A Novel Neuroimaging Phenotype in the Pediatric Paroxysmal Kinesigenic Dyskinesia

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Abstract

Paroxysmal kinesigenic dyskinesia (PKD) is a rare disorder characterized by recurrent attacks of hyperkinetic movements which can be isolated or associated with benign infantile seizures as part of the infantile convulsions with choreoathetosis syndrome. We present a case of hyperkinetic movement disorder in the form of choreoathetosis, ballismus, dystonia triggered by sudden movements with a past history of benign infantile convulsions in a 12-year-old girl. The contrast-enhanced brain and spine magnetic resonance imaging showed bilaterally symmetric superior cerebellar cytotoxic edema sparing the vermis with swollen cerebellar foliae. Whole-exome sequencing identified a homozygous frameshift duplication NM_145239.3(PRRT2):c.649dupC (p.Arg217Profs*8) in the *PRRT2* gene. This case report highlights the frameshift duplication in the *PRRT2* gene and rare neuroimaging findings which further expand the phenotypic characteristics of PKD in children.

Keywords
► PRRT2
► hyperkinetic
► dyskinesia
► paroxysmal
► choreoathetosis

Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is a rare paroxysmal hyperkinetic movement disorder with a prevalence of 1 in 50,000 individuals. PKD is characterized by sudden attacks of involuntary movements, such as dystonia, choreoathetosis, and ballism, without alteration in consciousness.[1] PKD has been associated with pathogenic mutations in the gene encoding proline-rich transmembrane protein-2 (*PRRT2*), located on chromosome 16 (16p12.1-q12.1), although the precise role of PRRT2 in PKD remains unclear.[2] PKD can occur independently of or concurrently with benign infantile convulsions (BIC), a condition characterized by nonfebrile convulsions with onset between 3 and 12 months of age and favorable outcomes, including normal development.[3] PRRT2 mutations have also been identified in other paroxysmal disorders, such as paroxysmal nonkinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, hemiplegic migraine, and episodic ataxia.[4] Diagnosis of PKD is based on clinical features and genetic testing. Most often this rare condition is misdiagnosed as epilepsy or psychogenic illness.[5,6] Neuroimaging is generally normal; however, functional magnetic resonance imaging reveals abnormalities in the cerebello-thalamo-striato-cortical circuit.[7] We present a case of 12-year-old girl with hyperkinetic movement disorder in the form of choreo-athetosis, ballism, dystonia triggered by sudden movements with a history of BIC and rare neuroimaging findings.

A 12-year-old girl with normal development, born to a nonconsanguineous marriage presented with abnormal involuntary paroxysmal movements involving her neck and four extremities in the form of twisting, flinging, writhing,

