What is CDKL5 deficiency disorder (CDD)?

CDKL5 deficiency disorder (CDD) is a rare developmental and epileptic encephalopathy (DEE) caused by variants in the CDKL5 gene. The CDKL5 gene, located on the X chromosome, provides instructions for making a protein that is essential for normal brain development. The CDKL5 protein acts as a kinase, which is an enzyme that changes the activity of other proteins by adding oxygen and phosphate. This protein is widely distributed throughout the brain and acts both in the nucleus of brain cells and at the synapse, the area where brain cells communicate. Some of the molecular targets of CDKL5 are known and others remain to be discovered. Variants in the CDKL5 gene reduce the amount of functional CDKL5 protein or alter its activity in brain cells. A deficiency of CDKL5 or an impairment of its function disrupts brain development, but it is unclear how these changes lead to the specific features of CDD. CDD has been classified as a DEE because the severe impairment of development is thought to be related both to the disease-causing changes in the CDKL5 gene and the related epileptic activity.

What types of seizures (and epilepsies) are associated with CDKL5 deficiency disorder (CDD)?

The main features of CDD are the onset of seizures at a very early age (usually by about 3 months but may be as early as the first week of life) and severe neurodevelopmental delay impacting cognitive, motor, speech, and visual function. CDD has a broad range of clinical severity and may be associated with other symptoms such as gastrointestinal issues and sleep challenges.

Seizures are a key clinical concern for individuals with CDD because they are usually severe and difficult to control with anti-seizure medications. The most common seizure types are epileptic spasms (which can present with a pattern called hypsarrhythmia on the EEG), tonic, myoclonic, and generalized tonic-clonic seizures. About a third of individuals can have seizures with multiple phases. Clonic, atonic, and absence seizures occur in individuals with CDD, but are less common.

Core features of CDD epilepsy:

1. Epileptic seizures starting in early infancy.
2. In the majority of people, epileptic spasms often occur without hypsarrhythmia.
3. Multiple different types of seizures can occur, often in mixed clusters.
4. Seizures are very difficult to control and happen frequently throughout the day.

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What non-seizure symptoms are seen in individuals with CDKL5 deficiency disorder (CDD)?

Everyday functioning can be severely impaired in individuals with CDD, including in the areas of gross motor, fine motor, language, and social functioning. About half of CDD individuals have some purposeful use of their hands and about a quarter can walk. Most individuals have severe intellectual disability and little or no speech. Though, some individuals on the milder end of the spectrum can communicate through signs. Movement disorders such as stereotypies, dystonia, and choreoathetosis are reported in a subset.

About three quarters of all individuals with CDD have been found to have some degree of cortical visual impairment. Disrupted sleep, feeding difficulties, gastrointestinal symptoms, and breathing irregularities are also reported.

Non-Seizure Symptoms Reported in Individuals with CDD:

- Limited ability to walk
- Inability to speak but may use complex gestures/vocalization
- Low muscle tone (hypotonia)
- Limited hand skills
- Lack of eye contact and visual difficulties (cortical visual impairment)
- Constipation
- Sleep difficulties
- Repetitive hand movements (stereotypies)
- Teeth-grinding (bruxism)
- Swallowing and feeding difficulties (may require a gastrostomy tube placement)
- Gastroesophageal reflux
- Breathing irregularities (such as hyperventilation)
- Loss of developmental milestones (regression) in some individuals
- Abnormal movements (known as movement disorders) in some individuals
- Recurrent respiratory infections

How is CDKL5 deficiency disorder (CDD) diagnosed?

CDKL5 variants can only be identified by genetic testing. Diagnosis is initially suspected based on clinical presentation and is confirmed by molecular genetic testing for CDKL5 variants, by multigene panel testing for early onset epilepsy, or through whole exome (WES) or whole genome sequencing (WGS).

Genetic counseling prior to genetic testing is an important step in making sure that the best testing strategy is selected, and that patients and families understand the risks, benefits, limitations, and outcomes of testing.

Most of the CDKL5 gene variants that have been reported are "*de novo*," meaning that they occur spontaneously and are new in the affected individual, and are not passed down through families. However, rare families in which multiple siblings are affected with the same variant do exist in the literature. In these cases, the CDKL5 gene variant likely occurred in a small number of cells in one parent's body (somatic mosaicism) or in their reproductive cells (germline mosaicism).

How is CDKL5 deficiency disorder (CDD) treated?

Currently no curative treatment is available for individuals with CDD, so medical management is symptomatic and supportive. A multidisciplinary team approach is the most effective way to deliver necessary treatments, aimed at maximizing the individual's abilities and facilitating any skills that may be emerging. An emphasis should be placed on early intervention therapies such as physical therapy, occupational therapy, vision therapy, and speech and augmentative communication therapy. Important aspects of management include psychosocial support for the family, development of an appropriate education plan, and assessment of available community resources.

Seizure control is challenging, and often requires multiple anti-seizure medications as well as non-pharmacological approaches. No single anti-seizure medication has proven superior in comparison to others, and effectiveness often wanes over time. Ganaxolone is now the first anti-seizure medication FDA approved for CDD. Non-medication treatment approaches for seizures including ketogenic diet and vagal nerve stimulation have both been used in CDD with mixed results but improvement in some individuals.

Other symptoms related to abnormal muscle tone include scoliosis, hip dysplasia, and walking difficulties. Individuals should be screened for these orthopedic complications and treated appropriately. Physiatrists and physical therapists may help with supportive equipment for tone management as well. In children with feeding or growth difficulties, a dietitian with expertise in the management of individuals with severe intellectual disability can help to achieve optimal nutritional status.

How common is CDKL5 deficiency disorder (CDD)?

Although rare, the occurrence of CDD may be between ~1:40,000 and 1:60,000 live births. This estimate may be lower than the true number due to the fact that most research in CDD currently takes place in developed countries. CDKL5 variants have been identified in many ethnic groups, with more females than males being reported with an approximate ratio of 4:1.

What is the outlook for CDKL5 deficiency disorder (CDD)?

Disclaimer: This field is rapidly evolving, and each individual has their own course. We are constantly learning, and published data may be slow to come.

The natural history of CDD is incomplete and research is ongoing to improve understanding of the long-term outlook for patients diagnosed with CDD. The International CDKL5 Disorder Database was established in September 2012 and gathers data from families throughout the world who have children with CDD.

The CDKL5 Centers of Excellence, established by the International Foundation for CDKL5 Research (IFCR), deliver multidisciplinary clinical care and collect clinical or research data on patients with CDD in the USA. The first site was established in 2013 and the network has grown to include eight sites across the United States. These sites have allowed the development of a CDD-specific multicenter clinical research network structure to support clinical research goals and to further knowledge of the disorder.

In individuals with CDD, seizures are typically difficult to control, and most children will have severe neurodevelopmental disabilities and other associated health concerns. An early diagnosis is helpful so that an individual with CDD can establish care with a multidisciplinary team dedicated to supporting therapies and addressing any health concerns related to the diagnosis.

For more information

- IFCR video library
- Visit the Telethon Kids Institute for information about the International CDKL5 Database and associated publications
- Register form for the CDKL5 database

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