CASO CLÍNICO/CASE REPORT

PRRT2-Associated Disorders: A Phenotypic Spectrum of Paroxysms

Doenças Associadas ao Gene *PRRT2*: Um Espectro Fenotípico de Paroxismos

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Abstract

PRRT2 is a presynaptic plasma membrane protein involved in neurotransmitter release. Disorders associated with *PRRT2* pathogenic variants are a spectrum of clinical conditions with autosomal dominant inheritance, characterized by a paroxysmal presentation. The three main ones are self-limited infantile epilepsy, paroxysmal kinesigenic dyskinesia, and hemiplegic migraine, but other presentations have been reported. Patients carrying *PRRT2* variants may present with one or more of these clinical phenotypes simultaneously or subsequently. We report 5 cases of self-limited infantile epilepsy presenting between 4 and 10 months of age and 1 case of paroxysmal kinesigenic dyskinesia presenting at 8 years old, all associated with the c.649dup p.(Arg217Profs*8) *PRRT2* heterozygous pathogenic variant. This case series highlights the disease clinical spectrum between and within individuals, phenotypic variability between and within families, good treatment response to sodium channel blockers and self-limiting character.

Resumo

A PRRT2 é uma proteína membranar plasmática pré-sináptica envolvida na libertação de neurotransmissores. As doenças associadas às variantes patogénicas do *PRRT2* incluem um espectro de condições de hereditariedade autossómica dominante e apresentação paroxística. As três principais são a epilepsia autolimitada do lactente, a discinésia paroxística cinesigénica e a enxaqueca hemiplégica, mas outras apresentações têm sido reportadas. Os indivíduos com variantes patogénicas do *PRRT2* podem apresentar-se com um ou mais fenótipos em simultâneo ou de forma subsequente. Relatamos 5 casos de epilepsia autolimitada do lactente com início entre os 4 e 10 meses e 1 caso de discinésia paroxística cinesigénica aos 8 anos, todos associados à variante patogénica c.649dup p.(Arg217Profs*8) em heterozigotia do *PRRT2*. Esta série de casos ilustra o espetro clínico inter e intra-individual, a variabilidade fenotípica inter e intra-familiar, a boa resposta à terapêutica com bloqueadores dos canais de sódio e o carácter autolimitado desta doença.

Introduction

PRRT2 variants are associated with three main paroxysmal neurological disorders: self-limited infantile epilepsy (SeLIE), paroxysmal kinesigenic dyskinesia (PKD), and hemiplegic migraine (HM).

There is significant intra and interfamilial variability and individuals may present one or more phenotypes simultaneously or sequentially.[1]

Here, we report six cases of *PRRT2*-associated disorders presenting in pediatric age that exemplify the spectrum of phenotypes associated with this disease.

Cases Reports

Case 1

A 4-month-old female developed repetitive paroxysmal events of impaired consciousness and masticatory movements (7 per day, around 1 minute duration). An event observed during examination was associated with left gaze deviation and sustained asymmetric tonic posturing. All had spontaneous resolution and recovery to basal status. There were no symptoms of an infectious disease.

She was a full-term vaginal delivery child with an uneventful pregnancy and delivery. There was no relevant disease history; growth and psychomotor development were age-appropriate. There was no family history of migraine, epilepsy or conditions suggestive of paroxysmal dyskinesia.

Neurological examination was unremarkable.

Routine blood tests and brain magnetic resonance imaging (MRI) did not reveal relevant findings. An electroencephalogram (EEG) documented a focal seizure originating in the left temporal region (**Fig. 1**).

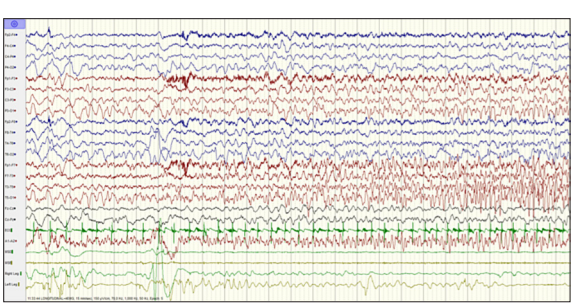

Figure 1. Electroencephalogram documenting a focal seizure originating in the left temporal region.

Patient was diagnosed with probable genetic focal infantile epilepsy and was started on clobazam. Due to seizures persistence despite clobazam titration to 10 mg/day, valproate was added at a dosage of 40 mg/kg/day with seizures control.

