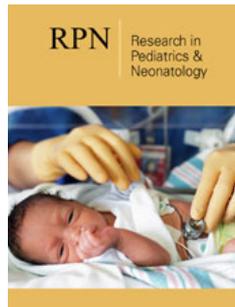Mini Review

The Genetic Architecture of CDKL5 Disorder in Childhood

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Introduction

In 2004, a second gene was discovered whose mutations induce an atypical form of Rett syndrome, mutations in the CDKL5 gene. In the following period, it became clear that children with mutations in the CDKL5 gene have similar symptoms to classic Rett syndrome, but also differences, so it was stated to be treated as a neurodevelopmental disorder with an own entity [1-16]. CDKL5 disorder is defined as defect of the cyclin dependent kinase like 5 and defined as a difficult to treat epileptic encephalopathy [1-16]. Incidence varies from 1:40000-1:60000 [2-7, 9-16]. It is defined as early life difficult to treat epilepsy with abberant synaptic physiology. The CDKL5 protein is found in the cortex of the cerebrum, hippocampal areas like the fornix, the cerebellum, thalamic areas and the brain stem [4,5]. The female/male distribution is predominant in females with a 4:1 ratio [1-16]. Females are most often heterozygote, males are hemizygote. Up to 270 different pathological variants of the CDKL5 gene are still described [15,16]. Point mutations, de novo-, missense and frameshift mutations were found [1-16]. The gene is found on 27 exons, whereas 6 are undefined and 21 expiring exons of the CDKL5 gene [2,3,6,8,16].

CDKL5 protein plays a major role in neuronal and dendritic growth and excitatory functions in the synaptic gap [1-16]. CDKL5 influences different pathways: the AKT-mTOR signaling pathway, the AKT/GSK 3 b signaling pathway, the BDNF-Rac-1 signaling pathway, the NGL-1-PSD 95 interaction and the microtubule development. CDKL5 Substrate in the brain are MeCP2, DNMT1, Rac1, Amphyphsin 1, PSD 95, NGL-1, Mind Bomb 1, Shoot in 1, HDAC 4 and IQGAP1 [3,6,7,9,12]. Symptoms are epileptic seizures, microcephalus, global developmental delay, speech developmental delay, autism, sleeping disorder, cortical visual impairment, hand stereotypies, gastrointestinal problems and SUDEP (sudden infant death in epilepsy) [1-16]. Patients with the CDKL5 gene defect show severe motor and cognitive developmental disorders shortly after birth. The majority of affected children develop severe epileptic seizures, among other symptoms [4,5]. Epileptic seizures generally begin by 6 weeks of age, and approximately 90% of affected CDKL5 patients struggle with these seizures daily [1-16]. Interesting new treatment approaches were summarized in detail in Table 1.

Table 1: Study Aspects of new therapy options for CDKL5 disorder in childhood.

