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Marked Improvement in Epilepsy, Movement Disorder and Behaviour in a Child With CDKL5 Deficiency Disorder Treated With Ganaxolone and Fenfluramine: A Case Report

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Abstract

CDKL5 deficiency disorder (CDD) is a severe developmental and epileptic encephalopathy characterised by early-onset, treatment-resistant seizures and severe neurodevelopmental impairment. Ganaxolone is approved for the treatment of seizures associated with CDD, while fenfluramine has shown potential antiseizure activity in a small series of patients with CDD.

We report the case of a girl with CDD who experienced a marked and partially sustained clinical response to combination therapy with ganaxolone and fenfluramine. Ganaxolone reduced major motor seizure frequency by approximately 50-60%, with additional improvements in alertness, responsiveness, mood, communication and motor development. Following the addition of fenfluramine, motor seizures ceased for eight weeks before recurring at a lower frequency after a febrile illness. Overall, combination therapy was generally well tolerated, although dose escalation was limited by somnolence, which resolved promptly following dose reduction. Serial echocardiograms remained normal. Complete long-term seizure control and EEG normalisation were not achieved.

This case suggests that combined ganaxolone and fenfluramine therapy may provide benefits beyond seizure reduction in CDD, including improvements in development, behaviour and overall quality of life, and warrants further investigation.

Categories: Neurology, Genetics, Pediatrics
Keywords: case report, cdd, cdkl5 deficiency disorder, developmental epileptic encephalopathy, drug-resistant epilepsy, epilepsy, fenfluramine, ganaxolone, pediatric epilepsy, seizure reduction

Introduction

CDKL5 deficiency disorder (CDD) is a rare, severe genetic developmental and epileptic encephalopathy caused by pathogenic variants within the cyclin-dependent kinase-like 5 (CDKL5) gene, located on the X chromosome [1]. The affected protein kinase is crucial for a variety of molecular neuronal functions and interacts with MECP2, which is associated with Rett syndrome [2]. Indeed, Rett syndrome and CDD may show some clinical overlap, but both are genetically and clinically distinct entities. The majority of CDD patients are female, but male children may also be affected and frequently exhibit mosaicism [3].

Epilepsy is usually very severe in CDD, with epileptic spasms, tonic seizures, and focal tonic seizures being most frequently observed [4]. The course of epilepsy may be divided into three phases. Epilepsy typically begins with tonic, tonic-clonic, or focal seizures in early infancy (phase 1). This phase may be followed by a temporary “honeymoon period”, typically beginning at around two years of age and with a median duration of six months, during which approximately 40% of children experience a markedly reduced seizure burden or even complete seizure freedom [4,5]. This phase is usually followed by infantile spasms and possibly hyper-motor tonic spasms (West syndrome, phase 2) and may later progress to therapy-resistant epilepsy with spasms, tonic seizures, alternating focal seizures (phase 3) [5]. Electroencephalogram (EEG) findings in phase 1 may be largely unremarkable, later followed by generalized slowing, focal or multifocal discharges, hypsarrhythmia, and eventually also slow spike-and-wave pattern, as found in Lennox-Gastaut syndrome in some cases [5]. Seizure symptoms in patients with CDD may be unique, with reports of a hypermotor-tonic-spasm sequence and a form of tonic/tonic-vibratory contraction followed by spasms fading to distal myoclonic jerk in some children [4].

Investigators report the coexistence of epileptic and non-epileptic movements with episodic chorea, dystonia and handwringing movements [6]. Given that EEG may be continuously abnormal in many children with CDD and repeated long-term recordings are difficult to obtain, at times it may be challenging to discern seizures from non-epileptic movements [6]. In many children, the reduced or absent visual fixation and eye contact may serve as a clinical clue, or a presenting clinical sign, as it was in our case.

Case Presentation

The patient is an eight-year-old girl. She was born at term after an uneventful pregnancy and birth. Postnatal routine clinical screening examinations were normal. At four months of age, muscular hypotonia and reduced visual fixation were first documented, and physiotherapy was initiated. At five months of age, roving eye movements, absent visual fixation and increasing gross motor developmental delay led to inpatient admission and assessment. Diagnostic investigations including MRI, EEG (at rest and sleep), lumbar puncture, ophthalmological examination, visual evoked potentials, basic metabolic investigations and single-nucleotide polymorphism (SNP) array found no remarkable results. Occupational therapy for children with visual impairment was added to physiotherapy.

