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증 례

뇌전증 유전자 패널 검사를 통해 확인된 PCDH 19 연관 뇌전증 1예

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A Case of Epilepsy with Mental Retardation Limited to Females in a Patient with PCDH19 Mutation Confirmed using an Epilepsy Gene Panel

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PCDH19-related epilepsy is an inherited disease occurring in female patients and characterized by early onset seizure, intellectual disability, and behavioral disturbances. It is caused by de novo or familial heterozygous variation of the PCDH19 gene located on Xq22.1. Our patient was hospitalized for multiple focal seizures. The magnetic resonance imaging was normal and electroencephalogram showed focal epileptiform discharges. The child's development did not progress; she began to manifest, cognitive, behavioral and language delays. Because of that, we performed an epilepsy gene panel test. We report a case of epilepsy with mental retardation limited to female patients with mutation of PCDH19.

Key words: EFMR, PCDH19, X-linked inheritance

Introduction

Epileptic encephalopathies (EEs) were defined by the International League Against Epilepsy (ILAE) in 2001 as epileptic conditions characterized by abnormalities contributing to progressive cognitive and behavioral impairment[1-3]. According to the ILAE, EEs are classified into eight types: early myoclonic encephalopathy; Ohtahara syndrome; West syndrome; Dravet syndrome; myoclonic status in nonprogressive encephalopathies; Lennox-Gastaut syndrome; Landau-Kleffner syndrome; and epilepsy with continuous spike-waves during slow-wave sleep[3]. They are all characterized by recurrent seizures and prominent interictal epileptiform discharges during the early infantile period. The clinical and electroencephalogram (EEG) characteristics of these conditions depend on the age at onset, and may change over time[2]. Recently, high-throughput sequencing methods, such as whole-exome sequencing, have uncovered an expanding number of causative genes for EEs, and epilepsy with mental retardation limited to females(EFMR) is one such condition[4].

EFMR was first reported by Juberg and Hellman, and is also known as early infantile epileptic encephalopathy type 9 (EIEE9, OMIM# 300088)[5]. The typical features of EFMR are divided into

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two stages. First, seizures usually occur in infancy or early childhood, and are fever sensitive. Intellectual disability and behavioral disturbances ensue[5,6]. The main types of seizures in this condition are generalized, partial tonic-clonic, tonic, and clonic. Rarely, atypical absences, atonic seizure, and myoclonic jerks are observed[6,7]. The behavioral problems are often part of the clinical picture, and can manifest with autistic, obsessive, or aggressive features. Intellectual disability is variable, ranging from normal to severe[6-8].

PCDH19-related epilepsy is caused by de novo or familial heterozygous variation in the *PCDH19* gene. The *PCHD19* gene is located on chromosome Xq22.1 and encodes protocadherin 19. Protocadherin 19, in particular, is highly expressed in the developing brain and may play a role in neuronal migration and formation of synaptic connections[9]. We report a case involving a girl with epilepsy and a mutation of the *PCDH19* gene.

Case Report

The patient was of Korean descent and was at born full-term with no other reported perinatal or neonatal complications. Her birth weight was 2.92 kg and newborn screening for 55 diseases at 5 days was normal. She was the second of two children born to non-consanguineous Korean parents. Her older brother had normal developmental status, with no history of seizure.

At 5 months of age, she was first hospitalized due to multiple focal seizures without fever for 4 days. The seizures were controlled with anti-epileptic drugs; she did not experience seizure for approximately 3 months thereafter. After that she was hospitalized approximately every 3-4 months thereafter due to repeated seizures which were usually provoked by fever. During a viral infection with high fever, the patient developed febrile status epilepticus for 1 h. After the fever resolved, recurrent brief seizures were observed over the next several days.

Initial brain magnetic resonance imaging (MRI) analysis was unremarkable. On EEG, spikes and sharp waves were recorded from the left central area. Follow-up EEG at 12 months of age revealed multifocal poly-spikes; however, a subsequent follow-up MRI revealed no abnormalities. At 22 months of age, the patient exhibited minimal changes on EEG, consisting of high-amplitude slow waves and multifocal spikes or polyspikes.

