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Case Report

Epilepsy and Mental Retardation Restricted to Females (EFMR Syndrome) in a Child: PCDH19 Mutation with Pathogenic Heterogenous Variant C. 1720G>T

Stefan Bittmann[1*], Elisabeth Luchter[2], Lara Bittmann[2] and Gloria Villalon[2]

[1]Visiting Professor, MD, MA, PhD, Head of Ped Mind Institute, Visiting Professor (SVCT, Shangluo, China), Ped Mind Institute (PMI), Department of Pediatrics, Medical and Finance Center Epe, Gronau, Germany

[2]Ped Mind Institute (PMI), Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany

[*]**Corresponding Author:** Stefan Bittmann, [1]Visiting Professor, MD, MA, PhD, Head of Ped Mind Institute, Visiting Professor (SVCT, Shangluo, China), Ped Mind Institute (PMI), Department of Pediatrics, Medical and Finance Center Epe, Gronau, Germany.

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Abstract

An epilepsy with intelligence impairment, restricted to the female sex, is a rare X-linked epilepsy syndrome called EFMR syndrome. It is characterized by febrile or afebrile seizures, mainly tonic-clonic, but also absence, myoclonic, and atonic. Seizures are beginning in the first years of life and developmental delay and intelligence impairment of varying severity is found. Behavioral disorders with autistic traits, hyperactivity and aggressiveness are also commonly associated. This disease exclusively affects females. Male carriers are not affected despite an X-linked inheritance. The authors present the first pediatric case of a PCDH19 mutation with pathogenic heterogenous variant c. 1720G>T to date.

Keywords: Epilepsy; Female; Child; PCDH19 mutation.

Introduction

X-linked epilepsy with mental retardation, also known as epilepsy and mental retardation limited to females (EFMR), was described as early as 1971 based on a family of 15 affected female patients. In 2008, the gene locus was localized to chromosome Xq22 in additional families. First seizures occurred before 14 months of age and were often associated with fever. Seizure types included tonic-clonic, tonic, partial, atonic, myoclonic, and absences. Developmental delay and intelligence development can be highly

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variable. The cause of X-linked epilepsy with intellectual disability is pathogenic variants in the gene for protocadherin 9 (PCDH19). Protocadherin 9 is expressed during brain development and represents the first member of the cadherin family to be altered in epilepsy and mental retardation. To date, more than 200 different pathogenic PCDH19 variants have now been described. Genomic deletions within the Xq22.1 region involving the entire PCDH19 gene or multiple exons have been identified in 3% of female patients. Only heterozygous carriers of pathogenic variants are affected, whereas hemizygous male carriers are asymptomatic. This unusual mode of inheritance of an X-linked disease is termed cellular interference. While clinically inconspicuous male carriers only have cells with pathogenic PCDH19 variants, the presence of cells with and without pathogenic PCDH19 variants in the female organism creates mosaics due to random X inactivation, which only then become pathogenic. Isolated symptomatic male patients with a pathogenic PCDH19 variant have been described in the literature, in which these were also present as mosaics. This confirms the mechanism according to which cells with and without a pathogenic variant must be present for disease development. The authors present the first pediatric case of a PCDH19 mutation with an atypical heterogenous variant c. 1720G>T to date.

Case Report

The patient is the second child of the parents. Birth in the 37 + 3rd week of pregnancy by section. Birth weight was 3000 g, body length was 49 cm, head circumference was 34 cm. Umbilical artery pH was measured with pH 7.31 and Apgar score was 6/9/10. Developmental history and socio-emotional aspects showed following results makes eye contact, fixates, recognizes people familiar to the patient. Speech/Communication skills showed: Spells, cries, turns head to familiar voices and sticks out tongue. Cognitive analysis revealed opens mouth when looking at bottle and breast food and puts things in mouth. When feeling full, the patient sticks tongue out or presses mouth together. Motor skills are with good head control, holds toys with hands. Regular medication was vitamin D 500 IU, 1 x/day. Vaccinations were performed with 2 x Hexyon, 2 x Prevenar13, 2 x Rotarix.

Clinical examination findings were as followed with Integument bland; no exanthema was found. Eutrophic fat pad differentiation. Enorally no irritation was present. Neck was freely mobile. Pulmo was ventilated on both sides. Cor heart sounds were pure and rhythmic as far as can be judged in a crying child. Inguinal pulses were palpable on both sides. Abdomen was soft with no tenderness, no guarding, no hepatosplenomegaly, whereas bowel sounds were regular.

Genitals presented as female non-irritant, Tanner stages were PH 1, B 1. Neurology showed good head control, reaches for objects, attempts to go into forearm support. Muscle reflexes like BSR, PSR and ASR were symmetrically triggerable. Moro was negative. Fontanelle was soft and in level. Syndactyly of the 2nd and 3rd toes on both sides were found. Body weight was 7350 g (84th percentile) and body length 64 cm (58th percentile).

