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 \textit{de novo} variants, however, there are some inherited cases, with an atypical way of X-linked transmission. \textbf{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. \textbf{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

Keywords:
Epilepsy; PCDH19; autism; intellectual disability
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. Subsequently, the *PCDH19* gene was involved, identifying pathogenic variants in six families, including the original one reported by Juberg. Clinical manifestations correspond to an epileptic encephalopathy resembling Dravet syndrome (OMIM#607208).

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 and appear as a characteristic epileptic syndrome of early-onset, with clusters of febrile seizures, ID, and autistic features. 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).

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. 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.

There are “critical periods” of development, during which the brain undergoes crucial changes for the development of behavior and cognitive processes. The frontal cortex is involved in multiple cognitive functions, so functional alterations appear with cognitive and behavioral symptoms. 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, associated with rapid development of new synapses in the first years of life and an increase in cortical gray substance. The frontal lesions present deficits in executive functioning (attention), as well as psychiatric disorders, such as schizophrenia, depression, and Obsessive-Compulsive Disorder (OCD). The epileptic activity during the first 12 months of life can then interrupt this neuronal development causing a cognitive dysfunction.

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. 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. They have also presented different degrees of ID and autism, and seizures of varying severity and behavioral changes in men with mosaicism. 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 guidelines21.

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 neurosteroids14,22,23. 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 patients24,25.

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 movements26.

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 absences27. 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 IEDs6. Treatment with antiepileptic drugs
Epilepsy - V. Venegas Silva et al

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCN1A</th>
<th>PCDH19</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>+</td>
<td>+++</td>
<td>Depienne, 2009⁹</td>
</tr>
<tr>
<td>Age of onset</td>
<td>5-8 months</td>
<td>6-36 months</td>
<td>Dravet, 2011¹⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Scheffer, 2008¹⁸</td>
</tr>
<tr>
<td>Intellectual Disability</td>
<td>+++</td>
<td>++</td>
<td>Scheffer, 2008¹⁸</td>
</tr>
<tr>
<td>Neuropsychiatric Disorders</td>
<td>+</td>
<td>+++</td>
<td>Kolc, 201⁹</td>
</tr>
<tr>
<td>Seizure semiology</td>
<td>Clonic/Hemiclonic/Myoclonic</td>
<td>Motor focal tonic and hypomotor</td>
<td>Depienne, 2009³</td>
</tr>
<tr>
<td>Prolonged seizures</td>
<td>+++</td>
<td>+</td>
<td>Trivisano, 201⁶⁶</td>
</tr>
<tr>
<td>Seizure cluster</td>
<td>+</td>
<td>+++</td>
<td>Marini, 201⁰²²</td>
</tr>
<tr>
<td>Latency between seizures</td>
<td>2 m</td>
<td>10 m</td>
<td>Trivisano, 201⁶⁶</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>+++</td>
<td>+</td>
<td>Depienne, 2009³</td>
</tr>
<tr>
<td>Worsening seizures with Na+ blockers</td>
<td>+++</td>
<td>+</td>
<td>Lotte, 201⁶⁸⁸⁸</td>
</tr>
<tr>
<td>Remission with age</td>
<td>Stay refractory</td>
<td>End with adolescence</td>
<td>Marini, 201⁰²²</td>
</tr>
</tbody>
</table>

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.

References