At 14 months of age, five days after a routine vaccination, the patient developed recurrent afebrile generalized tonic seizures and focal seizures with head version to the right, which were documented on video by her parents. EEG initially showed bilateral sharp waves that soon developed into a discontinuous hypsarrhythmia. Focal seizures with bilateral head version and epileptic spasms occurred two to three times per day, lasting two to five minutes. EEG findings varied between multifocal sharp waves (Figure *1*) and hypsarrhythmia (Figure *2*), sometimes within a single recording. Levetiracetam was initiated and whole-exome sequencing identified a de novo variant in CDKL5. Sulthiame and steroids were introduced without success. Lacosamide was subsequently added to levetiracetam, after which no clinical seizures were observed until approximately three years of age, representing a seizure-free interval of almost two years. EEG findings improved only modestly, with persistent multifocal discharges and never normalized. Feeding was poor and a gastrostomy tube was subsequently placed.

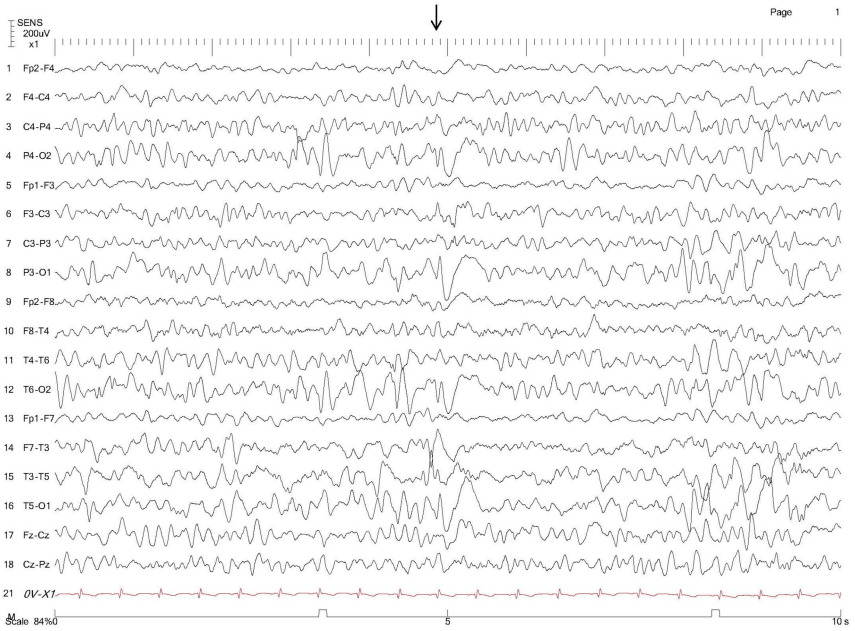


FIGURE 1: Sleep EEG recording at age 15 months.

Sleep EEG recording (10/20) at age 15 months showing multiple foci, with changing lateralization during repeated recordings.

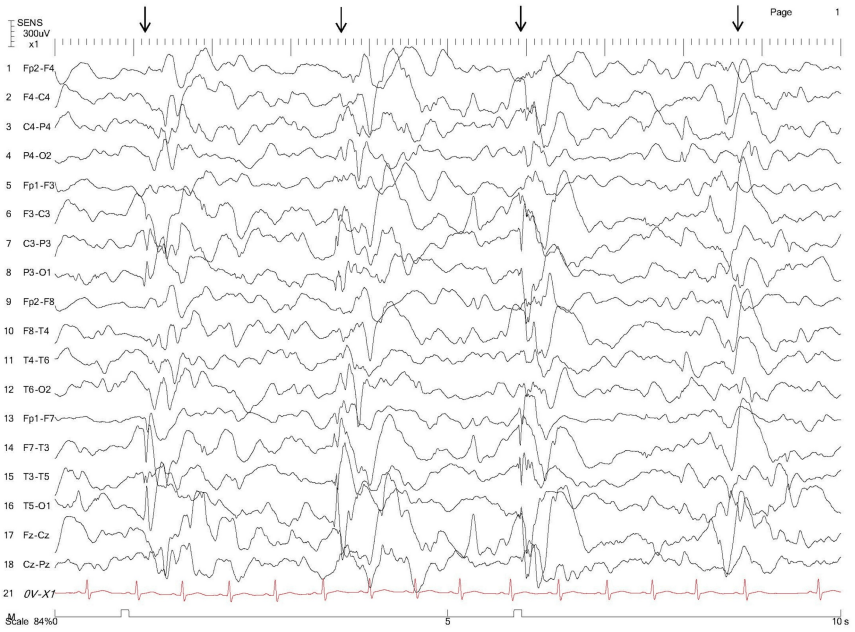


FIGURE 2: At rest EEG recording at age three years.

At rest EEG recording (10/20) at age three years showing hypsarrhythmia during an episode with several daily hypermotor spasms.

At three years of age, epilepsy reappeared, with nocturnal myoclonic seizures and daily tonic-clonic seizures. Hypermotor tonic-myoclonic spasms (Video *1*) started and increased in frequency, reaching three to five motor seizures per day, occasionally increasing to seven and lasting two to three minutes each.