Epilepsy next-generation sequence panel (ENGSP) identified a *PRRT2* pathogenic variant in heterozygosity, c.649dup p.(Arg217Profs*8).

Clobazam and valproate were gradually reduced at 1 year old with no seizure recurrence after one year of follow-up.

Case 2

A 4-month-old male developed paroxysmal events of impaired consciousness, right oculo-cephalic deviation, hypertonic posture and rhythmic limb movements of around 1 minute duration. The first one was isolated, but the following occurred in a cluster (4 in less than 12 hours). All had spontaneous resolution with recovery to basal status and there were no symptoms of infectious disease.

He was born full-term by vacuum delivery and no intercurrences were registered during pregnancy or delivery. There was no relevant disease history; growth and psychomotor development were age-appropriate. His mother had a history of infantile-onset epilepsy. Neurological examination was unremarkable.

Routine blood tests did not reveal relevant findings, as well as a brain MRI and EEG. Patient was diagnosed with probable genetic focal infantile epilepsy and was started on clobazam 5 mg 2id.

One week later, after a third seizure in a cluster episode (1 per hour), the EEG showed multifocal paroxysmal activity and two seizures involving bilateral parietotemporal and right temporal (**Fig. 2**) regions were documented, and therefore, levetiracetam was added at a dosage of 22 mg/kg/day.

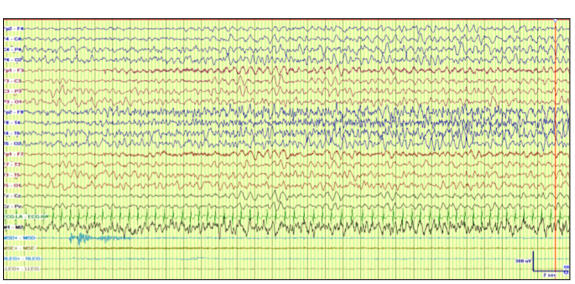

Figure 2. Electroencephalogram documenting a focal seizure originating in the right temporal region.

Due to seizures persistence despite levetiracetam titration to 40 mg/day over the course of one week, carbamazepine was added at a dosage of 10 mg/kg/day with seizures control.

ENGSP identified a *PRRT2* pathogenic variant in heterozygosity c.649dup p.(Arg217Profs*8).

Carbamazepine has been titrated to 13 mg/kg/day and clobazam and levetiracetam have been gradually reduced, with no seizure recurrence after three months of follow-up.

Case 3

A 5-month-old male developed paroxysmal events of impaired consciousness and hypertonic posture. Initially with seconds durations but over the course of a week, progressively more frequent and longer. All had spontaneous resolution with recovery to basal status. There were no symptoms of an infectious disease.

He was born full-term by c-section with an uneventful pregnancy and delivery. There was no relevant disease history; growth and psychomotor development were age-appropriate. There was a family history of infant-onset epilepsy in his maternal uncle.

Neurological examination was unremarkable.

Routine blood tests did not reveal relevant findings, as well a brain MRI. EEG showed interictal paroxysmal activity in the right medial (**Fig. 3**) and left posterior temporal regions and a focal seizure originating in the right temporal region was documented.

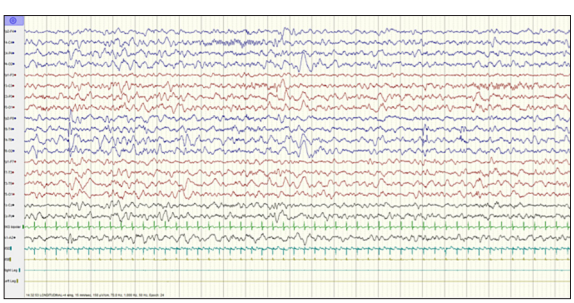

Figure 3. Electroencephalogram showing interictal paroxysmal activity in the right temporal region.

The patient was diagnosed with probable genetic focal infantile epilepsy and was started on clobazam. Due to seizures persistence despite clobazam titration to 25 mg/day, carbamazepine was added at a dosage of 8 mg/kg/day, with seizure control.

ENGSP identified a *PRRT2* pathogenic variant in heterozygosity c.649dup p.(Arg217Profs*8).

Patient remained seizure-free despite progressive clobazam weaning, and carbamazepine was gradually reduced at 2 years old with no seizure recurrence.

