A guide for healthcare professionals to learn about CDD.

CDKL5 South Asia

CDKL5 Deficiency Disorder (CDD)

Also known as:

- CDKL5 Disorder;
- CDKL5 encephalopathy;
- CDKL5-related epilepsy;
- Early infantile epileptic encephalopathy-2;
- X-linked dominant infantile spasm syndrome-2

Overview:

CDKL5 deficiency disorder (CDD) is a rare developmental epileptic encephalopathy (DEE) caused by pathogenic alterations in the CDKL5 gene. The hallmarks of CDD are the onset of drug-resistant epilepsy at a very early age, and severe neurodevelopmental delay impacting cognitive, motor, speech, & visual function.

1. Incidence

CDD has an estimated birth incidence of 1:40,000 to 60,000 livebirths worldwide. It affects predominantly females with a sex ratio of 12:1.

2. Etiology

The disorder is caused by mutations or deletions in the cyclin-dependent kinase-like 5 (CDKL5,Xp22.13) gene situated in the X chromosome. CDKL5 is a kinase predominantly expressed in the brain.

3. Diagnosis of CDD

Diagnosis is suspected in patients with early onset epilepsy with a severe developmental delay and with a poor response to antiseizure medications (ASMs). Genetic identification of a pathogenic CDKL5 alteration confirms diagnosis.

4. Age of onset

Presentation of seizures occur in the first 12 months of life; often within the first weeks after birth (median onset at 6 weeks after birth).

5. Seizure types at presentation

The most common initial seizure type at onset are tonic seizures, followed by epileptic spasms, generalized tonic-clonic seizures and focal seizures.

6. Seizure types during evolution

During the disorder course a seizure-free period (with ASM) might be observed, this is also reported as "honey-moon period", while majority of the individuals with CDD continue to have intractable spasms, often associated with multifocal and myoclonic seizures.

A peculiar seizure pattern has been also recognized with prolonged generalized tonic-clonic events, lasting 2–4 min, consisting of a tonic-vibratory contraction, followed by a clonic phase with a series of spasms, gradually transitioning into repetitive distal myoclonic jerks.

7. EEG features

EEG features range from mild EEG abnormalities to hypsarrhythmia at the initial presentation with seizures, with burst suppression being rare and atypical.

8. Comorbidities

Developmental milestones are severely delayed in affected individuals. Severe hypotonia can be present before seizure onset, as well as irritability, excessive crying, drowsiness, and poor sucking. Gross motor, fine motor, and communication skills

are also extremely impaired and most affected individuals cannot walk and many are confined to a wheelchair. Communication strategies are restricted to elementary non-verbal communication. Individuals do not develop autonomy to feed themselves.
Subtle dysmorphic facial features include a prominent/broad forehead, deep-set eyes, a well-defined philtrum, and everted lower lip, possibly associated with tapered fingers and hallux valgus.
Hand stereotypies are common. Some may have scoliosis, respiratory and gastrointestinal difficulties, and sleep problems.

A differentiating feature of CDD that was recognized early is poor eye fixation and associated avoidance of eye gaze and measures of visual acuity or cerebral visual impairment might be useful outcome measures in future clinical trials. Life expectancy is unknown due to underdiagnosis in adults, but adult patients are known. Prognosis is often poor with severe psychomotor deficits and intractable seizures remaining into adulthood. Autonomy is usually never reached. Future research needs to evaluate better, the variability in the phenotype and for example the effect of sex and somatic mosaicism on disease severity.

9. Treatment

Management is symptom-based and requires a multidisciplinary approach. Antiseizure medications according to seizure types and ketogenic diet are used for the management of seizures.

There are many ongoing clinical trials. A further mode of treatment used less commonly is vagal nerve stimulation (VNS).

Non-pharmacological management includes physical, occupational, visual and speech therapy.

10. Review of impact of seizures, drugs and comorbidities on:

- Day-to-day activities
- Overall well-being
- Mental health
- Physical health
- Independence

11. Provide patient/caregiver with:

- Individualized emergency protocol
- SUDEP risk management
- Genetic counselling
- Individualized habilitative program
- Patient and caregiver support (neuropsychological evaluation, guidance, potential psychiatric support)

Links:

CDD Orphanet summary

https://www.orpha.net/consor/www/cgi-bin/OC_Exp.hp?lng=EN&Expert =505652

Leonard H, Downs J, Benke TA, Swanson L, Olson H, Demarest S. CDKL5 deficiency disorder: clinical features, diagnosis, and management. Lancet Neurol. 2022 Jun;21(6):563-576.

CDKL5 South Asia:

A community that cares for CDD. With the belief of ‘Hope is in our DNA’, the community aims to build a support network to spread awareness about the disorder and help in providing resources to the families in need.

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