and fidgeting movements triggered by sudden voluntary movements. These paroxysms occurred intermittently, especially when trying to do activity after prolonged rest or inactivity, for the past 6 years. She was born at term via normal vaginal delivery with a birth weight of 2.8 kg without any adverse perinatal events. She developed multiple episodes of seizures at 3 months of age with semiology being tonic–clonic movements of the upper limb with an upward deviation of eyes with each episode lasting for 1 to 2 minutes. She was started on antiseizure medications (ASM). The neuroimaging and electroencephalography (EEG) studies were normal. The 1-hour sleep EEG was done on Nicolet one (Model no Nicolet one V32 amplifier, Natus Neurology, United States) with 16 channel EEG recording, using 10 to 20 international system of electrode placement with bipolar and referential montages. The seizures were well controlled until 3 years of age and ASM was tapered off. She remained asymptomatic till 6 years of age and had a good scholastic performance. At the age of 6 years she developed hyperkinetic movement disorder involving all four limbs and neck in the form of dystonia, choreoathetosis, and ballism which were triggered by sudden voluntary movements, stress, intercurrent illness lasting for 1 to 2 minutes with the frequency of approximately four to five episodes per week. Her clinical course had been static, and these events did not interfere with activities of daily living. Her neuroimaging and EEG studies were normal. She was started on multiple ASMs (valproate at 30 mg/kg/d, clobazam at 0.75 mg/kg/d, levetiracetam at 30 mg/kg/d) with poor response. At 12 years of age, she was brought to our center with these movements and unsteadiness of gait and cerebellar signs for the last 2 weeks. There was no history of similar illness in the last three generations of the family tree. Physical examination revealed normal weight and height with age-appropriate head circumference (51 cm) and scholastic performance. The neurological examination revealed normal higher mental function with dysarthria and mild hypotonia of lower limbs and normal power and elicitable deep tendon reflexes with down going bilateral plantar. The cerebellar signs were present in the form of intentional tremors, nystagmus, dysdiadochokinesia, ataxia, and scanning speech. Sensations were intact with normal and bladder and bowel function. The clinical possibility of metabolic disorder in the form of maple syrup urine disease, partial urea cycle defects, organic acidemias, and mitochondrial cytopathy was considered. The other possibilities discussed were PKD, glucose transporter 1 deficiency, and possible autoimmune disorder. Tandem mass spectrometry /urine gas chromatography-mass spectrometry /ammonia and biotinidase were normal. The arterial blood gas analysis did not reveal any metabolic acidosis or increased lactate. The eye and hearing assessment was normal. EEG obtained during sleep was normal. The cardiac assessment with creatinine phospho-kinase and echocardiogram was normal. The autoimmune markers in the cerebrospinal fluid (CSF) and serum were negative with normal CSF lactate and glucose. The serum vitamin B12, folic acid, and vitamin D levels were normal. Contrast-enhanced brain and spine magnetic resonance imaging (MRI) showed bilaterally symmetric superior cerebellar edema sparing the vermis with swollen cerebellar foliae (►Fig. 1). Vascular imaging with CT and time-of-flight MR-angiograms ruled out any steno-occlusive lesions, vasculitis, and venous thrombosis. Both the lepto and pachymeninges showed no abnormal enhancement in the vicinity. The MR spectroscopy around dentate and basal ganglionic levels also showed no abnormality. Whole-exome sequencing identified a homozygous pathogenic frameshift duplication NM_145239.3(PRRT2): c.649dupC(p.Arg217Profs*8) in the PRRT2 gene. The parental testing for the same variant could not be done due to the cost associated with the testing. The child was started on injection mannitol along with low-dose carbamazepine and clonazepam and showed improvement after approximately 96 hours. She was stable thereafter till her discharge and continued to be on oral carbamazepine at 10 mg/kg/d, clonazepam at 0.02 mg/kg/d, physiotherapy, occupational therapy, and speech therapy. She remained free from fresh neurological complaints with good compliance to oral therapy. Her MRI at the time of discharge showed receding cerebellar edema with no new lesions (►Fig. 2). Early review at 4 weeks at our center revealed no new clinical abnormalities with complete resolution of cerebellar edema when compared with the prior neuroimaging (►Fig. 3). The attendants were counseled for compliance and regular clinical evaluation for further management.