When initially hospitalized, the development was normal and no facial dysmorphism but the patient exhibited mild axial hypotonia. The development did not progress. She had global developmental delay with inability to crawl and stand, and no expressive language.

Due to the possibility of other genetic problems, an epilepsy gene panel was performed. Missense mutation in the *PCDH19* gene was confirmed; more specifically, anonsynonymous single nucleotide variant,c.G361A (p.D121N), at chromosome Xq 22.1.To clearly confirm the result, her parents' Sanger sequencing was requested; however, this was not possible because the patient and her mother did not live together. Starting at approximately one year from the initial diagnosis, clustered seizures occurred every 3-4 months in association with mild upper respiratory infections and fever (38℃). At 36 months of age, the patient, who was being treated on an outpatient basis with sodium valproate, vigabatrin and topiramate, demonstrated some developmental progress, and could walk without assistance and vocalize approximately five words.

Discussion

The patient was diagnosed with EFMR according to the clinical manifestations and a *PCHD19* mutation on genetic testing. The *PCDH19* gene is located at chromosome Xq22.1 and its coding sequence consists of six exons[6,10]. The full length of the *PCDH19* processed messenger RNA is 9,765 nucleotides, which encodes an 1,148 amino acid protein belonging to the δ2 protocadherin subclass of the cadherin superfamily of cell–cell adhesion molecules. The PCDH19 gene contains a signal sequence, six extracellular cadherin (EC) repeats, a transmembrane domain, and a cytoplasmic region with conserved motifs(CM): CM1 and CM2[9]. The extracellular domains appear to be crucial for normal function and the amino acid sequence of the protocadherin EC domains appears to be highly conserved[11]. The gene is highly expressed in the human developing brain, including the amygdala, cortical plate, and subcortical regions[9]. *PCDH19* is a calcium–dependent adhesion protein involved in neural circuit formation during development and the maintenance of normal synaptic circuits[9,12]. *PCDH19* mutations are directly related to epilepsy and/or intellectual disability[11].

Initially, it was believed that EFMR affected only females. Previously, males homozygous for *PCDH19* were generally considered to be unaffected or asymptomatic. However, affected and/or symptomatic cases involving male patients have been reported. The male patients were tested with fluorescence in situ hybridization, confirming mosaic *PCHD19* variant status[7]. A so–called "cellular interference" model has been proposed in some studies. According to this hypothesis, two distinct cell populations exist in the developing brain of humans with *PCDH19*–related epilepsies: mutant cell populations, and those with normal protein. According to this model, the existence of two types of *PCDH19* protein–mutant and normal–interfere with cell–cell communication and manifest clinically as *PCDH19*–related epilepsy. In contrast, individuals with homogeneous cell populations would not develop the disease[7,9]. According to this model, only the heterozygous state has harmful effects on patients.

The majority of the reported *PCDH19* mutations have been observed in the extracellular domain of the protein encoded by exon 1. Missense variants are the most frequently reported type of *PCDH19* mutation[6,10]. Our patient had a missense mutation located atc.G361A (p.D121N) on exon 1 of the *PCDH19* gene. Although not confirmed by Sanger sequencing, we used a reference site to confirm that the mutation was the likely pathogen (https://www.ncbi.nlm.nih.gov/). Additionally, in a study by Depienne et al. in 2009, there was a missense mutation in the same location (NM_001184880)[10]. The phenotype of patients with the *PCDH19* gene mutation is EFMR.

