MINI REVIEW

Epilepsies with a wide clinical spectrum associated with a protocadherin 19 gene mutation

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Perez G. Epilepsies with a wide clinical spectrum associated with a protocadherin 19 gene mutation. J Neurol Clin Neurosci. 2022;6(2):11-13.

ABSTRACT

One of the most common genes linked with epilepsy syndromes is Protocadherin 19 (PCDH19). PCDH19 is one of the six genes most associated in genetic epilepsies, according to the literature. PCDH19 is a gene that regulates neural connections and signal transduction and is found on chromosome Xq22.1. Epilepsy and Mental Retardation Limited to Female (EFMR) is the most common clinical manifestation of PCDH19 mutation, characterised by epileptic and non-epileptic symptoms affecting primarily females. The clinical spectrum of these mutations, however, varies greatly, ranging from hereditary epilepsy with febrile seizures to epileptic encephalopathies. The unusual female-only participation appears to be due to cellular interference in heterozygosity, however impacted mosaic-males have also been documented. Generalized tonic-clonic, tonic, atonic, absences, and myoclonic jerks are all forms of seizures. Drug resistance and the lack of specific therapy indications restrict the treatment of PCDH19-related epilepsy. Seizures, on the other hand, grow less severe as adolescence progresses, and some individuals may even go seizure-free. Adult individuals with PCDH19 mutations have the most difficulties with non-epileptic symptoms. The goal of this study is to look at the very diverse phenotypic manifestation of the PCDH19 gene mutation, which has been linked to epilepsy.

Key Words: *Epilepsies; Biomarker; Protocadherin 19; Gene Mutation*

INTRODUCTION

The most recent ILAE classification highlights the necessity of determining the aetiology of epilepsy in order to enhance prognosis and, if possible, commence targeted therapy. Indeed, distinct patterns of gene mutations might show differential drug-response and lead to target therapy, in addition to providing for risk classification based on genotype-phenotype association. The five activities of the primary epilepsy genes are: (i) ion transport; (ii) cell development and differentiation; (iii) synaptic processes modulation; (iv) small molecule transport and metabolism within and between cells; and (v) gene transcription and translation [1]. Protocadherin 19 (PCDH19), which is found on chromosome Xq22.1, is one of the most widely implicated genes in epilepsy. PCDH19 is one of the six genes most implicated with hereditary epilepsies. The PCDH19 gene is found in a variety of organs, but most notably in the limbic system of the nervous system. It has a six-exon structure and codes for a Cadherin transmembrane adhesion molecule. Cadherins, protocadherins, and desmosomal cadherins are the three subgroups of transmembrane cell adhesion molecules that make up the Cadherin superfamily. Protocadherins are the most common subgroup, with over 80 members involved in neural connections and signal transduction. Almost 150 PCDH19 mutations have been identified as clustered or de novo mutations. The majority of mutations are missense variants in the extracellular protein domains encoded by exon. However, a few intracellular domain alterations have been found, which might impact the intracellular signal route. Effective cell-cell contacts are required for the proper development of neural architecture and neuronal connections, and changes in protocadherins might cause serious disruption in early brain morphogenesis. It's unclear how PCDH19 mutations cause epilepsy to develop. However, a role for this gene in neural progenitor proliferation and cell motility control during the early phases of neurulation has been hypothesised. In vitro experiments using patient-derived induced pluripotent stem cells revealed that cells with the PCDH19 mutation differentiate faster. Increased neurogenesis occurs sooner in PCDH19-mutated cultures, as shown by increased neurite length and the appearance of premature neural rosettes. At the stage of brain progenitors, accelerated neurogenesis is associated with a malfunction in the cell division plane. PCDH19 mutations may also affect the proper location of the mitotic spindle, resulting in

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Received: 04-Mar-2022, Manuscript No. PULJNCN-22-4434; Editor assigned: 06-Mar-2022, PreQC No. PULJNCN-22-4434(PQ); Reviewed: 20Mar-2022, QC No. PULJNCN-22-4434(Q); Revised: 23-Mar-2022, Manuscript No. PULJNCN-22-4434(R); Published: 28-Mar-2022, DOI:10.37532/2752-809X.2022.6(2).11-13

a larger number of asymmetric divisions and accelerated brain development. A shift in the balance between symmetric and asymmetric cell division might play a role in the disease's aetiology. PCDH19's participation in synaptogenesis by demonstrating disruption of excitatory synaptic connections between PCDH19-knock-out and wild-type neurons in "mosaic" neuronal cultures. Furthermore, the PCDH19 mutation impairs the formation of mossy fibre synapse via reducing N-cadherin-dependent signalling. The interaction of PCDH19's cytoplasmic domains with the GABAa receptor's alpha subunits may change the excitatory-inhibitory balance that underpins epilepsy [2]. PCDH19 modulates channel gating in addition to GABAa receptor surface expression. In fact, PCDH19-mutated cortical neurons show a spontaneous Ca2+ intracellular flow, suggesting that these cells are more excitable. Another notion argues that PCDH19 is involved in the malfunctioning of the Blood-Brain Barrier (BBB). In reality, the gene is abundantly expressed in endothelial cells, and the limbic area, which is proximal to the periventricular region where BBB is lacking, is the epileptic foci. Furthermore, because to the development of BBB, this idea might explain seizure remission with growth. PCHD19 mutations have a wide range of phenotypes, including neurological and mental disorders. Although the most common clinical manifestation of PCDH19 mutation is Epilepsy and Mental Retardation Confined to Females (EFMR), additional major clinical symptoms include Genetic Epilepsy with Febrile Seizures Plus (GEFS+) and epileptic encephalopathies. The goal of this review is to look at the phenotypic manifestation of a PCDH19 gene mutation linked to epilepsy [3].