PKD is an autosomal dominant neurologic condition characterized by recurrent and brief attacks of involuntary movements triggered by sudden voluntary movements. These episodes have onset during childhood and early adulthood and usually present with dystonia, chorea, athetosis, ballism, or a combination of these symptoms.[8] The prognosis of PKD is favorable and patients usually show excellent response to treatment.[9] PKD can be classified as primary or secondary depending on the causes as secondary PKDs are mostly related to multiple sclerosis, head injury, metabolic derangements, or cerebral perfusion insufficiency. Primary PKD can be classified as idiopathic or familial. Familial PKD is more common, with the condition usually inherited in an autosomal dominant manner. The exact function of the PRRT2 protein has not been fully established. PRRT2 is likely expressed in the brain and spinal cord during the embryonic and postnatal stages of development. This is thought to interact with synaptosomal-associated protein 25 (SNAP25), a member of the family of soluble N-ethylmaleimide-sensitive factor attachment protein receptor proteins, which fuse synaptic vesicles to the presynaptic plasma membrane and release neurotransmitters.[10] The SNAP25 is thought to modulate the functionality of voltage-gated Ca^{2+} channels. The interaction between these two proteins gets disrupted due to mutations in the PRRT2 gene leading to neuronal hyperexcitability thus leading to a cascade of different phenotypic presentations. The study by Ekmen et al showed that patients with PRRT2-related dyskinesia have dysfunction of cerebellar output toward the cerebello-thalamo-striato-cortical network resulting in abnormal cerebellar output which could be the primary dysfunction in a PRRT2 pathogenic variant.[11] PRRT2 deficiency regulates
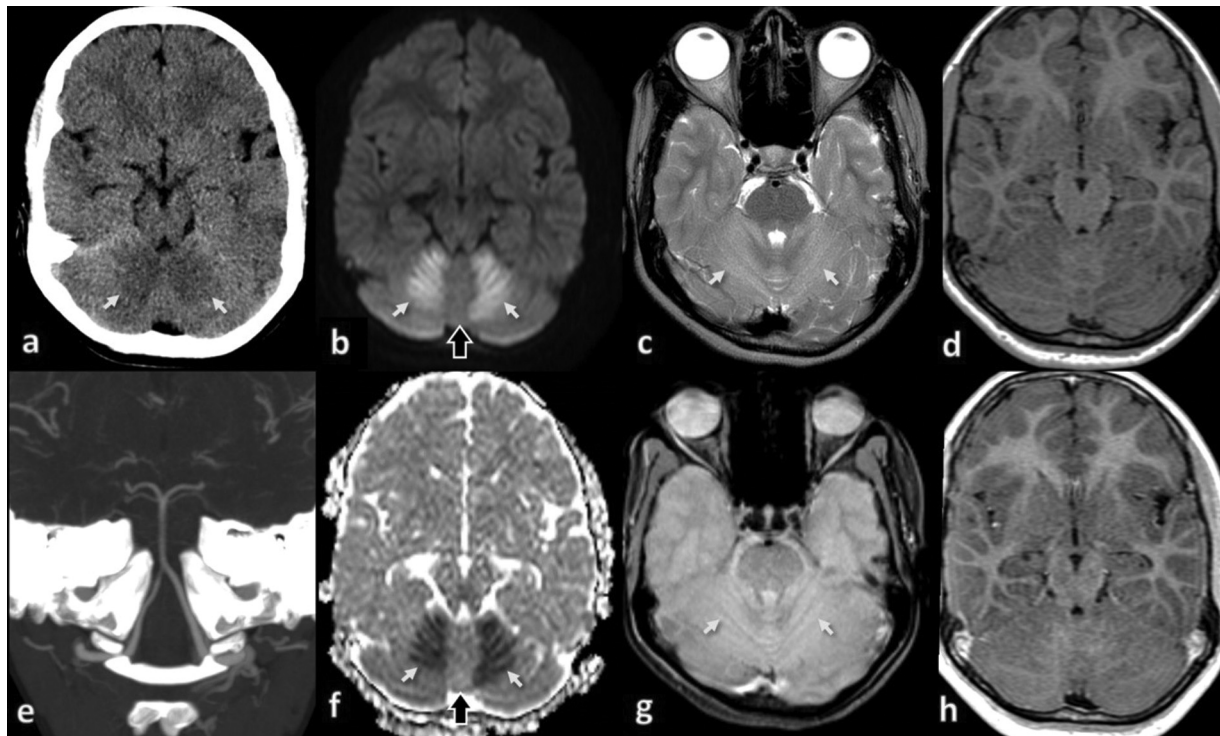
Fig. 1 Axial images of noncontrast CT (**a**), diffusion-weighted imaging (**b**) with apparent diffusion coefficient (**f**), T2-weighted (**c**), and T2*weighted (**g**) imaging, pre- and postcontrast (**d and h**) T1 show bilaterally symmetric involvement of paramedian superior cerebellar hemispheres (*paired white arrows*) with vermian sparing (*thick black arrow*). Oblique coronal thick maximum intensity projection of CT-angiogram (**e**) shows the normal configuration of arteries in the posterior circulation. The cerebellar foliae show diffusion restricting, nonblooming and nonenhancing symmetric cytotoxic edema with no significant mass effect.
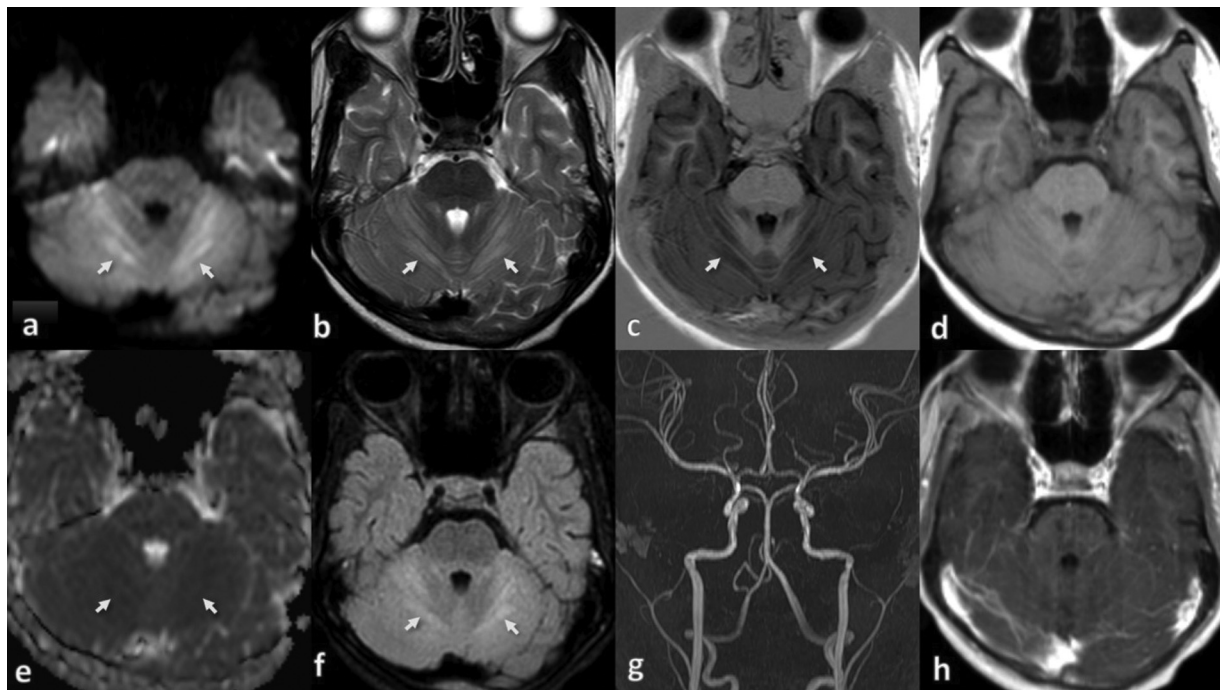

