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Unraveling the complexities of CDKL5 deficiency disorder: Is an emerging treatment on the horizon?

Odkrywanie złożoności encefalopatii rozwojowej i padaczkowej związanej z genem CDKL5 — czy na horyzoncie pojawiła się nowa terapia?

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ABSTRACT

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental and epileptic encephalopathy in which epilepsy and impaired development are prominent features. Previously, CDD was considered a variant of Rett syndrome (Hanefeld variant). However, it is now recognized as an independent clinical entity. It is characterized by early-onset epilepsy, typically occurring within 3 months of age in majority of cases and presenting with polymorphic seizures. Severely impaired development leads to only a small percentage of affected patients achieving independent walking. Other notable clinical features include cortical visual impairment, sleep disturbances, stereotypical hand movements, hypotonia, gastrointestinal problems, scoliosis and respiratory tract infections. The management of epilepsy in CDD is highly demanding due to its refractory nature. The results of conventional antiseizure management have been disappointing, exhibiting minimal or transient clinical effects. Alternative treatments like the ketogenic diet and vagus nerve stimulation have shown limited efficacy. However, new treatment options, such as ganaxolone are emerging and the results seem promising. Further research is needed to explore the potential of other treatments such as soticlestat, fenfluramine and cannabidiol, particularly in larger cohorts.

CDD is a multifaceted disorder and its underlying mechanisms remain incompletely elucidated. Further research is needed to better understand the pathological processes of the disorder and to develop more effective treatments for individuals with CDD. Healthcare professionals should be aware of the clinical symptoms and challenges associated with CDD to provide appropriate care and support to individuals affected by this complex disorder.

Keywords: Cyclin-depedent kinase-like 5, CDKL5 deficiency, epilepsy, ganaxolone

STRESZCZENIE

Encefalopatia padaczkowa i rozwojowa związana z genem CDKL5, czyli deficyt kinazy cyklino-zależnej typu 5 (CDD, *CDKL5 deficiency disorder*), manifestuje się napadami padaczkowymi oraz istotnym opóźnieniem w rozwoju psychorucho-wym. Wcześniej uważano CDD za wariant zespołu Retta (wariant Hanefelda), aktualnie jednak jest uznawany jako odrębna jednostka kliniczna. CDD charakteryzuje się wczesnym występowaniem padaczki, zwykle w ciągu pierwszych 3 miesięcy życia. Napady mają charakter polimorficzny. Rozwój psychoruchowy jest znacznie upośledzony; jedynie niewielki odsetek pacjentów potrafi chodzić samodzielnie. Inne istotne cechy kliniczne to korowe upośledzenie widzenia, zaburzenia snu, stereotypowe ruchy rąk, hipotonia, problemy gastroenterologiczne, skolioza oraz infekcje dróg oddechowych. Znaczna lekooporność sprawia, że leczenie jest wyjątkowo wymagające. Wyniki konwencjonalnego leczenia przeciwnapadowego są rozczarowujące, dają jedynie minimalne albo krótkotrwałe rezultaty. Alternatywne metody leczenia, takie jak dieta ketogenna i stymulacja nerwu błędnego, wykazują również ograniczoną skuteczność. Dostępne są jednak nowe możliwości terapeutyczne, takie jak ganaxolone, którego wyniki w zakresie leczenia przeciwnapadowego wydają się obiecujące. Konieczne jest również dalsze badanie potencjału innych leków, takich jak soticlestat, fenfluramina i kannabidiol, zwłaszcza na większych kohortach.

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Encefalopatia padaczkowa i rozwojowa i związana z genem *CDKL5* to złożone zaburzenie o wielu aspektach, a mechanizmy leżące u jego podstaw nie zostały w dalszym ciągu w pełni wyjaśnione. Konieczne jest dalsze badanie procesów patologicznych towarzyszących temu zaburzeniu oraz opracowanie skuteczniejszych metod leczenia. Klinicyści powinni być świadomi objawów chorobowych i wyzwań terapeutycznych, aby zapewnić odpowiednią opiekę i wsparcie osobom dotkniętym tym złożonym schorzeniem.