Epilepsy and mental retardation are only seen in women

Mental Retardation and Epilepsy Female-only epilepsy and mental retardation (EFMR) linked females with epilepsy and cognitive disability. This clinical presentation was only later linked to PCDH19 gene alterations. The brain MRI is typically normal, and the PCDH19 mutation has no unusual Electroencephalographic (EEG) characteristics. It depicts an EEG of a female patient with focal epilepsy and a PCDH19 mutation. Epileptic and non-epileptic symptoms describe the phenotypic manifestation of EFMR. Cluster focal seizures with a predisposition to extended bouts poorly responsive to antiepileptic medication are the defining feature, especially in the early stages of the disease. Early-onset seizures (6-36 months) are common in this child, and they are usually sensitive to fever. Generalized tonic-clonic, tonic, atonic, absences, and myoclonic jerks are all forms of seizures. Epilepsy severity varies greatly, from drug-resistant and progressing types to self-limiting forms. Seizures grow less severe as adolescence progresses, but non-epileptic symptoms are the primary handicaps of adult PCDH19 mutant patients. In 75.4% and 55.4% of patients, respectively, Intellectual Impairment (ID) and behaviour abnormalities are non-epileptic characteristics of EFMR. Only 28.2% of 195 patients with PCDH19 mutations had normal cognitive development, while 27.2, 22.2, and 17.4% had mild, moderate, and severe impairment, respectively. All patients have a delay in acquiring language milestones, and the absence of language before the commencement of the seizure is a possible poor prognostic indicator for cognitive development. Although most individuals show signs of cognitive delay after the age of two, 15% of instances show signs of intellectual disability prior to the beginning of epilepsy. As a result, intellectual disability is only partially linked to epileptic encephalopathy, and other genetic and environmental variables are among the phenotypic spectrum's causes [4]. A cellular interference in heterozygosity appears to be the reason of females' unusual exclusive participation. According to this view, the coexistence of mutant and wild-type cells leads the disease's neural network to be altered. While hemizygotic males are asymptomatic carriers, afflicted mosaic-males have been identified, confirming this notion. Indeed, postzygotic somatic variations in men would provide a picture that resembled that of heterozygous females. For both situations, a mutation penetrance of 80% was calculated. Because of the small number of afflicted individuals, phenotypic characterisation of these patients is challenging. Mosaic-males have phenotypic characteristics that are similar to those of afflicted females [5]. In addition, mental comorbidity has been reported in two males with germline mutations, albeit the link between the mutation and the psychiatric comorbidity is unclear. Several investigations have failed to find a link between genetics and phenotype. Missense variations, rather than loss of function mutations, appear to be more typically linked to normal cognitive development, according to a new study. Whole gene loss appears to be linked to a poorer prognosis as well. Truncating variations from Extracellular Domain 5 (EC5) to the cytoplasmic domain, according to Shibata et al., had a delayed seizure start and less severe intellectual impairment than missense variants and truncating variants from EC1 to EC4. Severity of seizures does not appear to be linked to cognitive impairment. To now, the main negative prognostic variables related with cognitive function are age at seizure start and seizure frequency. Indeed, the processing of new synapses and alterations in the frontal cortex, which occur mostly in the first years of life, may explain this link. Furthermore, the epileptic manifestation, as well as the neuropsychiatric profile, is exceedingly diverse, ranging from moderate to severe forms with autistic, attention-deficit hyperactivity, obsessive, or violent characteristics. Psychiatric comorbidity affects around 25% of people who do not have an intellectual handicap. Furthermore, there is evidence that sleep disturbances are a prevalent symptom in people with EFMR. Sleep disturbances as well as problems with absorption have been noted. A more thorough examination of these illnesses would be beneficial, especially given the link between sleep disruptions and worsening epileptic symptom management. X-inactivation in females might explain some of the considerable variation in phenotypic manifestation of EFMR. However, further research is needed to have a better understanding of the EFMR-related biological processes and to look into any genotype-phenotype relationships.