Clinical manifestations of patients with the PCDH–related epilepsy include seizures, intellectual disability, and behavioral disturbances. The seizures are early onset, clustered, and fever–sensitive[6,13]. Because of the manifestations, *PCDH19*–related epilepsy was initially believed to be similar to severe myoclonic epilepsy of infancy, known as Dravet syndrome. However, genetic testing did not reveal an SCN1A mutation[7,10,14]. The seizures are typically brief, lasting 1–5 min, and recur >10 times per day for several days; status epilepticus is not common[7,8]. Our patient also experienced recurrent cluster seizures and was hospitalized several times. Intellectual deficiency is highly variable, ranging from normal to severe. The cognitive prognosis is not related to epilepsy severity[6–8]. *PCDH19*–related epilepsy patients commonly

exhibit features of language delay and behavioral disturbances, including anxiety, obsessive–compulsive disorders, aggression, and social withdrawal[6–8]. In 2008, a study by Scheffer et al. reported severely affected female patients who were able to walk without assistance, feed themselves, and followed simple commands[15]. Some patients had autism spectrum disorders and obsessive conditions. One woman had both autism spectrum disorder and obsessive–compulsive disorder [15]. As these studies demonstrate, the clinical features of *PCDH19*–related epilepsy are varied and the spectrum is broad, ranging from normal to severe disability.

Because *PCDH19*–related epilepsy with seizure onset during the first year of life can have a variable presentation[2]; appropriate genetic testing, including an epilepsy gene panel, should be considered in infants with possible EE. EEs are related to structural brain problems and inherited metabolic disorders. However, many gene mutations, including those in *PCDH19*, are associated with early onset EE[16].

Intractable epilepsy usually begins in infancy or young age, and is associated with developmental delay and cognitive dysfunction. It may be caused by conditions such as hypoxic–ischemic encephalopathy and brain malformation; however, there are many other causes. For this reason, many researchers have speculated about an underlying genetic etiology. Copy number variants (CNVs) and other mutations have been identified by array comparative genomic hybridization (aCGH)[17]. However, the pathogenicity of CNVs can be unclear, because of the lower yield of aCGH, and the definitive diagnostic yield is <5% [18]. The panels can include many genes selected for a specific phenotype with >400 genes for clinically heterogeneous conditions. Usually, panel tests consist of approximately 100 genes, and the diagnostic yield is 15% to 25%[18]. Recently, in EE patients, the most commonly used method is the gene panel test[16]. Epilepsy gene panels can be used when specific phenotype–genotype correlation or non–specific causes is proposed. It usually takes 3–6 weeks to diagnosis. It targeted enrichment for a small number of genes specific for a certain epilepsy syndrome or a large number of genes (>100) for general epilepsy/seizures symptoms. 19 Gene panels include only previously identified genes; if the conditions are caused by an unknown gene, this could lead to missed diagnoses. Despite this disadvantage, in comparison to other methods that may enable the screening of only one gene at a time, expensive, and/or have a long turn–around time, gene panels are cost–effective and timesaving. Therefore, this approach is useful in patients with EEs, which are difficult to diagnose due to the multiple possible genes involved[16].

Next–generation sequencing (NGS), also known as high–throughput sequencing, can analyze thousands of genes in a single reaction. It uses a targeted gene panel directed at the patient's disease phenotype. Accordingly, epilepsy gene panel testing using NGS can be useful to diagnose epilepsy syndromes with their multiple associated genetic mutations[16]. *PCDH19*–related epilepsy should be considered in female patients with infantile uncontrolled cluster seizures and developmental delay without facial deformity, abnormalities in patients with epileptic encephalopathy, developmental delay, and uncontrolled seizure can be confirmed by gene panel testing.

요 약

EFMR은 뇌전증을 보이는 여자 환자에게서 지적장

애가 동반된 것이 특징적인데 이들 중 PCDH19 변이와 연관이 있는 경우를 PCDH19 연관성 뇌전증으로 분류하였다. *PCDH19* 연관성 뇌전증은 조기에 발병하며 열에 민감하고 잘 조절되지 않는 군집발작을 보이는 것이 특징이다. 발달장애나 인지 및 행동장애를 동반할 수 있으며 정상에서부터 중증까지 다양하게 나타날 수 있다. 최근 이러한 질환에서 유전적 원인을 찾고자 하는 노력으로 뇌전증 유전자 패널을 이용하는 경우가 많아지고 있다. 저자들은 EFMR 환자에서 뇌전증 유전자 패널을 이용한 유전자 검사상 *PCDH19* 돌연변이가 확인된 사례를 경험하였기에 보고하는 바이다.

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