Case 4

A 5-months-old male developed paroxysmal events of impaired consciousness and upper limb movements. The event observed during examination was associated with left oculo-cephalic deviation and sustained asymmetric tonic posturing. They developed in the context of a bronchiolitis and were initially brief (seconds of duration) and resolved spontaneously, but over the course of two weeks became more frequent.

He was born at 39 weeks by c-section because of fetal bradycardia, with an Apgar index of 9/10/10; no other intercurrences were registered during pregnancy or delivery. There was no relevant disease history; growth and psychomotor development were age-appropriate. There was a family history of infant-onset epilepsy in his mother, maternal grandmother, and an uncle, a cousin, two granduncles and a second-degree cousin from the maternal side. His mother also had migraine and complaints of episodes of abnormal postures (**Fig. 4**).

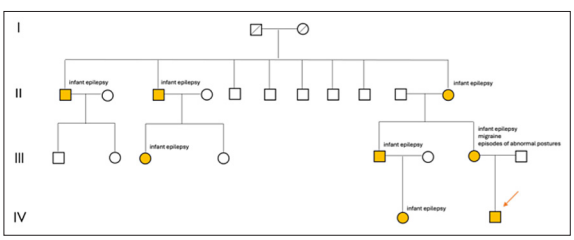

Figure 4. Genogram illustrating family history suggestive of infant-onset epilepsy, migraine and paroxysmal kinesigenic dyskinesia.

Neurological examination was unremarkable.

Routine blood tests and a brain MRI did not reveal relevant findings. EEG showed discontinuous slow activity in left temporo-occipital region.

The patient was diagnosed with probable genetic focal infantile epilepsy and was started on clobazam 10 mg/day. Due to seizure recurrence in the context of infectious intercurrences, valproate was added and titrated to 25 mg/kg/day, having remained seizure-free after two months (13 months age).

ENGSP identified a *PRRT2* pathogenic variant in heterozygosity c.649dup p.(Arg217Profs*8).

Case 5

A 10-month-old female developed paroxysmal events of impaired consciousness and rhythmic limb movements (5 in 5 days of around 5 minutes duration). There was complete recovery to basal status between episodes. Although apyretic, she had been diagnosed with acute otitis media in the previous week for which she was on amoxicillin.

She was born full-term by c-section with an uneventful pregnancy and delivery. There was no relevant disease history; growth and psychomotor development were age-appropriate. There was a family history of infant-onset epilepsy in her father and paternal uncle and her father also reported anomalous limb postures when running.

Neurological examination was unremarkable.

Brain MRI did not reveal relevant findings, as well as routine blood and cerebrospinal fluid tests and an EEG. The patient was diagnosed with probable genetic focal infantile epilepsy and was started on levetiracetam, titrated to 40 mg/kg/day.

One month later, in the context of another infectious intercurrence, she presented a new cluster of seizures, having the levetiracetam dosage been adjusted to weight.

ENGSP identified a *PRRT2* pathogenic variant in heterozygosity c.649dup p.(Arg217Profs*8).

After having a new cluster of seizures, levetiracetam was switched to carbamazepine 18 mg/kg/day, having been remained seizure free after four months (15 months age).

Case 6

An 8-year-old male was referred for a 1-year history of intermittent and brief abnormal postures triggered by sudden movements. He was born full-term by forceps delivery and no intercurrences were registered during pregnancy or delivery. There was no relevant disease history; growth and psychomotor development were age-appropriate, although there were learning difficulties attributed to dyslexia. There was a family history of paroxysmal kinesigenic dyskinesia in his father and paternal grandmother. His father was known to have a *PRRT2* pathogenic variant in heterozygosity – c.649dup p.(Arg217Profs*8) – and he was under carbamazepine 200 mg.

During neurological examination, when distracted, he assumed repetitive subtle dystonic postures in lower limbs and while walking, intermittent dystonic postures on his hands were observed.

EEG did not reveal relevant findings. *PRRT2* genetic test identified the same pathogenic variant as the father.

Initially, no treatment was considered due to the absence of impact in daily activities, but two years after first assessment, he was started on carbamazepine 1.5 mg/kg/day, because of increased episode frequency with significant improvement.