Dravet-like syndrome

Dravet Syndrome (DS), also known as "severe myoclonic epilepsy of infancy," is one of the most severe inherited epilepsy syndromes that strike children. The typical DS is described by febrile and afebrile seizures in a newborn with normal development in the first year of life, followed by myoclonus, atypical absences, and focal seizures, according to the ILAE classification. Seizures develop drug-resistant, resulting in a bad prognosis for patients with motor, cognitive, and mental impairment. Fever is the most common cause of DS and DS-like seizures, while PCDH19 mutations have less provocation variables for seizure commencement. SCN1A mutations cause clonic and hemiclonic seizures, as well as a greater incidence of generalised tonic-clonic seizures and atypical absences with more prevalent status epilepticus. Seizures linked to PCDH19 mutations are more likely to be focal and hypomotor, with a greater incidence of cluster seizures. Many publications have characterised seizures with affective symptoms and frightened screaming as a defining feature of DS-like. When compared to DS, the DS-like phenotype is less related with photosensitivity. Another important distinction is the time interval between the first and second seizures: 10 months for DS-like *vs.* 2-3 months for DS, owing to the increased frequency of seizures in the first year of life and the earlier start in DS patients. Although no abnormalities have been recorded in interictal EEG, isolated or widespread slow wave, sharp, and polyspike discharges have been described.

Treatment for epilepsy caused by pcdh19

Drug resistance and the lack of specific therapy indications restrict

the treatment of PCDH19-related epilepsy. Due to the normal shifting tendency of seizures and the many cluster triggers, these patients commonly require polytherapy with poor effectiveness. Physicians have a significant problem in managing drug-resistant patients, particularly in syndromes with a diverse seizure aetiology and history. Various drug associations have been investigated, but none has been definitely demonstrated to be superior. However, because familiar mutations have the same responsiveness to Antiseizure Medicine (ASM), pharmacological treatment can be tailored to afflicted people in the same family. Despite DS, sodium channel blockers such lamotrigine and carbamazepine have been demonstrated to reduce seizure aggravation in PCDH-19-related epilepsy. After 3 months of therapy, bromide and clobazam had a greater efficacy in decreasing seizures, with a partial decline in efficacy over long-term follow-up. Valproate and levetiracetam were shown to be among the most effective antiepileptic medicines, with response rates of 61% and 57% after 12 months of therapy, respectively [5]. The efficacy of phenytoin is unknown. Following phenytoin treatment, who reported a significant level of ineffectiveness and seizures increasing? However, given the small number of individuals treated with phenytoin in these investigations, the results' validity is questioned. Stiripentol was utilised in combination to valproate and clobazam in a female patient with PCDH19-related refractory epilepsy with significant success, based on the parallels between DS and PCDH-19-related epilepsy. Stiripentol was later administered as an add-on to valproate and clobazam in six individuals with PCDH-19 linked epilepsy, with a 50% reduction in seizure frequency. It's unclear if the effectiveness shown following stiripentol was attributable to the drug's intrinsic impact or pharmacokinetic interactions that caused clobazam and valproate blood levels to rise. Reduced steroidogenesis has been linked to a mutation in the PCDH19 gene [6]. This idea was confirmed by the discovery of dysregulated AKR1C1-3, a gene implicated in the synthesis of allopregnanolone. The development of seizures with PCDH19 mutation may be linked to a reduction in neuroactive hormones such allopregnanolone, pregnenolone sulphate, 17-OH progesterone, and cortisol. As a result, restoring steroidogenesis may be a treatment target that might help with this disorder's management. Although corticosteroids can be used to manage seizure clusters, they don't have a long-term benefit and come with a substantial risk of recurrence. In a Japanese trial, oral corticosteroid prophylaxis was given during febrile episodes with no recurrence of moderate severe clusters. In 50% of patients, the ketogenic diet had a beneficial effect. Only one example of vagus nerve stimulation was performed, and it resulted in a 75%-90% reduction in seizure frequency after three months, which lasted for a year [7].

CONCLUSION

The advancement of next-generation sequencing tools has allowed us to take diagnosis to a new level, allowing us to identify particular gene variations and examine any genotype-phenotype connections. PCDH19, along with SCN1A, is one of the most important epilepsy genes. In recent years, researchers have focused on the broad phenotypic range of PCDH19-related epilepsy, which has resulted in better and earlier detection of symptoms. More research is needed to better understand the non-epileptic aspects and overall quality of life of these people. To further understand the expression of this gene and its unusual inheritance pattern, researchers should look at examples of hemizygous males with psychiatric symptoms. The majority of PCDH19 mutations are found in the extracellular domain, and include full and partial gene deletion as well as missense, nonsense, and frameshift variants. Several researches have looked at the genotype-phenotype relationship; nevertheless, it is still unclear how distinct gene variants affect clinical symptoms. Protocadherin-19's extracellular domain is recognised to have an important function in cell adhesion and neural architecture. However, this molecule's function extends beyond cell-cell interactions to include essential signal transmission pathways via its intracellular domain. Thus, in order to maximise precision therapeutics aimed at addressing underlying pathophysiology, a better understanding of the molecular processes in which PCDH19 is engaged, as well as how they are affected by the mutations investigated thus far, is required. Finally, PCDH19 should be taken into account while discussing genetic epilepsies. PCDH19 mutation testing is strongly advised for female patients with early-onset seizure clusters, acquaintance with or features comparable with GEFS+ or DS, and instances with cognitive and psychiatric comorbidities.

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