Virus mediatr gene transfer (AAV-gene transfer of CDKL5)	Virus-mediated gene transfer with adenovirus vector, previously mannitol 25 percent, intrajugular or intrathecal attempts to apply with overcoming blood brain barrier ([17], Mice).
CDKL5-protein-substitution (TAT-CDKL5-fusion protein)	Therapeutic options are CDKL5-protein-substitution (TAT-CDKL5-fusion protein)
	It has been reported that a protein transduction domain (TAT) is able to deliver macromolecules into cells and even into the brain when fused to a given protein. TAT-CDKL5 fusion protein were efficiently internalized by target cells and retains CDKL5 activity. Intracerebroventricular infusion of TAT-CDKL5 restored hippocampal development, hippocampus-dependent memory and breathing pattern in Cdkl5-null mice. Notably, systemically administered TAT-CDKL5 protein passed the blood–brain-barrier, reached the CNS, and rescued various neuroanatomical and behavioral defects, including breathing pattern and visual responses.
Establishing excitatory/inhibitory balance in the synaptic gap	IEM-1460
	Targeting Glutamatergic Pathways with Amelioration of recurrent seizures:
	Competitive, selective, voltage-dependent open-channel Ca2+permeable GluA2 (GluR2)-lacking AMPA receptor blocker (IC50 values are 2.6 and 1102 μM at GluA2-lacking and GluA2-containing AMPARs respectively). IEM-1460 can be utilized as an indicator of the distribution of AMPA receptor subtypes among populations of brain cells. IEM-1460 can also be used to selectively target GABAergic interneurons, as several subpopulations of these neurons express a significant proportion of GluA2-lacking Ca2+-permeable AMPARs. IEM-1460 blocks synaptic excitation of fast-spiking interneurons and blocks NMDAR-mediated currents. IEM-1460 shows anticonvulsant properties.
Ganaxolone	high affinity allosteric modulator of GABARs that act to restore the balance of excitation and inhibition
TAK-935	Cholesterol 24 hydroxylase involved in over activation of the glutamatergic pathway through modulation of the NMDA channel, suggesting a potential role in epilepsy.
GSK 3 Beta/HDAC Dual Inhibitors	Tidegulsib
	C11-Compound 11
	Restores neuronal survive and maturation in CDKL5 KO Mice Model
NMDA-Rezeptor Modulators	Allopregnanolone
	Trianeptine
Mikrotubuli-targeting Agents	Paclitaxel
	Epothilone D (Epo D)
	NAP/Davunetide

Other commonly used treatment alternatives that CDKL5 patients have tried over the years include the ketogenic diet, one-third of CDKL5 patients have tried this method at least once. Vagus nerve stimulation have tried 20 per cent of all pediatric patients with CDKL5 disorder with different success. Treatment of epilepsy generally involves the use of 3 or more antiepileptic drugs with an average of 6 antiepileptic drugs. Other commonly used treatment alternatives that CDKL5 patients have tried over the years include the ketogenic diet. One-third of CDKL5 patients have tried this method at least once and vagus nerve stimulation. Approximately 20% CDKL5 patients have tried this method. However, epilepsy remains a serious complication for most people with CDKL5 disorder. Other commonly used treatment alternatives that CDKL5 patients have tried over the years include the ketogenic diet (one-third of CDKL5 patients have tried this method at least once) and vagus nerve stimulation (approximately 20% CDKL5 patients have tried this method). However, epilepsy remains a serious complication for most people with CDKL5 disorder.

Pharmacologic studies on Ataluren were initiated but only in nonsense mutation of the disease. Ataluren does not effectively cross the brain barrier. Fenfluramine is useful in Dravet syndrome and could be helpful in CDKL5 disorder, but its role is still not ruled out completely in pharmacological trials. Sabril (Vigabatrin), Valproat and Cortisone were frequently used in CDKL5 disorder patients. To establish excitatory and inhibitory balance in the synaptic gap to target the glutaminergic pathway, studies on NMDA and AMPAR blockers were initiated (IEM-1460, Ganaxolone, TAK-935, Tidegusib, Compound-11, Allopregnanolone, Trianeptine). Nevertheless, CDKL5 protein substitution with TAT-CDKL5 fusion proteins are interesting research aspects for the future [1-16].

A few studies focus on deep brain stimulation of fornix structures of the hippocampus to restore hippocampal areas were evaluated and published. Nevertheless, green tea application, epigallocatechin-3-gallate, was used to restore CDKL5 dependent synaptical defects in vitro and in vivo. Microtubuli targeting agents like Paclitaxel, Epothilone D (Epo D) and NAP/Davunetide play a significant role in the disease and could diminish the degree of neuronal and dendritic impairment of CDKL5 gene dysfunction. Gene therapeutics cure the patient, but this is still in childhood shoes. The study by Gao et al. [17] published in Brain 2020, is a

promising attempt to repair mutated genes by AAV transfer of CDKL5 [17]. Further studies in rodents and preclinical gene transfer studies must follow to develop the aspect of gene transfer to help the children with CDKL5 disorder to master their life without these incisive developmental complications in childhood.

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