Discussion

PRRT2 variants have an autosomal dominant inheritance, although de novo findings are estimated to occur in around 5% of cases.[2] The pathogenic variant c.649dupC occurs in an unstable DNA sequence, a mutation hotspot, accounting for most cases (>75%) worldwide, and all cases in our case series.[1]

PRRT2 is a presynaptic plasma membrane protein and is mainly expressed in glutamatergic (excitatory) neurons, interacting with other synaptic proteins involved in neurotransmitter release and modulating voltage-gated sodium channels inactivation.[3] This explains the paroxysmal character of *PRRT2*-associated disorders, the improvement seen with sodium channel antagonists, and the similarities between them and other channelopathies.[2]

This gene is mostly expressed in the cerebral cortex, basal ganglia and cerebellum and its expression declines during adulthood, clarifying the disease clinical phenotypes and their self-limiting character.[4] Their different age windows may suggest a yet to be explored expression pattern shift across different brain regions.[4]

PRRT2 pathogenic variants account for most cases of SeLIE[5] and PKD.[6] Familial HM is more frequently caused by variants in *CACNA1A*, *ATP1A2* or *SCN1A*, but may also be associated to *PRRT2* variants.[7]

As illustrated in this case series, SeLIE is characterized by focal onset seizures that may progress to bilateral tonic-clonic events, with onset in the first year of life.[8] Seizures may be unprovoked and often occur in clusters.[8] Despite this pattern, it has an excellent response to anti-seizure medications and is self-limited, resolving around two years of age. Patients present a normal neurodevelopment and interictal EEG recordings are generally normal or show sporadic focal epileptiform activity.[8] In this case series, most patients presented interictal or ictal activity, probably because EEGs were performed acutely during emergency room admission.

PKD is characterized by sudden attacks of involuntary movements (dystonia, chorea, ballism or athetosis) that have a kinesigenic trigger (sudden movement).[6] There is no associated loss of conscience and episodes are of short duration (less than 1 minute) but may occur very frequently (as many as 100 times per day). It usually begins during childhood and may resolve in adulthood.[9]

HM is characterized by transient hemiparesis (motor aura) and other non-motor aura (visual, sensory, speech/

language impairment) usually associated with migraine during or after aura.[10] It may be prolonged (as much as 72 hours) and its frequency may vary between a few per week or year.[7] It usually begins in puberty and, as PKD, may have spontaneous remission during life.

More recently, the spectrum has been growing and heterozygous *PRRT2* variants have been associated with other subtypes of paroxysmal dyskinesias; episodic ataxia and migraine with or without aura.[11] In all these disorders neurological examination is normal between episodes, as well as brain MRI.

Our case series reflects this disease clinical spectrum throughout life, with patients presenting SeLIE in the first year and PKD in childhood, and some of their relatives describing a suggestive history of SeLIE in the first year and PKD and migraine in adulthood.

The treatment decision should take into consideration the functional impact and potential comorbidities. Traditionally, first-line anti-seizure medications have been considered appropriate in SeLIE,[1] but a recent study suggested a more favorable effect of sodium channel blockers, disfavoring the use of levetiracetam. Our case series corroborates these results, with both of our patients started on levetiracetam recurring or even worsening while all the patients started or switched to carbamazepine remaining seizure-free. In the first four cases, clobazam was used while awaiting the complete work-up, due to its broader spectrum of action.

For PKD, sodium channel blockers are considered first-line treatment, generally requiring lower doses than those used in epilepsy. However, other first-line anti-seizure medications may be used with efficacy.[9] There is a few evidence also suggesting the efficacy of low doses of sodium channel blockers in hemiplegic migraine,[7] nevertheless the use of acetazolamide and other drugs for typical migraine with aura may be considered.

Considering the self-limitedness and great therapeutic response to a specific drug class of *PRRT2* variants, ENGSP should always be considered in patients presenting with seizures in the first year of life, even in the absence of family history, as this result may help guide the treatment and define the prognosis. ■

Contributorship Statement / Declaração de Contribuição

CB: Conception, data analysis and interpretation, writing and final approval.

CS and JA: Critical review and final approval.

FP and JR: Conception, critical review and final approval.

CP: Data analysis and interpretation, critical review and final approval.

CB: Conceção, análise e interpretação de dados, redação e aprovação final.

CS e JA: Revisão crítica e aprovação final.

FP e JR: Conceção, revisão crítica e aprovação final.

CP: Análise e interpretação de dados, revisão crítica e aprovação final.

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