VIDEO 1: Hypermotor-tonic-spasm with tonic-vibratory contraction fading to distal myoclonic jerks.

View video here: https://youtu.be/0p91ys5cB7c

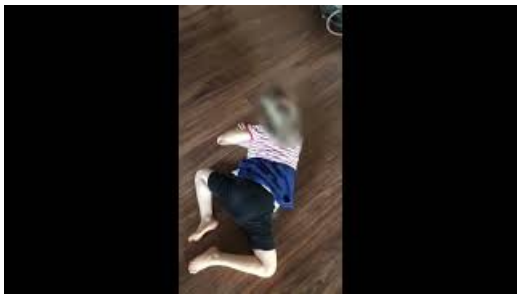
EEG showed multifocal activity at age four, with discontinuous hypsarrhythmia which finally evolved into a generalized slow spike wave pattern (age seven; Figure *3*).



FIGURE 3: At rest EEG recording at age seven years.

At rest EEG recording (10/20) at age seven years showing a generalized slow spike wave pattern. Medication: ganaxolone (40 mg/kg/d), fenfluramine (0.4 mg/kg/d), lacosamide (6 mg/kg/d).

Concomitantly, the patient showed repetitive episodes of hypermotor tonic movements with head version without a recordable change in EEG pattern, likely resembling frontal or frontotemporal seizures (Video *2*).



VIDEO 2: Frontotemporal seizure with tonic head version. EEG showing multiple foci and hypsarrhythmia during these events with little changes between ictal and interictal episodes.

View video here: https://youtu.be/PDR7qrSot4w?si=h_pQYKgA25QiTg5K

Treatment with topiramate, perampanel, and eventually a ketogenic diet did not result in meaningful improvement. Episodes of ballistic movements emerged, which at times could be influenced by stimulation or increased affection appeared. These most likely reflected temper tantrums (i.e. non-epileptic spells), possibly as a side effect to perampanel, which was subsequently tapered. During this period (three to five years of age) the child was predominantly bad-tempered, frequently whining and of unhappy demeanour. She remained unable to stand or crawl independently, even though the muscular hypotonia clearly improved with age (Video *3*).



VIDEO 3: Typical scale of movements, orientation and behavior before ganaxolone and fenfluramine treatment. Note handwringing automatisms.

View video here: https://youtu.be/k8e5cTRFd3A?si=VRspd4aS-LaOlWEe

At five years of age, ganaxolone (Ztalmy®) was initiated at the recommended dose. At 30 mg/kg/d the parents observed an approximate reduction in epileptic spasms and myoclonic seizures of 50-60% ("less than half the amount"), including periods of one to two weeks without observed seizures. However, EEG showed only mild quantitative remittance of epileptiform activity. Non-epileptic spells also improved, although hand wringing movements continued to occur intermittently. The patient's parents and professional caregivers reported increased alertness and well-being, better response to auditory "started turning her head to noises" and visual stimuli and improved mood. Both parents reported feeling brief periods of visual fixation on their faces at close range, which they never had before. During this period, the child made small but continual progression in motor development, started to sit independently with stable posture. During periods of lower seizure burden she learned to make use of an NF-Walker gait trainer, initially without any meaningful independent locomotion.

When the patient was seven years old, fenfluramine was added to ganaxolone. Motor seizures subsequently stopped for eight weeks before recurring following a febrile infection. Motor seizures (spasms and myoclonic seizures) initially recurred at a frequency of approximately one to two per day, without a further reduction in frequency following intermittent dose escalation up to the limit of individual tolerance. Parents stated that during periods of illness, or reduced well-being (e.g. fever, prolonged obstipation, severe heat, or injury), myoclonic seizures and hypermotor spasms may recur at much higher frequency (five to 10 per day). Other antiseizure medications were gradually withdrawn and a combination of ganaxolone, fenfluramine, and lacosamide was continued (Video *4*). The patient's parents report that her general condition, responsiveness, alertness, and mood increased with lower seizure rate in general. She is now able to walk walker-aided, up to 100 m, under constant vocal motivation, but entirely on her own. Figure *3* shows the patient's EEG on ganaxolone (40 mg/kg/d), fenfluramine (0.4 mg/kg/d), and lacosamide (6 mg/kg/d) during a period of increased seizure activity, likely provoked by a febrile infection, when motor seizures occurred approximately two to three times per day. Figure *4* shows the patient's EEG 14 days later, following dose escalation to the maximum recommended doses of ganaxolone (60 mg/kg/d) and fenfluramine (0.7 mg/kg/d), with lacosamide unchanged. Compared with Figure *3*, the EEG showed a mild reduction in epileptiform activity and some slowing, while seizure duration was shorter (approximately one to two minutes on average).



