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CLINICAL CASE

Pathogenic variant in the PCDH19 gene in a patient with epilepsy and cognitive disability

Variante patogénica en el gen *PCDH19* en una paciente con epilepsia y discapacidad cognitiva

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What do we know about the subject matter of this study?

Epilepsies of genetic etiology are new in the neurological field. Although some genetic epilepsies are more recognized, epilepsies associated with the PCDH19 gene mutation are poorly reported despite that they occur with easily recognizable clinical features.

What does this study contribute to what is already known?

This clinical case presents the natural history of genetic epilepsy, whose diagnosis, evolution, and complications allow to assess the importance of early diagnosis to establish therapeutic strategies that improve the quality of life of patients and their families.

Abstract

The association of family cases of epilepsy and intellectual disability in women was reported in 1971. In 2008, the role of pathogenic variants of the *PCDH19* gene in some families were identified. The disease presents with febrile seizure clusters, intellectual disability, and autistic features. Most cases are due to *de novo* variants, however, there are some inherited cases, with an atypical way of X-linked transmission. **Objective:** To report the case of a patient with epilepsy carrier of a pathogenic variant of the *PCDH19* gene, reviewing the natural history of this condition and the available evidence for its management. **Clinical Case:** Female patient, with normal history of pregnancy and perinatal period. At 6 months, while febrile, she presented focal motor seizure clusters that repeated at 14, 18, 21 months and 3 years old, always associated with fever, even presenting status epilepticus. She is on therapy with topiramate and valproic acid, achieving 13 seizure-free years. The analysis of the *SCN1A*

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gene showed no abnormalities and the study of the *PCDH19* gene revealed a *de novo* heterozygous pathogenic variant. The patient evolved with intellectual disability and severe behavioral disorders that require mental health team support. **Conclusions**: *PCDH19* pathogenic variants have varied phenotypic expression. The genetic diagnosis should be guided with the clinical features. Long-term psychiatric morbidity can be disabling.

Introduction

The association between epilepsy and intellectual disability (ID) in women was reported by Juberg (1971) in 15 cases with a direct family relationship (sisters and cousins from the father side), with an X-linked pattern of inheritance[1]. Subsequently, the *PCDH19* gene was involved, identifying pathogenic variants in six families, including the original one reported by Juberg[2]. Clinical manifestations correspond to an epileptic encephalopathy resembling Dravet syndrome (OMIM#607208)[3].

Dravet syndrome (DS) occurs in healthy infants in the first year of life, with unilateral or generalized tonic-clonic seizures triggered by fever. Later, they have myoclonic seizures and atypical absences. The psychomotor development progressively deteriorates during the second year of life, with persistent susceptibility to presenting seizures with fever, with frequent convulsive status epilepticus. Seizures persist despite appropriate anticonvulsant treatment, even with polytherapy. It mainly occurs due to heterozygous mutations of the *SCN1A* gene, which encodes the voltage-gated sodium channel alpha subunit. The pathogenic variants *PCDH19* are the second most frequent genetic cause[4,5] and appear as a characteristic epileptic syndrome of early-onset, with clusters of febrile seizures, ID, and autistic features[6]. Given its predominant occurrence in women, it has been called *Epilepsy in Females with Mental Retardation* (EFMR) and recently has been proposed the name *Girls Clustering Epilepsy* (GCE) (MIM#300088)[7].

The *PCDH19* gene (MIM#300460) is located on the Xq22.1-3 chromosome. It encodes for protocadherin-19, a transmembrane protein of the family of calcium-dependent cell adhesion molecules, important in neuronal migration and formation of synaptic connections during brain development[2]. A recent systematic review concluded that an early onset of seizures associates more severe ID, and more adverse behavioral phenotype. There is no described association between the type or location of *PCDH19* mutation and the age of seizures onset, which is typically triggered by fever[7].

There are "critical periods" of development, during which the brain undergoes crucial changes for the development of behavior and cognitive processes[8]. The frontal cortex is involved in multiple cognitive functions[9], so functional alterations appear with cognitive and behavioral symptoms[10]. The first epileptic seizures due to *PCDH19* mutation occur at an average age of 10 months, coinciding with a period of increased frontal cortex glucose metabolism[11], associated with rapid development of new synapses in the first years of life and an increase in cortical gray substance[12]. The frontal lesions present deficits in executive functioning (attention), as well as psychiatric disorders, such as schizophrenia, depression, and Obsessive-Compulsive Disorder (OCD)[9]. The epileptic activity during the first 12 months of life can then interrupt this neuronal development causing a cognitive dysfunction[7].

The pathogenic variants *PCDH19* present incomplete penetrance, phenotypic variability, and mainly occur *de novo*. In inherited cases, this condition occurs in heterozygous women who are clinically affected. Males with hemizygous mutation are not affected, regardless of their carrier status[1,2,13]. No epilepsy has been reported in men, but there is present a special behavioral phenotype in carriers, reporting rigid personalities, restricted interests, and obsessive features, which has also been frequently observed in patients[14]. They have also presented different degrees of ID and autism[15-17], and seizures of varying severity and behavioral changes in men with mosaicism[18-20]. The cause of gender-related clinical variability is unknown.