Słowa kluczowe: kinaza cyklino-zależna typu 5, encefalopatia padaczkowa i rozwojowa związana z genem CDKL5, deficyt kinazy cyklino-zależnej typu 5,, padaczka, ganaxolone

INTRODUCTION

Cyclin-dependent kinase-like 5 (CDKL5) plays a crucial role in the morphogenesis and development of the central nervous system (CNS). It exhibits high expression in the CNS, particularly in cerebral cortex and hippocampus during fast development in the peri- and postnatal stages [1]. CDKL5 appears to have an important role in proliferation, neuronal migration and formation, as well as in synaptic development and plasticity [2]. Cytoplasmic CDKL5 also influences the growth and branching of dendrites, contributing to the formation of complex neuronal networks [2, 3].

The Cyclin-dependent kinase-like 5 (CDKL5) gene was first identified in 2004 [4], and its pathogenic variants were initially associated with a variant of Rett syndrome (Hanefeld variant) [5]. However, nowadays, it has been recognized as an independent clinical entity. Based on available data from molecular studies, it appears that CDKL5 phosphorylates the product of the MECP2 gene, which pathogenic variants constitute etiology of Rett syndrome in most cases. This suggests a common signaling pathway that may explain the similarities between these disorders [6, 7]. CDD is a rare disease, making it challenging to evaluate its frequency of occurrence. According to studies its estimated prevalence is one to 40,000–60,000 livebirths [8, 9]. CDD is an X-linked developmental and epileptic encephalopathy. Due to the rarity of CDD, an international CDKL5 Disorder Database was established in 2012 to consolidate clinical information and evaluate potential treatment options [10].

Epilepsy in CDKL5 deficiency disorder is characterized by early-onset seizures (in > 90% of cases within 3 months of age) [11, 12, 15]. Epileptic spasms (initially often without hypsarrhythmia) are the most frequent seizure type in CDD [12]. Over the course of life, patients usually experience various seizure types that occur multiple times daily. Development is severely impaired, with only a small percentage of affected patients achieving independent walking [10]. Other comorbidities in CDD include gastrointestinal problems, feeding difficulties, sleep and respiratory problems and others [11]. The management of epilepsy in CDD is highly demanding due to its refractory nature [8]. Conventional antiseizure medications seem to have little or short-lived clinical effect. Some advantages have been observed with a ketogenic diet and vagus nerve stimulation. New treatment options are emerging, such as ganaxolone, a neuroactive steroid that enhances GABAergic signaling [13]. As of 18th March 2022, ganaxolone is FDA-approved medicine for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder.

The aim of this publication is to summarize the current knowledge about the clinical aspects and management of CDD, with a particular focus on the new emerging treatment.

CLINICAL SYMPTOMS
Epilepsy in CDKL5 disorder

Epilepsy is present in almost all affected patients (98%, n = 145/148) [11]. According to the International CDKL5 Database, the median age of onset is 5–6 weeks [11, 12]. Seizure onset within 3 months of age is present in 90% of individuals [12, 15]. Over the course of the disease, the most common seizure type is epileptic spasms (ES), present in 60–82% of cases, followed by generalized tonic seizures (60–64%), focal seizures (51%), generalized myoclonic seizures (39–44%), and generalized tonic-clonic seizures (34–42%) [8, 12]. Tonic seizures are the most common seizure type at the beginning of epilepsy, observed in approximately 32% of individuals according to Demarest et al. (2019) [12]. Unique seizure pattern with multiple phases such as hypermotor-tonic-spasm sequence (HTSS) were initially described in four patients with CDD [15]. According to further research HTSS and HTSS-like seizure (multiple phases with clustering of tonic seizures and epileptic spams) were overall reported in 57% of patients (n = 92) [12]. Over the course of a patient's life, usually various seizure types are observed. Studies have shown that seizures occur daily in 69.3–71.2% of cases, with a median seizure rate of 2 per day [11, 16]. However, there have been reports of individuals who never developed epilepsy despite having a pathogenic variant in the CDKL5 gene [16]. In 43% of individuals with infantile-onset epilepsy, there is a seizure-free period known as the *honeymoon period* [12]. The duration of this phase varies among patients, ranging from 2.5 months to 6 years, with a median of 6 months. The age of onset for the seizure-free period ranges from 2 months to 11 years [16].