Fig. 2 Neuroimaging at the same level of cerebellum after 1 week of presentation with contrast enhanced MRI brain. Axial images of diffusion-weighted imaging (**a**), with apparent diffusion coefficient (**e**), T2 (**b**), FLAIR (**f**), T1-inversion recovery (**c**), pre- and postcontrast (**d and h**) T1 show receding bilaterally symmetric involvement of the paramedian cerebellar hemispheres (*paired white arrows*). Oblique coronal thick maximum intensity projection of MR-angiogram (**g**) shows the normal configuration of the craniocervical arteries. The cerebellar foliae show nonrestricting, nonenhancing fading hyperintensities toward the periphery suggestive of resolving cytotoxic edema.
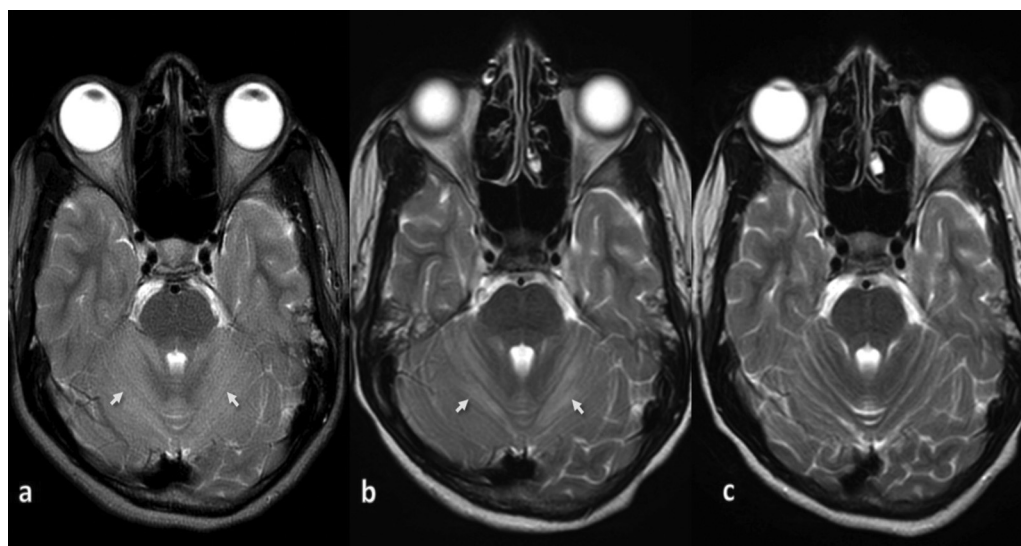
Fig. 3 Serial images of axial T2-weighted MRI brain at the level of superior cerebellum around the time of presentation (**a**), after 1 week (**b**) and 4 weeks (**c**) of treatment showing gradual resolution of the bilaterally symmetric cerebellar edema (*paired white arrows*) as well as the effacement of the interfolial spaces. The abnormal hyperintensities showed complete resolution on follow-up with discernible normal interfolial cerebrospinal fluid spaces.