The objective of this work is to present the natural history of a clinical case with this very rare condition and the difficulties that arise in its differential diagnosis, as well as in its evolution.

Clinical Case

16-year-old female patient, with the onset of seizures at 6 months of age. Her psychomotor development was normal until the onset of the disease. She has no relevant perinatal history and no family history of epilepsy. She has one healthy sister and healthy parents, not consanguineous.

At the age of 6 months, with fever (39 °C) and during sleep, the patient presented sudden screaming, consciousness involvement, and clonic movements of the lower left limb lasting less than 5 minutes. In

the emergency department (ED), she had three focal seizures, therefore it was administered phenobarbital (FBB) and was hospitalized for study. The electroencephalogram (EEG) showed frequent interictal epileptiform discharges (IED) in the left frontal-central area, with propagation towards contralateral homologous regions.

The patient developed recurrence of motor focal seizure and some events of discharges interruption, with bilateral rhythmic blinking, generalized hypertonia, and seconds long oxygen desaturation. EEGs at 48 hours and day 6 were normal, as well as brain MRI with epilepsy protocol. The infectious and metabolic study showed no abnormalities (amino acids in blood and cerebrospinal fluid (CSF), study of organic acids and CSF neurotransmitters). Given the recurrence of seizures, Valproic Acid (VA) was administered showing no response, so Phenytoin (PHT) and Midazolam (MDZ) were administered, managing to stop them. She was discharged with VA, lasting 4 months without seizures. After a temporary suspension of VA, she presented six brief and recurrent generalized tonic seizures. Later, at 14 months and 18 months of age, she presented generalized tonic-clonic seizures (GTCS) repeated while febrile. She developed with GTCS convulsive status epilepticus that was managed with PHT load and MDZ infusion. EEG showed bilateral synchronous frontal IED, and monitoring at 48 hours, it showed diffuse slow basal brain activity. VA- Clobazam (CLB) were combined, remaining in bi-therapy at discharge.

At 21 months, the patient presented febrile seizure status (GTCS), which was managed in the ICU. At the age of three, during a new febrile episode, she presented two GTCS, managed with Lorazepam (LRZ). After this hospitalization, VA-Topiramate (TPM) were combined, maintaining this schedule until today, without repeating seizures with this combination, completing 13 years of follow-up. The patient presented normal posterior EEG and normal control brain MRI.

Regarding the neurodevelopment, Bayley's test at 16 months showed a delay, with a mental scale 76 (85-115) and a motor scale 86 (85-115). At 27 months, she has a mental scale of < 50 (17 months) and a motor scale 61 (21 months). PEP-R test (3.5 years) showed significant delay, with a score of 1.6 years with better performance in fine motor skills and worse cognitive/verbal difficulty. The patient developed with poor language skills, severe cognitive disability, and behavioral alterations, with repetitive movements and catastrophic reactions to frustration, which significantly affects social dynamics and school integration. Although she has evolved without epileptic seizures, the behavioral disorder has been the main difficulty, receiving treatment with Aripiprazole and support by the mental health team.

Given the association of recurrent seizures and fever, Dravet syndrome was considered, and a study of the *SCN1A* gene was carried out at the Institute of Medical and Molecular Genetics (INGEMM) in Madrid, with PCR, study of specific mutations and Sanger sequencing, and MLPA analysis of deletions and duplications, with normal results. Subsequently, the genetic study was extended, with sequencing of coding regions and exon-intron structure of the *PCDH19* gene, which detected the missense mutation c.1019A>G; p.(Asn340Ser) (chrX:99662577T>C, hg19) in heterozygosis, in the *PCDH19* gene (NM_001184880.2). The study of both parents was negative; thus, it was concluded that this was a *de novo* mutation. This variant was classified as pathogenic, according to the ACMG variant classification guidelines[21].

Discussion

We describe a female case with seizure clusters of difficult initial management, ID, and psychiatric difficulties in the long-term evolution due to a pathogenic variant p.(Asn340Ser) in the *PCHD19* gene. The clinical profile of this case was oriented to a genetic etiology, so a search was conducted for specific genes according to the protocol of that time. Currently, multigene panel tests are used simultaneously for an accurate diagnosis in patients with epilepsy of genetic etiology.

Epilepsy due to alterations in the *PCDH19* gene presents a reduction or remission of seizures in adolescence, in relation to pubertal onset and the production of neurosteroids[14,22,23]. In our case, although unusual, the seizures were controlled with polytherapy at 3 years of age. However, behavioral and cognitive symptoms have remained, increasing with age, which are the most distinctive and disabling feature in some patients[24,25].

Table 1 shows the differences and similarities with DS. This case had an onset earlier than usually reported in the literature, which is described between 6 and 36 months (average 14 months)[14]. In most cases (90%), the seizures are induced or worsened by fever, as in our case. Screaming or shouting in fear can be a characteristic manifestation of the seizures in these cases, associating staring, stopping motor activity, or bilateral clonic movements[26].