Currently, data on EEG abnormalities in CDKL5 deficiency disorder (CDD) are insufficient to establish a specific pattern unique to the condition. However, reports of EEGs performed during the initial stages of the disease indicates a diverse spectrum of findings, ranging from mild abnormalities to hypsarrhythmia [17]. Among cohorts of CDD patients with epileptic spasms (the most common seizure type), hypsarrhythmia was observed in only 34% of cases according to study conducted by Olson et al. (2023) [18]. This factor likely contributes to a longer lead time for initiating first-line treatment for epileptic spasms in CDD. As time progresses, EEG patterns in CDD tend to exhibit a more encephalopathic pattern. A study conducted among CCD patients older than 18 months revealed EEG findings such as general slowing, hypsarrhythmia, discontinuity, slow spike and wave, continuous spike and wave during sleep [19].

Psychomotor development

Milestones in development are significantly delayed among the CDD cohort. Due to the X-linked pattern of inheritance, development is strongly associated with sex. Female patients tend to achieve gross motor and fine motor skills, as well as communication, at a much higher level than males [20].

In an analysis based on the International CDKL5 Disorder Database in 2015, it was demonstrated that three-quarters of female patients with CDKL5 deficiency disorder were able to sit independently by the age of 5, while only a third of males achieved this milestone in development [10]. Independent walking was achieved by only 22% of females (n = 24/109) at a median age of 4.5 years, ranging from 12 months to 6.5 years. There were only single case reports of males achieving independent walking [10]. In terms of fine motor skills, raking grasp was attained by 49% of females compared to 10% of males, and pincer grip was observed in 10% of females, with only 1 male patient (n = 1/7) demonstrating this skill [10]. Regarding speech development, babbling was observed in 44% of female (n = 43/97), but only 16% (n = 17/107) were able to produce single words. Reports on speech development in males are sparse, but it has been shown that a significantly smaller percentage of males have speech and communication abilities as developed as females [10, 20].

While developmental achievements in CDD are significantly delayed compared to what is expected for age, a clear regression in skills and abilities is not frequently seen [20]. This is an important distinction between CDD and Rett syndrome, highlighting the unique clinical presentation and course of these two disorders (Tab. 1).

Other neurological problems

Cortical visual impairment (CVI) is characterized by visual dysfunction without any ocular or anterior visual pathway abnormalities. In children with CDD, it has been observed that they exhibit disturbed eye fixation and poor visual attention, initially classified as an autistic feature. Furthermore, a correlation between occurrence of CVI and impaired milestones achievement has been established in research by Demarest et al. [12]. In the same study, patients with CVI presented also more frequently with hypsarrhythmia in EEG pattern. Ophthalmological examinations have also revealed the presence of nystagmus (n = 10/26) and strabismus (n = 24/26). Visual acuities were found to be lower than expected for their age [21].

Sleep disturbances are a relatively common problem among patients with CDD, with an overall occurrence rate of 86.5% (n = 122/141). Various sleep-related issues have been reported by Mangatt et al., including night walking (58.5%), diurnal problems (46.8%), teeth grinding (39.7%), night laughing (26.8%), night screaming (22.8%) and others [11]. These disturbances can significantly affect the quality of sleep and overall well-being of individuals with CDD.

It appears that stereotypical hand movements, similar to those observed in Rett syndrome, were found in 85% (n = 17/20) of individuals with a median age of onset at 2.5 years. These hand stereotypies were predominantly bilateral. It's important to note that this study was conducted on a small number of patients, and further research is needed to validate these findings. In addition to hand stereotypies, other movement disorders were present in 23% (n = 35/154) of cases, including choreoathetosis, dystonia, and dyskinesia [8].

Seizure onset in CDKL5 deficiency disorder is often accompanied by the presence of severe generalized hypotonia in approximately 85% of cases as reported by Bahi-Buisson et al. in 2008 [22].

Other clinical features

Gastrointestinal (GI) problems are a significant health concern in CDD. Patients commonly experience various GI symptoms, including constipation (71%), gastroesophageal reflux (64%) and air swallowing (27%) [11]. The severe developmental delay and hypotonia commonly observed in CDD can contribute to feeding difficulties, further complicating the GI problems. As a result, approximately 28.8% of CDD cases (n = 42/146) require the implementation of a gastrostomy [11].

Respiratory tract infections, particularly those affecting the lower respiratory tract, have a higher prevalence among individuals with CDD [11]. Additionally, patients with CDD face an increased risk of developing musculoskeletal problems, such as scoliosis. According to the study conducted by Mangatt et al., 20.3% (n = 28/138) of individuals with CDKL5 deficiency disorder (CDD) develop scoliosis by the age of 10 [11].

