKD [15–17]. With advancing age, the need for pharmacological therapy reduces in patients with PKD.

Challenges faced by clinicians in managing patients with PRRT2 gene-related PKD

1. Diagnostic dilemma—Detailed history is important to differentiate PKD from other entities that resemble it.
2. Management—PKD responds dramatically to sodium channel blockers, especially carbamazepine/oxcarbazepine. Choice of medications should be done carefully in those who do not tolerate carbamazepine, as other available options are a lot less efficacious than carbamazepine.

Conclusions

Recognition of PKD requires a high index of suspicion on the part of the clinician. The entity is a benign one but may become disabling in a few requiring pharmacological intervention. Oxcarbazepine is equally efficacious as carbamazepine and is currently the drug of choice. Phenytoin is a reasonable alternative. However, the options are limited for those who do not tolerate the first-line medications. In this group of patients, topiramate is the most effective medicine. Other ASMs may be tried, but levetiracetam appears to be least effective.

Acknowledgments

We acknowledge the family for their kind understanding and for giving the consent to share this case to contribute to the currently existing data pool.

Competing interests

Not applicable.

Authors' contributions

All authors contributed to the case management, manuscript preparation and review.

Cite this article as: Sonali Singh and Rahul Sinha (2025). PRRT2 related Paroxysmal Kinesigenic Dyskinesia (PKD): The Therapeutic Challenges. Journal of the International Child Neurology Association, 1(1).

References

[1] LandolfiA, Barone P, Erro R. The spectrum of PRRT2-associated disorders: Update on clinical features and

[2] MéneretA, Gaudebout C, Riant F, Vidailhet M, Depienne C, Roze E. PRRT2 mutations and paroxysmal disorders. Eur J Neurol. 2013;20(6):872–8.

[3] ErroR, Bhatia KP, Espay AJ, Striano P. The epileptic and nonepileptic spectrum of paroxysmal dyskinesias: Channelopathies, synaptopathies, and transportopathies. Mov Disord. 2017;32(3):310–8.

[4] Ebrahimi-FakhariD, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain. 201;138(12):3476–95.

[5] ValenteP, Castroflorio E, Rossi P, Fadda M, Sterlini B, Cervigni RI, et al. PRRT2 Is a key component of the Ca2+-dependent neurotransmitter release machinery. Cell Rep. 2016;15(1):117–31.

[6] ChouIC, Lin SS, Lin WD, Wang CH, Chang YT, Tsai FJ, et al. Successful control with carbamazepine of family with paroxysmal kinesigenic dyskinesia of PRRT2 mutation. BioMedicine. 2014;4:15.

[7] CaoL, Huang X, Wang N, Wu Z, Zhang C, Gu W, et al. Recommendations for the diagnosis and treatment of paroxysmal kinesigenic dyskinesia: an expert consensus in China. Transl Neurodegener. 2021;10:7.

[8] ZhaoQ, Liu Z, Hu Y, Fang S, Zheng F, Li X, et al. Different experiences of two PRRT2-associated self-limited familial infantile epilepsy. Acta Neurol Belg. 2020;120(4): 1025–8.

[9] ZhaoQ, Hu Y, Liu Z, Fang S, Zheng F, Wang X, et al. PRRT2 variants and effectiveness of various antiepileptic drugs in self-limited familial infantile epilepsy. Seizure. 2021;91:360–8.

[10] YangY, Su Y, Guo Y, Ding Y, Xu S, Jiang Y, et al. Oxcarbazepine versus carbamazepine in the treatment of paroxysmal kinesigenic dyskinesia. Int J Neurosci. 2012;122(12):719–22.

[11] HuangYG, Chen YC, Du F, Li R, Xu GL, Jiang W, et al. Topiramate therapy for paroxysmal kinesigenic choreoathetosis. Mov Disord. 2005;20(1):75–7.

[12] PengG, Wang K, Yuan Y, Zheng X, Luo B. Clinical analysis of nine cases of paroxysmal exercise-induced dystonia. J Huazhong Univ Sci Technol Med Sci. 2012;32(6): 937–40.

[13] SpaceyS, Adams P. Familial paroxysmal kinesigenic dyskinesia – retired chapter, for historical reference only. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, et al., editors. GeneReviews§[Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2022 Nov 8]. Available from: **PubMed**

[14] Motoyama R, Matsudaira T, Terada K, Usui N, Yoshiura KI, Takahashi Y. PRRT2 mutation in a Japanese woman: Adult-onset focal epilepsy coexisting with movement disorders and cerebellar atrophy. Epilepsy Behav Rep. 2022;19:100554.

[15] Zhao Q, Hu Y, Liu Z, Fang S, Zheng F, Wang X, et al. PRRT2 variants and effectiveness of various antiepileptic drugs in self-limited familial infantile epilepsy. Seizure. 2021 t;91:360–8.

[16] Döring JH, Saffari A, Bast T, Brockmann K, Ehrhardt L, Fazeli W, et al. Efficacy, tolerability, and retention of antiseizure medications in PRRT2-associated infantile epilepsy. Neurol Genet. 2022;8(5):e200020.

[17] Fen P, Shangda L, Haimei L, Yi X, Manli H. Misdiagnosed atypical paroxysmal kinesigenic dyskinesia: A case report. Neuropsychiatr Dis Treat [Internet]. 2018 Jun 5 [cited 2022 Nov 8];14. Available from: **PubMed**