The most common types of seizures are focal or generalized, tonic, clonic, or tonic-clonic, and less frequently other types of seizures, such as atypical, myoclonic, or atonic absences[27]. The seizures are usually brief, in clusters, as the characteristics of the seizure our patient presented. There is a lack of descriptions of EEGs reported, without a consistent abnormal pattern. Activity may be normal, focal or generalized slowness and/or IEDs[6]. Treatment with antiepileptic drugs

(AEDs) in the first years of life is complex since the seizures are usually refractory.

Seizure frequency and drug resistance decrease during the course of the disease. In this case, we observed a favorable response to PHT, unlike DS, where the use of sodium channel blockers tends to worsen the seizures.

In a retrospective multicenter study (25 centers in 12 countries), the response with different AEDs was described in 58 patients with pathogenic variants of the *PCDH19* gene[28] after 3 months of use, concluding that the most effective treatments were clobazam (CLB) and bromides (BR), compared with other AEDs that were significantly less effective. However, it was a retrospective study, based on parental reports and where almost all patients were on polytherapy, which makes it difficult to evaluate the effectiveness of each AED separately. In addition, the cyclical nature of this condition -seizure with febrile events with seizure-free intervals over months- did not distinguish the effect of an AED versus spontaneous remission by natural course.

The intermittent use of benzodiazepines rectally, orally, or intravenously has been useful in the control of seizure clusters in some patients[26]. On the other hand, in studies that examined regulatory elements of genes associated with *PCDH19*, they demonstrated that 22% of them have regulatory sites of progesterone and estrogens, some of them are of particular interest given their function in neurosteroidogenesis, including the synthesis of allopregnanolone, a progesterone-derived neurosteroid that acts as GABA positive allosteric modulators, developing current research protocols in its use in pediatric patients with *PCDH19* and convulsive status epilepticus with promising results[29].

Brain MRI is usually normal, as in our case. However, mesial temporal sclerosis associated with febrile status has also been described[30], as well as cortical developmental malformations, including focal cortical dysplasia, therefore, this condition is not a contraindication for surgical option in focal refractory epilepsies. In animal models, it has been studied how the pathogenic variants in *PCDH19* can affect neuronal migration, with interruption of the columnar organization in mice[31], and increased cell proliferation in the zebrafish model[32]. Regarding post-surgical prognosis, there would be a potential positive evolution in terms of seizure frequency, but with persistent cognitive and behavioral impairment, which are determined by the underlying genetic condition[33].

ID is present in 75% of cases, which can be variable in degree[34]. The development described can follow three paths, normal development during childhood with regression after the onset of seizures, as occurred in this case; normal development from birth without regression; or delay from birth, maintaining delay in adulthood. As for psychiatric morbidity, it is common to observe autistic features (present in approximately 60% of cases)[27], behavioral problems, aggression, ADHD, anxiety, and OCD[7,34]. In our patient, the adaptive difficulties, rigidity, perseverance, and aggressiveness, limit the degree of participation and integration of her and her family in social activities. In adolescents and adults, it has been reported depression, bipolar disorder, schizophrenia, psychosis among other mental illnesses. Sleep disorders, muscle tone disorders, motor deficits, language disorders, sensory integration disorders, delayed dental eruption, and autonomic dysfunction have also been described[27].

Table 1. Main differences between patients with epilepsy associated with SCN1A (DS) and PCDH19 mutations

Variable	*SCN1A*	*PCDH19*	REF
Sex (Female)	+	+++	Depienne, 2009[3]
Age of onset	5-8 months	6-36 months	Dravet, 2011[35] Scheffer, 2008[14]
Intellectual Disability	+++	++	Scheffer, 2008[14]
Neuropsychiatric Disorders	++	+++	Kolc, 2019[7]
Seizure semiology	Clonic/Hemiclonic/Myoclonic	Motor focal tonic and hypomotor	Depienne, 2009[3]
Prolonged seizures	+++	+	Trivisano, 2016[36]
Seizure cluster	+	+++	Marini, 2010[22]
Latency between seizures	2 m	10 m	Trivisano, 2016[36]
Photosensitivity	+++	+	Depienne. 2009[3]
Worsening seizures with Na+ blockers	+++	+	Lotte, 2016[28]
Remission with age	Stay refractory	End with adolescence	Marini, 2010[22]

DS: Dravet syndrome.

Conclusions

The pathogenic variants in *PCDH19* in women, or men with mosaicism appear with a varied clinical spectrum. The most common presentation is early-onset clusters of febrile seizures, with a variable degree of ID. Female presentation and temporary remission of seizures are other characteristic features. Psychiatric disorders are common which, in the long term, deteriorating quality of life beyond the seizures *per se*. An ideal schedule of AEDs has not been described yet, but despite the difficult control of the seizures in the early years of life, these decline in frequency and severity to adolescence. Since the clinical presentation can be confused with other epileptic encephalopathies such as DS, which has different therapeutic management, it is now recommended to use genetic studies with panels that include among others both genetic conditions.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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