Table I. Clinical comparison between Rett syndrome and CDKL5 deficiency disorder
Tabela I. Porównanie objawów klinicznych zespołu Retta i deficytu CDKL5

	RS	CDD
Ethiology (gene affected)	MECP2	CDKL5
Epilepsy	~60–80%	~98%
Onset of seizures	~48 months	~6 weeks
Response to ASM	Drug-resistant in 30%	Drug-resistant in most cases
Seizure types	Focal seizures (frequent) Generalized tonic-clonic seizures Absence seizures Myoclonic seizures Tonic seizures Febrile seizures (no specific seizure semiology)	Epileptic spasms (most common) Tonic seizures Focal seizures Generalized myoclonic seizures Generalized tonic-clonic seizures HTSS and others
Seizure frequency	Daily in ~11% of cases	Daily in ~70% of cases
Regression of psychomotor development	~99% (between 12–24 months of age)	Development severly delayed, but regression appears rarely
Cortical visual impairment	Rare (intense eye communication is common among patients with RS)	~76% (disturbed eye fixation and poor visual attention)
Microcephaly	~80% (postnatal)	Rare
Streotypical hand movements	~100%	~80%
Laughing and screaming spells	Frequent	Rare
Muscle tone	Hypotonia	Hypotonia (more prominent)
Sleep distubances	~67%	~90%
GI problems (feeding problems, constipation, gastroesophageal reflux, air swallowing)	~90%	~78%
Scoliosis	~52%	~20%

ASM — antiseizure medication; CDD — CDKL5 Deficiency Disorder; GI — gastrointestinal; HTSS — Hypermotor-tonic-spasm sequences; RS — Rett syndrome

MANAGEMENT
Anti-seizure medication

The management of seizures in individuals with CDD has been challenging due to the highly refractory nature of epilepsy associated with the condition. Currently, there is no established consensus regarding the specific order or sequence of antiseizure medications (ASM) in CDD [23]. ASM may initially demonstrate satisfactory efficacy, with responder rates of up to 69% (n = 27/39) observed at 3 months of therapy according to Müller et al. (2016) [24]. Certain medications, such as felbamate, vigabatrin, clobazam, and valproate, have shown promising results during the early stages of treatment. However, over time, the response to ASM tends to diminish, with only 24% of individuals maintaining a positive response at 12 months [24]. Valpronates achieved the highest response rate after 12 months, although it remained relatively low at 9% (n = 3/34). Interestingly, sodium channel blockers (SCBs) exhibited unsatisfactory response rates in one study, with reports of seizure aggravation in some individuals receiving carbamazepine [24]. However, study by Aledo-Serrano et al. (2021) demonstrated more favorable results with SCBs, particularly with carbamazepine and oxcarbazepine. In the aforementioned study, two patients remained seizure-free for 10 years while on carbamazepine monotherapy (n=2/19) [25]. It is important to note that exacerbation of seizure frequency has been reported in 31% of individuals in response to at least one ASM [24].

In a retrospective observational study, it was found that the implementation of first-line treatment for epileptic spasms in CDD cohort took longer compared to other etiologies. This delay could be attributed to the less frequent occurrence of hypsarrhythmia on initial EEGs in CDD patients (34%, n = 20/59), as reported by Olson et al. (2023) [18]. Furthermore, the response to first-line treatment, even with a shorter lead time, was reported to be less satisfactory in CDD patients with epileptic spasms. The clinical remission rate at 14 days was 26% in the CDD cohort, while it was 58% in other etiologies [18].

An open-label study was conducted on 17 CDD patients, evaluating the use of cannabidiol (CBD) as a treatment. The study showed a 41% reduction in convulsive seizures after 12 weeks of therapy, and a 53% reduction after 48 weeks [26]. Another study in 2021, which included 14 patients, reported a positive response to CBD in 21% of

cases (n = 3), but also observed an aggravation of seizures in 29% of cases (n = 4) [8]. Additionally, an open-label phase II study with soticlestat demonstrated a reduction of 23.6% in motor seizures and 30.5% in all seizures from baseline at 12 weeks of therapy in the CDD group (n = 12) [27]. Efficacy of fenfluramine was also assessed in an open label trial by Devinsky et al. (2021), where the reduction of tonic-clonic seizures were observed in 90% (n = 4/5) [28]. However, it is important to notice that CBD, soticlestat and fenfluramine studies had small number of patients, limiting the ability to draw definitive conclusions regarding their effectiveness in CDD. Further research with larger cohorts is warranted to validate these findings.