VIDEO 4: Child sitting and standing with no or little support during a period of low seizure burden under ganaxolone, fenfluramine, and lacosamide.

View video here: https://youtu.be/zjLEctVVi1g?si=F_G7_L5cj2sRcVQg



FIGURE 4: At rest EEG recording at seven years, 14 days after the recording in Figure 3.

At rest EEG recording (10/20) 14 days subsequent to the recording of EEG in Figure 3, after dose escalation of ganaxolone (60 mg/kg/d) and fenfluramine (0.7 mg/kg/d).

Echocardiography was performed at six-month intervals following fenfluramine initiation, with normal findings at all assessments, including the most recent in September 2026. Somnolence was observed during dose escalation and resolved promptly following dose reduction. As the patient receives nutrition via a gastrostomy tube, changes in appetite could not be meaningfully assessed.

Genetic findings

Exome sequencing and segregation analysis revealed a rare variant in *CDKL5*, c.611T>G, p.Leu204Arg (het), rs1602276088, Chr. pos.: 18606130 (GRCH37), NM_001323289.2. The variant is located in a highly conserved position of the protein kinase domain and there is no report of a minor allele frequency (MAF) in healthy subjects. In our patient the variant appeared de novo, which makes its causative role in our patient highly likely [7].

Discussion

We report the case of a young girl with CDD whose clinical presentation was consistent with the typical spectrum of the disorder. Conventional antiseizure medications are often of limited efficacy in patients with CDD; however, transient reductions in seizure frequency lasting several weeks have been reported with a range of antiseizure medications [4,8]. In contrast, ganaxolone is an FDA-approved product with proven effectiveness in CDD, as shown in a placebo-controlled, double-blind trial [9]. Ganaxolone reduced major motor seizures (defined as bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic) in a 28-day study period by 30.7% vs. 6.9% in the placebo group. Long-term follow-up in a two-year open-label extension demonstrated sustained reductions in major motor seizure frequency, with safety findings consistent with the double-blind phase [8].

Fenfluramine, a serotonin-releasing agent, is FDA-approved for the treatment of Dravet syndrome and Lennox-Gastaut syndrome [10,11]. In a small series of six patients with CDD, it was reported as well tolerated and appeared to reduce convulsive seizures, including tonic-clonic and tonic seizures [12].

In this patient ganaxolone was associated with an approximately 50-60% reduction in epileptic spasms and myoclonic seizures, together with improvements in alertness, responsiveness, mood and motor development. Following the addition of fenfluramine, motor seizures ceased for eight weeks before recurring at a lower frequency after a febrile illness. Although complete long-term seizure control was not achieved, the improvements in communication, development, behaviour and overall wellbeing reported by the patient's parents and caregivers were particularly notable.

Initially, this patient responded well to lacosamide, experiencing a prolonged seizure-free interval lasting until approximately three years of age. However, this response may have coincided with the recognised “honeymoon period”, which has been reported in up to 40% of CDD patients, making it difficult to attribute this period of seizure freedom solely to lacosamide [5].

This report describes a single patient; as such the findings should be interpreted cautiously and cannot be assumed to apply to the wider CDD population. Some of the observed improvements in development, behaviour and wellbeing were based on reports from the patient’s parents and caregivers rather than formal standardised assessments. In addition, seizure frequency varied over time and was affected by factors such as intercurrent illness, which makes it difficult to attribute all observed changes solely to treatment. However, the longitudinal clinical, EEG and video documentation provides a detailed picture of the patient’s response over time.

Conclusions

In this patient, combination treatment with ganaxolone and fenfluramine was associated with a partially sustained reduction in seizure burden and notable improvements in development, communication, behaviour, well-being and overall quality of life. Treatment was generally well tolerated, although dose escalation was limited by somnolence, which resolved promptly following dose reduction. Serial echocardiograms remained normal. Further investigation of this combination in CDD is warranted.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Bernd A. Neubauer, Hartwig Spors

Acquisition, analysis, or interpretation of data: Bernd A. Neubauer, Hartwig Spors

Drafting of the manuscript: Bernd A. Neubauer, Hartwig Spors

Critical review of the manuscript for important intellectual content: Bernd A. Neubauer, Hartwig Spors

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Bernd A. Neubauer declare(s) personal fees from Immedica Pharma. Bernd A. Neubauer gave a teaching talk sponsored by Immedica on CDKL5 disorder and received an honorarium. **Other relationships:** Medical writing support was provided by William Stainsby of Vigour Communications (Sydney, Australia) and funded by Immedica Pharma (Stockholm, Sweden).

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The authors were responsible for the development and writing of the manuscript and take full responsibility for its content.

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