A Novel Neuroimaging Phenotype in the Pediatric Paroxysmal Kinesigenic Dyskinesia

Rahul Sinha1  Bharat Hosur2  Sonali Singh3  Gautam Kamila4  Ankit Kumar Meena4

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 which can be isolated or associated with benign infantile seizures as part of the infantile convulsions with choreoathetosis syndrome. 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 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.
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 hypertonic 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 intention 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 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.

The SNAP25 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. The prognosis of PKD is favorable and patients usually show excellent response to treatment. 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 gene is not 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. The SNAP25 is thought to modulate the functionality of voltage-gated Ca²⁺ 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.
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.
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.\textsuperscript{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.\textsuperscript{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 cranio- cervical 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.\textsuperscript{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.\textsuperscript{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.

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