Ganaxolone

The preliminary results of clinical trials have shown promising outcomes in the use of ganaxolone for CDD. Efficacy of ganaxolone was proven in the randomized, double-blind, placebo-controlled Marigold Study (NCT03572933) [13]. It was conducted among patients aged 2–21 years with molecularly proven pathogenic or probably pathogenic CDKL5 variants. The inclusion criteria also required at least 16 major motor seizures, defined as bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic seizures. In the aforementioned study, 101 patients (median age 6 years) participated and were randomly assigned to receive either enteral ganaxolone (n = 50) or placebo (n = 51) for 17 weeks. After a 4-week titration period, participants received full dosages, which were 63 mg/kg/day for < 28 kg and 1800 mg/day for > 28 kg. The median reduction in major motor seizures was 30.7% in the ganaxolone group and 6.9% in the placebo group (p = 0.0036). Patients who completed the 17-week period had the opportunity to continue treatment in the open-label extension of the Marigold trial [29]. At 12 months of treatment the reduction in major motor seizures was 49.6% (n = 48). Treatment-emergent adverse event (TEAE) were observed in 86% in ganaxolone group and 88% in placebo group and were mostly classified as mild to moderate. The most frequent TEAE in ganaxolone were somnolence (36% vs 16% with placebo), pyrexia (18% vs 8%) and upper respiratory tract infection (10% vs 6%) [13].

Ganaxolone (ZYTALMY®) is a neuroactive steroid that enhances GABAergic signaling by acting as a positive allosteric modulator of synaptic and extrasynaptic GABA A receptors. Ganaxolone gained its first approval on March 18th 2022 in the USA for the treatment of epilepsy in CDKL5 deficiency disorder. It is approved for use in patients above 2 years of age. It is administered orally and reaches its maximum plasma concentration after 2–3 hours. It is metabolized with CYP enzymes (CYP3A4/5, CYP2B6, CYP2C19 and CYP2D6). Ganaxolone concentration might reach higher level in patient with hepatic disorders. At that time reduction of dosages might be required [29].

Ketogenic diet

The ketogenic diet (KD) was initiated in approximately 50% of individuals with CDKL5 deficiency disorder (CDD) [8,30], and positive effects of the KD were achieved in 50–58.7% of patients. The median duration of KD treatment is 17 months [30]. Particularly interesting is the statistically better response observed in children who commence the KD before 12 months of age (p = 0.0670) [8]. Regarding the clinical response in epileptic spasms (ES) in CDD, the use of the KD within 3 months of ES onset resulted in remission at 1 month and sustained results at 3 months in 15% of cases [18]. Unfortunately, studies have shown that the KD does not sustain long-term efficacy in CDD, with 51% of patients discontinuing this form of treatment. Different reasons for discontinuation include the occurrence of severe side effects (18.26%), worsening seizure control (7%) and others [30].

VAGUS NERVE STIMULATION

Another adjunctive treatment option for refractory epilepsy in CDD is Vagus Nerve Stimulation (VNS). According to data from the international CDKL5 deficiency disorder database, VNS was implemented in 17.1% of individuals (n = 38/222), with a median age at the procedure of 4.9 years. Improved seizure control was observed in 69% of cases (n = 25/36). However, it is important to note that despite these satisfying results, a reduction in antiseizure medications among CDD patients was not achieved [31].

CONCLUSIONS

In summary, CDKL5 deficiency disorder is a complex condition characterized by severe developmental delay, early-onset epilepsy (including epileptic spasms), and a range of associated clinical features. Antiseizure management in CDD has been challenging, with no established consensus on treatment options. Conventional antiseizure medications, ketogenic diet, and vagus nerve stimulation have shown some initial efficacy but limited long-term response rates. Emerging treatment options, such as ganaxolone, show promise in enhancing epilepsy management in CDD. Further research is needed to better understand the underlying mechanisms of the disorder and to develop more effective treatments for individuals with CDD.

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