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

Viviana Venegas Silva, Elisa García Venegas, M. Gabriela Repetto Lisboa, Eva Barroso Ramos, Pablo Lapunzina Badia

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

Keywords: Epilepsy; PCDH19; autism; intellectual disability

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.
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. 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
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.

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 PCDH19 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. 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.

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). 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.

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. 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. 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 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. 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.

Brain MRI is usually normal, as in our case. However, mesial temporal sclerosis associated with febrile status has also been described, 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, and increased cell proliferation in the zebrafish model. 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.

ID is present in 75% of cases, which can be variable in degree. 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), behavioral problems, aggression, ADHD, anxiety, and OCD. 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.
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.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References


