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EFMR Syndrome: Epilepsy and Mental Retardation Restricted to Females in Childhood

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

Epilepsy with intelligence impairment, restricted to the female sex, is a rare X-linked epilepsy syndrome. It is characterized by febrile or afebrile seizures, mainly tonic-clonic, but also absence, myoclonic, and atonic beginning in the first years of life. In most cases, developmental delay and intelligence impairment of varying severity is present. Behavioral disorders, autistic traits, hyperactivity, and aggressiveness are commonly associated. This disease exclusively affects females. Male carriers are not affected despite an X-linked inheritance.

Keywords: EFMR; PCDH19; children; mutation; epilepsy.

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1. INTRODUCTION

An epilepsy with intelligence impairment, focused to the female sex, is a rare X-chromosomal epilepsy syndrome described as EFMR syndrome [1-6]. It is based on febrile or afebrile seizures, tonic-clonic aspect, but also absental, myoclonic aspect, and atonic features are described [1,7,8]. Seizures start in the first years of life and developmental problems and low intelligence level of varying severity is present. Behavioral disturbances with autistic features, hyperactivity signs and aggressiveness in behaviour are also commonly found [9,10]. This disease exclusively is present in females [11,1,9,2,3,12,7,13,8,14,15,4,16-21]. Male carriers are not ill despite an X-chromosomal inheritance [11,1,9,2,3,12,7,13,8,14,15,4,16-21-28,5,6,10,29,30]. X-chromosomal epilepsy with mental retardation, also known as epilepsy and mental retardation limited to females (EFMR), was described in 1971 based on a gross family of 15 female children [7]. In 2008, the gene focus was localized to chromosome Xq22 in further familial analysis. First seizures occur normally before 14 months of age and were often associated with fever signs. Seizure includes tonic-clonic, tonic, partial, atonic, myoclonic features, and absences. Developmental delay and intelligence development can be highly variying [2,8,4,18]. The cause of X-linked epilepsy with intellectual disability is found in pathological variants in the gene for protocadherin 9 (PCDH19) [1,2,3]. Protocadherin 9 shows it expression during brain development and represents on of the first members of cadherin family to be changed in epilepsy and mental impairment [1,2,3]. More than 200 different pathogenic PCDH19 variants have now been described [1,2,3]. Genomic deletions are found in the Xq22.1 region with the entire PCDH19 gene or multiple affected exon regions have been found in 3% of female patients [8]. Heterozygous carriers of pathogenic variants of the disease are affected, whereas hemizygous male carriers are frequently asymptomatic. It is an untypical mode of inheritance of an X-chromosomal 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 through random X-inactivation, which only then become pathogenic. In the literature, isolated symptomatic male patients with a pathogenic PCDH19 variant have been described 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. Mutations in PCDH19 can cause developmental delays of varying severity [11,1,9,2,3,12,7,13,8,14,15,4]. Developmental regression is also observed in about 50 % of patients, although normal development has been described in some patients [v. In addition, seizures are typical of mutations in the above gene and may be convulsive, tonic-clonic, focal, atonic or myoclonic [1-12,17,18,20,21]. In addition, affected women show various psychiatric manifestations such as symptoms from the autism spectrum, aggression and compulsive behaviour [13,17,25]. The penetrance of the pathogenic PCDH19 variants is estimated to be about 90% [9,2,13,14, 26,27,28]. The non-penetrance of the remaining 10% has not yet been definitively clarified.

2. EFMR SYNDROME

Like Dravet syndrome, it is classified as an early infantile epileptic encephalopathy (EIEE9) [MIM 30088] [6,10,19]. Typically, an X-linked inheritance pattern is expressed by affected males and unaffected females who are heterozygous for this trait [1,9,13,8,18,22]. In the case of the EFMR inheritance pattern, it is the other way around: the pedigree of affected patients falls through exclusively affected females into unaffected males. EFMR was first described in 1971 by Juberg and Hellman in a North American family [11,1,9,2,3,12,7,13,8,14]. In this family, female members were found to have seizure onset in infancy followed by developmental regression with mild to severe intellectual impairment. The average age at seizure onset was approximately 14 months [11,1,9,2,3,12,7,13,8,14,15,4,16-21-28,5,6,10,29, 30]. The seizures are described as afebrile focal and generalized tonic-clonic seizures, with a gradual increase in seizure frequency [9,2, 13,29,30]. Scheffer et al. studied the clinical picture of 27 girls and women from four different families suffering from EFMR. They found tonic-clonic focal and generalized seizures, absences, myoclonic, tonic, and atonic seizures. Sixty-three percent of these seizures occurred with fever. At an average age of 12 years, the seizures ceased. In addition, Scheffer found that developmental regressions varied widely.

Furthermore, both status epilepticus and the occurrence of myoclonia are much less frequent in EFMR. While 92% of patients with Dravet

syndrome have experienced status epilepticus, status epilepticus occurs in approximately 33% of EFMR patients [12]. In contrast, a cluster of seizures within a short period of time is more common in EFMR, whereas this phenomenon is much less common in Dravet syndrome. Overall, the prognosis of PCDH19-positive patients appears to be more favorable than that of SCN1A-positive patients; PCDH19 patients usually experience seizure remission at puberty, whereas SCN1A patients have a high mortality rate and epileptic seizures in adulthood. EFMR patients are characterized by greater variability in their cognitive abilities, with up to one-third of girls having normal intellect and the remainder mildly to moderately impaired, in contrast to patients with Dravet syndrome, who are usually more difficult cognitively. Severe cases of intellectual impairment, however, can occur in both. Autistic features are again more common in EFMR [13]. In addition to autistic features, compulsive and aggressive behaviors may occur [13,8]. In some patients, social withdrawal plays the greatest role among the disease features, especially as patients grow older. As a therapy, left lobectomy was performed successfully in a 2 years old child [11]. Levitiracetam therapy showed efficacy in PCDH19 girls [29].

3. CONCLUSION

EFMR syndrome is a difficult to treat epilepsy of the female population. Differentiation must be made with patients with Dravet syndrome. The cure of EFMR syndrome should be focused on gene therapy and mutation repair like CRISP/CAS 9 technology or other curing therapies. Therefore, more intensive research is necessary in this rare population of female children.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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