synaptic transmission in the cerebellum. In a recent study, it was demonstrated that PRRT2 deficiency leads to dysregulated synaptic transmission in the cerebellum and the ablation of PRRT2 in cerebellar granule cells induces PKD.[12] The neuroimaging features described in the literature in few case reports are cerebellar atrophy or cerebellar edema and, in our case, the patient had typical features of PKD with neuroimaging features in the form of edema of the bilateral cerebellar hemisphere which showed resolution in the follow-up scans.[13–15] The prompt and detailed work-up optimally ruled out the possibilities of postinfective or autoimmune vasculitis, venous thrombosis, or metabolic spectrum of disorders. The absence of enhancement in the craniospinal imaging and normal configuration of craniocervical vessels on CT and MR angiograms augmented these conclusions. Sparing of the brainstem and dentate nuclei also negates the possibility of toxic encephalopathy. The reversible cytotoxic edema is usually found in the supratentorial neuroparenchyma in treated cases of venous thrombosis, epilepsy, encephalitis, and vasculitis[16] In this study, striatal dysfunction in paroxysmal dyskinesia might be secondary to aberrant cerebellar output transmitted by thalamic relays. The compound heterozygosity heterozygous pathogenic variants in PRRT2 mutation might confer a more severe phenotype compared with homozygous variant.[17,18] The clinical and radiological response to the low dose of carbamazepine and clonazepam in our patient was optimal and well-sustained. However, such symmetric cerebellar hemispheric involvement sparing the thalami and hippocampi are hitherto undescribed as seizure effects or drug-related neuroparenchyma changes. Prolonged follow-up and detailed evaluation of the first-degree relatives may throw more light on the clinico-radiological patterns of this rare neurological affliction.