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Discussion

Mutations in PCDH19 can cause developmental delay of varying severity [1-12]. Developmental regression is also observed in approximately 50% of patients, although normal development has been described in some patients [1-12]. Moreover, in mutations in the above gene, seizures are typical, which may be convulsive, tonic-clonic, focal, atonic, myoclonic [1-12]. In addition, affected women show different psychiatric manifestations such as symptoms from the autism spectrum form, aggression, and obsessive-compulsive behavior. The penetrance of pathogenic PCDH19 variants is estimated to be about 90% [3,4,8,10]. The non-penetrance of the remaining 10% has not been definitively determined. EFMR (Epilepsy and mental retardation limited to females), also known as Juberg-Hellman syndrome, is a disorder with an X-linked inheritance pattern and an unusual sex-limited expression pattern [8,9,11]. Like Dravet syndrome, it is classified as an early infantile epileptic encephalopathy (EIEE9) [MIM 30088]. Typically, an X-linked inheritance is expressed by affected males and non-affected females who are heterozygous for this trait [2,3,8,9]. In the case of the EFMR inheritance pattern, it is exactly the opposite: the stem tree of diseased patients falls through exclusively diseased women in non-diseased males. EFMR was first described by Juberg and Hellman in 1971 in a North American family [1-12]. In this family, it was noticed that the female members had seizure onset in infancy and subsequently showed developmental regression with mild to profound intellectual impairments. The average age at seizure onset was about 14 months. Seizures are described as afebrile focal and generalized tonic-clonic, with seizure frequency gradually increasing. Scheffer et al. studied the clinical picture of 27 girls and women from four different families suffering from EFMR. Researchers found tonic-clonic focal and general seizures, absences, myoclonic, tonic, and atonic seizures. Sixty-three percent of these seizures developed with fever. At an average age of 12 years, the seizures arrested. In addition, Scheffer concluded that developmental regression varied widely. Thus, developmental regression may occur with the first seizure or only within the second to fourth year of life, or there may be nonnormal development from birth [13]. The majority of patients with EFMR are mildly to severely intellectually impaired, and only two out of twenty women are normally gifted. In addition, female patients with EFMR show psychiatric abnormalities, including autism-spectrum disorders and compulsions. Overall, the clinical symptoms of EFMR are difficult to delineate because they vary widely and thus overlap with other disorders, such as Rett syndrome, attention deficit disorder (ADHD), and various forms of epilepsies. In 2008, 737 genes of the X chromosome were sequenced and different mutations in the PCDH19 gene were discovered in seven families with members suffering from EFMR, so that mutations in the PCDH19 gene can be assumed to be the cause of this disorder.

The EFMR caused by a PCDH19 mutation is very similar to Dravet syndrome. Both are associated with febrile seizures, but they differ slightly in the mean age of the first seizure; on average, the seizure in EFMR

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occurs about five and a half months later (6.3 months versus 11.9 months). In addition, both status epilepticus and the occurrence of myoclonia are much less frequent in EFMR. While 92% of Dravet syndrome patients have experienced status epilepticus, status epilepticus occurs in approximately 33% of EFMR patients. In contrast, in EFMR, clustering of seizures occurs more frequently within a short period of time, whereas this phenomenon is much less common in Dravet syndrome. Overall, the prognosis of PCDH19 -positive patients seems more favorable than that of SCN1A-positive patients; in PCDH19 patients, remission of seizures usually occurs at puberty, whereas SCN1A patients have a high mortality rate and epileptic seizures in adulthood. EFMR patients are characterized by a higher variability in their cognitive faculties, up to one-third of the girls have a normal intellect, and the rest are mildly to moderately impaired, in contrast to patients with Dravet syndrome, who are mostly harder cognitively. However, severe cases of mental impairment can occur in both. Autistic features again occur more often in EFMR [1-13]. In addition to autistic features, compulsive and aggressive behaviors may occur. In some patients, social withdrawal plays the greatest role among the features of the disease, especially as patients become older. Neurological abnormalities such as ataxias can occur equally in both Dravet syndrome and EFMR. In addition, a strong sensitivity to light in the EEG (photosensitivity) is frequently reported in Dravet syndrome patients, whereas it does not occur in EFMR. In conclusion, EFMR is a very rare disease in childhood with a very low incidence worldwide [1-13]. In conclusion, EFMR syndrome is very rare in childhood. To date, more than 200 different pathogenic PCDH19 variants have been described. Genomic deletions within the Xq22.1 region involving the entire PCDH19 gene or multiple exons have been identified in 3% of female patients.

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