Movement Disorders
CLINICAL PRACTICE

Early Onset Paroxysmal Dyskinesia in PRRT2-Related Disorders

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Epilepsy and paroxysmal movement disorders coexist in several neuro genetic conditions, with heterogeneous clinical characteristics and etiology, which recently led to the constantly expanding concept of "genetic epilepsy-dyskinesia spectrum".[1] The advent of next generation sequencing methodologies has broadened the genetic knowledge of these conditions, with a wide number of genes involved, presenting with their own characteristics.[2]

Here, we report the case of an infant experiencing a concomitant onset of epileptic seizures and paroxysmal dyskinesia at 3 months of age.

The patient was the first child of healthy unrelated parents, born at term after normal pregnancy and delivery. Family history was unremarkable. At 3 months of age, he was hospitalized because of the onset of paroxysmal episodes occurring multiple time per day, lasting <1 min, clinically characterized by sudden loss of consciousness, lateral gaze deviation, eyelid blinking, and lips jerking (type 1 episodes, Video 1). Neurological examination at admission was normal. Interictal electroencephalographic (EEG) registrations showed a sleep and awake normal background activity for age, without epileptiform discharges (EDs). Because the episodes were consistent with focal motor epileptic seizures, phenobarbital up to 5 mg/kg/day was promptly started and seizures significantly reduced in frequency. During the hospitalization, however, several paroxysmal episodes of different semeiology were also observed, which always occurred at awakening, and were clinically characterized by subtle, erratic, variable, and involuntary movements involving face, limbs head, and trunk. These sub continuous movements were sometimes superimposed by more patterned, twisting limbs movements. The episodes lasted 2 to 3 min, and showed slow, spontaneous, progressive resolution (type 2 episodes, Video 2). No loss of consciousness was observed.

Prolonged Video 1-EEG registrations confirmed the epileptic correlate of type 1 episodes, characterized by a recruiting spike–wave activity on the occipital regions lasting 1 and 2 min, followed by a sharped theta activity, replaced in few seconds by high voltage generalized spike-waves, corresponding to a focal evolving to bilateral tonic–clonic seizures. Type 2 episodes were also observed, but no EDs were registered.

The diagnostic work up, including magnetic resonance imaging, cerebrospinal fluid investigations, and metabolic screening, was unrevealing. Given the incomplete efficacy of phenobarbital on epileptic spells and the absence of any effects on paroxysmal dyskinesia, a switch to carbamazepine up to 20 mg/kg/die was done, with prompt and complete resolution of both types of paroxysmal manifestations.

At last evaluation (15 months of age) the child showed a complete control of both types of paroxysmal manifestation. Neurological examination and neurodevelopment were normal for age.

Trio based whole exome sequencing was performed, revealing the unreported de novo heterozygous mutation, p.Pro154AlafsTer16 (c.458 dup), in *PRRT2* gene. This rearrangement is extremely rare in general population and determines a change in the amino acid sequence causing the insertion of a premature stop codon.

Pathogenetic variants on *PRRT2* have been associated to an evolving spectrum of paroxysmal manifestation including early onset focal epileptic seizures and/or later onset non epileptic paroxysmal manifestation,[3] that includes paroxysmal kinesigenic dyskinesia (PKD), non-kinesigenic paroxysmal dyskinesia (PNKD),[4] hemiplegic migraine, and episodic ataxia.[5,6] A small number of patients with biallelic mutations in *PRRT2* has also been described, showing a more severe phenotype characterized by prolonged episodes of ataxia, paroxysmal dyskinesias, and intellectual disability or learning difficulties.[6]

Although the epileptic phenotype, as well as the response to treatment, observed in our patient was in line with literature,[7] the paroxysmal dyskinesia has some peculiarities.

First, it started at 3 months of age, much earlier than in the patients reported so far. In 2014, Ebrahimi-Fakhari et al[8] reported the largest study on *PRRT2*, including 1444 *PRRT2*-mutated patients with a mean age at onset of seizures of 6.3 ± 3.2 months, whereas paroxysmal movement disorder was