This case report highlights a pathogenic frameshift duplication mutation in the *PRRT2* gene associated with rare abnormal neuroimaging findings and expands phenotypic characteristics of PKD for consideration in episodic hyperkinetic movement disorders.

Author Contribution
R.S. was responsible for conceptualization. R.S. and B.H. were responsible for data curation. R.S. was responsible for formal analysis. S.S. was responsible for methodology. G.K. was responsible for visualization. R.S., S.S., A.M., and B.H. were responsible for writing review and editing.

Conflict of Interest
None declared.

References
1 Bhatia KP. Paroxysmal dyskinesias. Mov Disord 2011;26(06): 1157–1165
2 Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet 2011;43(12):1252–1255
3 Ono S, Yoshiura K, Kinoshita A, et al. Mutations in PRRT2 responsible for paroxysmal kinesigenic dyskinesias also cause benign familial infantile convulsions. J Hum Genet 2012;57(05):338–341
4 Riant F, Roze E, Barbance C, et al. PRRT2 mutations cause hemiplegic migraine. Neurology 2012;79(21):2122–2124
5 Ebrahimi-Fakhari D, Kang KS, Kotzaeridou U, Kohlhase J, Klein C, Assmann BE. Child neurology: PRRT2-associated movement disorders and differential diagnoses. Neurology 2014;83(18): 1680–1683
6 Huang XJ, Wang T, Wang JL, et al. Paroxysmal kinesigenic dyskinesia: clinical and genetic analyses of 110 patients. Neurology 2015;85(18):1546–1553
7 Long Z, Xu Q, Miao HH, et al. Thalamocortical dysconnectivity in paroxysmal kinesigenic dyskinesia: combining functional

magnetic resonance imaging and diffusion tensor imaging. Mov Disord 2017;32(04):592–600

8 Wang JL, Cao L, Li XH, et al. Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias. Brain 2011;134(Pt 12):3493–3501

9 Mehta SH, Morgan JC, Sethi KD. Paroxysmal dyskinesias. Curr Treat Options Neurol 2009;11(03):170–178

10 Méneret A, Gaudebout C, Riant F, Vidailhet M, Depienne C, Roze E. PRRT2 mutations and paroxysmal disorders. Eur J Neurol 2013;20 (06):872–878

11 Ekmen A, Meneret A, Valabregue R, et al. Cerebellum dysfunction in patients with PRRT2-related paroxysmal dyskinesia. Neurology 2022;98(10):e1077–e1089

12 Tan GH, Liu YY, Wang L, et al. PRRT2 deficiency induces paroxysmal kinesigenic dyskinesia by regulating synaptic transmission in cerebellum. Cell Res 2018;28(01):90–110

13 Legris N, Chassin O, Nasser G, Riant F, Tournier-Lasserve E, Denier C. Acute-onset ataxia and transient cerebellar diffusion restric-tion associated with a PRRT2 mutation. J Stroke Cerebrovasc Dis 2019;28(02):e3–e4

14 Moritani T, Ekholm S, Westesson P-L. Diffusion-Weighted MR Imaging of the Brain. 2nd ed. Springer; 2009

15 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

16 Kastrup O, Schlamann M, Moenninghoff C, Forsting M, Goer-icke S. Posterior reversible encephalopathy syndrome: the spectrum of MR imaging patterns. Clin Neuroradiol 2015;25 (02):161–171

17 Delcourt M, Riant F, Mancini J, et al. Severe phenotypic spectrum of biallelic mutations in PRRT2 gene. J Neurol Neurosurg Psychia-try 2015;86(07):782–785

18 Döring JH, Saffari A, Bast T, et al. The phenotypic spectrum of PRRT2-associated paroxysmal neurologic disorders in childhood. Biomedicines 2020;8(11):456