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BRIEF REPORT

How do We Treat CDKL5 Disorder in Children?

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ABSTRACT

CDKL5 is a very rare genetic disorder of the X chromosome that causes difficult-to-control epilepsy and severe developmental delays in the first months of life. Internationally, in addition to the genetic name "CDKL5", "CDD" (for CDKL5 deficiency disorder) has become the established name for the disorder. Although CDKL5 is extremely rare, thanks to novel genetic tests, more and more affected children (and also adults who previously could not be correctly diagnosed) now have the chance of an early diagnosis. CDKL5 is now shown to be one of the most common genetic causes of severe early childhood epilepsy worldwide.

KEYWORDS

CDKL5; Genetic disorder; Epilepsy; Neurodevelopmental disorder

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It was not until 2004 that a second gene was discovered whose mutations cause an atypical form of Rett syndrome: Mutations in the CDKL5 gene (cyclin-dependent kinase like-5). In the following years, it became clear that patients with mutations in the CDKL5 gene have similarities to classic Rett syndrome, but also differences, so it was accepted to be treated as a separate neurodevelopmental disorder [1,3]. CDKL5 disorder is defined as defect of the cyclin dependant kinase like 5 and described as epileptic encephalopathy [1-5]. The incidence ranges from 1:40000-1:60000 [1-5]. It is described as early life epilepsy with abnormal synaptic physiology [1-5]. The gene location is found on 27 exons on short arm of X-chromosome. The CDKL5 protein is found in cerebral cortex, hippocampus, cerebellum, thalamus and brain stem [2,4,5]. The female/male ratio is 4:1 [1-5]. Females appear as heterozygote, males as hemizygote. 265 different pathogenic variants of the CDKL5 gene are known. Moreover, this are point mutations, de novo-, missense and frameshift mutations [5]. CDKL5 influences different pathways, the AKT-mTOR-, AKT/GSK 3 b- and the BDNF-Rac-1 signaling pathway [4,5]. Moreover, CDKL5 plays an important role of NGL-1-PSD 95 interaction and microtubuli development [2-5]. CDKL5 substrates in the brain are MeCP2, DNMT1, Rac1, Amphiphysin 1, PSD 95, NGL-1, Mind Bomb 1, Shoot in 1, HDAC 4 and IQGAP1 [1-5]. CDKL5 protein influences the neuronal and dendritic growth and excitatory functions in the

synaptic gap. A possibly elevation of NMDA glutamate receptors and AMPAR receptors in the synaptic gap will be discussed, therefore synaptic overexcitation could play an important pathophysiologic role in this ultrarare disease [4]. Symptoms are recurrent epileptical seizures, microcephalus, global developmental delay, speech developmental delay, autism, sleep disorder, cortical visual impairment, hand stereotypies, gastrointestinal problems and SUDEP (sudden infant death in epilepsy). Epileptic seizures generally begin by 6 weeks of age, and approximately 90% of affected CDKL5 patients struggle with these seizures daily. Treatment of seizures generally involves the use of 3 or more antiepileptic drugs (average 6 antiepileptic drugs). Other commonly used treatment alternatives that CDKL5 patients have tried include ketogenic diet and vagus nerve stimulation of the left nervus vagus. Recurrent, sometimes daily seizure episodes remain a serious complication for the most children with CDKL5 disorder. Innovative new research aspects include U1-sn-RNA-based splicing therapy, deep brain stimulation of fornix, CDKL5 protein substitution, the establishment of excitatory and inhibitory balance in the synaptic gap and microtubuli targeting agents. An important role for future treatment could play a gene therapy with AAV-mediated gene transfer of CDKL5, which was recently successfully performed in mice model [5]. An adequate therapy of this rare disease in childhood is still not found.

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