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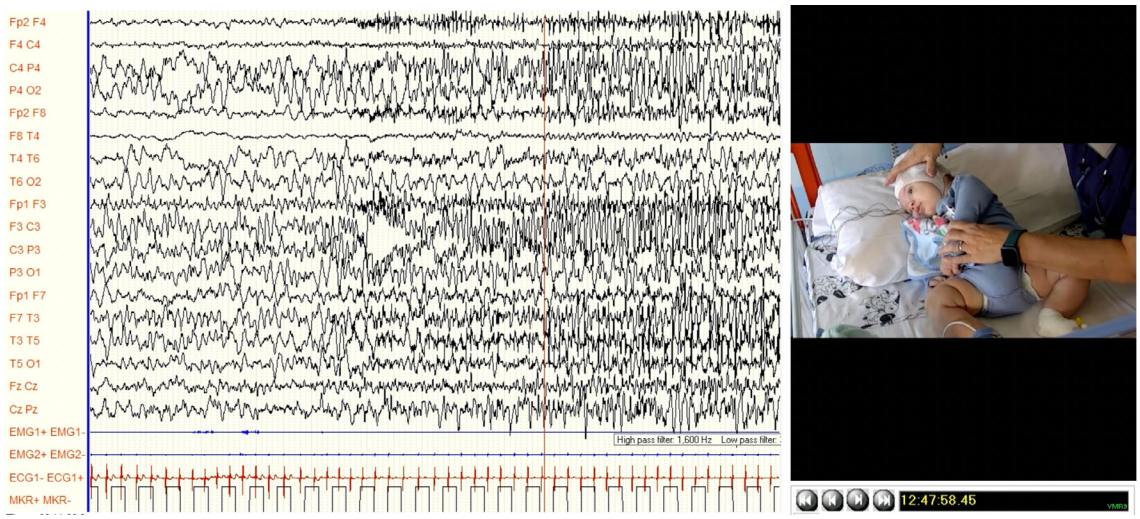
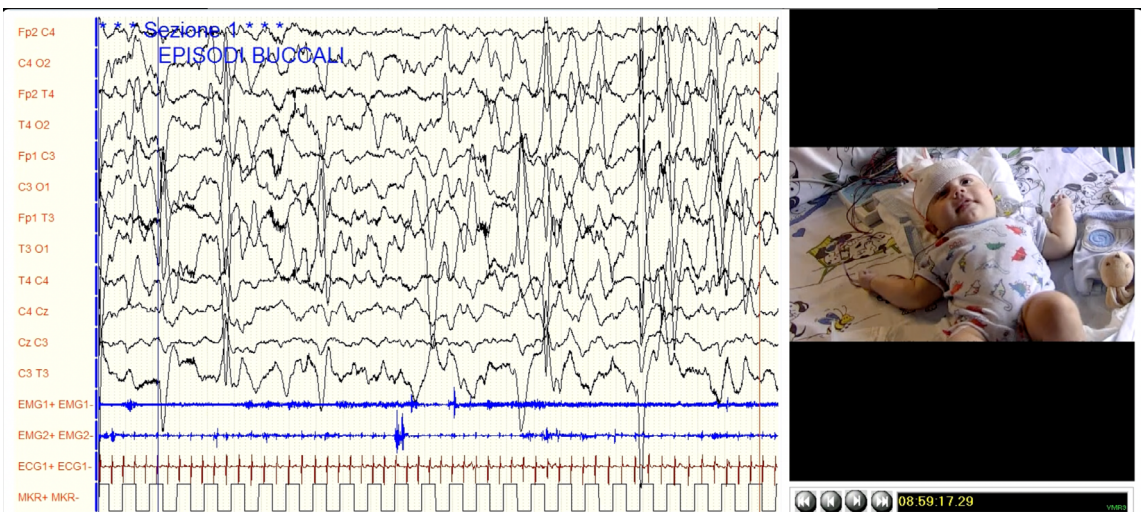


Video 1. Ictal electroencephalographic (EEG) and clinical manifestations. Video-polygraphic EEG/electromiographic (ECG1, deltoid muscles bilaterally/EMG1-2) monitoring recorded with the 10–20 international system: ictal rhythmic sharped waves start from left frontal-central regions, followed by polyspikes, which rapidly spread to both hemispheres. Clinically, the patient presents right head and gaze deviation, eyelid blinking, and lips jerks.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13674

reported at a mean age of 10.3 ± 4.9 years. A similar range of age at onset of movement disorder in *PRRT2* mutated patients was also described in 2019 by Okumura et al,[9] who described 104 patients. In these series, median age at onset of the seizures was 5 months (range, 2–14 months), whereas median age at onset of the movement disorder was 9 years (range, 2–16 years).[9]

Second, in our patient the duration of the episodes were also uncommonly long, lasting a few minutes, whereas the duration of paroxysmal dyskinesias is widely reported as lasting <1 minute.[10] From a semeiologic standpoint, they appeared as generalized choreo-dystonic movements, with a streaking involvement of facial area, a feature rarely reported.



Video 2. Paroxysmal movement disorder. Video-polygraphic electroencephalographic (EEG)/electromiographic (ECG1, deltoid muscles bilaterally/EMG1-2) monitoring recorded with the 10–20 international system: non epileptic subtle, erratic, and involuntary movements involving face, head, trunk, and limbs. These sub continuous movements are sometimes superimposed by more patterned, twisting limbs movements. Facial grimacing is also observed.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13674

Some studies have been conducted aiming at clarifying why *PRRT2* mutations manifest with seizures in infancy and dyskinesia later in childhood.[11] However, our observation makes these concepts arguable because it suggests the possibility that, in *PRRT2* patients, movement disorder can have a much earlier onset than previously thought.

These paroxysmal events mimic and could be misdiagnosed as epileptic spells and raise the question if they are underestimated in early infancy. In this regard, prolonged Video 2-EEG monitoring represents a fundamental tool in the diagnostic work up of such young patients, allowing clinicians to characterize paroxysmal episodes and avoid misdiagnosis.

In conclusion, our case broadens the phenotypic spectrum of *PRRT2*-related disorders that should also include very early onset paroxysmal dyskinesia.

Author Roles

(1) Research project: A. Conception. (2) Manuscript: A. Writing of the First Draft, B. Review and Critique.

Y.V.: 1A, 2A, 2B.
R.P.: 2B.
S.M.: 2B.
A.P.: 2B.
S.M.: 2B.
M.A.M.L.: 2B.
P.V.: 2B.
D.T.: 1A, 2B.

Disclosures

Ethical Compliance Statement: All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient's parents for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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