EpiCARE

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, and visual function.

Incidence

CDD has an estimated birth incidence of 1/42,400 livebirths in the UK (Scotland). It affects predominantly females with a sex ratio of 12:1.

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.

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.

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).

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.

Seizure types during evolution

During the disease 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.

EEG features

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

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.

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. Ganaxolone is currently the first specifically approved ASM for this disorder (at the moment only by FDA in USA) and other clinical trials are ongoing. A further mode of treatment used less commonly is vagal nerve stimulation (VNS).

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

Review of impact seizures, drugs and comorbidities on:

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

Provide patient/carer with:

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

Links

- CDD Orphanet summary
- 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.
- Frontiers | International Consensus Recommendations for the Assessment and Management of Individuals With CDKL5 Deficiency Disorder

Authors: Carol-Anne Partridge (CDKL5-UK) and Prof. Reetta Kälviäinen (Kuopio University Hospital, Finland).

European Reference Network

Co-funded by the European Union

EpiCARE

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 genetic condition that mainly affects girls. It is caused by defects in a protein, called CDKL5, (cyclin-dependent kinase-like 5).CDKL5 defects occur due to variations in its gene located on the X-chromosome.

The X chromosome is one of the sex chromosomes - females have two X's and males have one X and one Y chromosome. Around 90% of people diagnosed with CDD are female. Females have a second copy of the gene that is able to work properly, but males do not. As such, Males tend to be more severely affected.

The CDKL5 gene provides instructions for making a protein that is essential in forming the connections for normal brain development, with variations in the gene causing a deficiency in the protein level. This deficiency causes seizures and a range of neurodevelopmental delay. But it is unclear how these changes cause the specific features of CDD.

Most of the CDKL5 gene variations are "de novo", meaning that they occur for the first time and are not passed down through families.

How common is CDD?

CDKL5 Deficiency Disorder is rare, with estimated incidence of between 1/40,000 and females outnumber males by a ratio of 12:1.

When do symptoms first appear?

Even before seizure onset, parents may have concerns about their child's development. They may notice that their child does not use their hands normally and some infants may not show as much interest in their surroundings as other children of the same age. Seizure onset may be in the newborn period but typically occurs within the first six months.

How are the type of seizures seen in CDD?

Several different seizure types may be seen. Features characteristic of CDKL5 syndrome are:

The initial seizure types can vary, but most commonly seen are tonic seizures (stiffness of arms, legs or trunk), epileptic spasms (stiffening of arms and legs and head bends forward) generalized tonic clonic seizures (stiffening and jerking phases of muscle activity) or focal seizures.

Over time, other seizure types can occur. The majority of individuals will have epileptic spasms and/or tonic seizures.

Some children may have hypermotor-tonic-spasms sequence seizures. The first part of this seizure begins with rocking, kicking, and vocalization which last 10–60 seconds. This is followed by a tonic (stiffening) phase, either with extension of all limbs or extension of the upper limbs and flexion of the lower limbs lasting 20–45 seconds. The seizure evolves to a series of extensor spasms which lasts 1–15 minutes. Similar seizures which involve multiple phases with clustering of tonic seizures and spasms are common. Facial flushing, dilated pupils and irregular breathing are commonly seen with the above seizures.

Myoclonic (brief muscle jerk), clonic (repeated jerking movements), absence (blank stare) and atonic seizures (loss of muscle tone) may be seen with time.

Is CDD linked to any other epilepsy syndromes?

CDD was previously classified as an atypical form of Rett syndrome. Rett syndrome individuals have common features, including seizures, intellectual disability, and problems with development. However, the signs and symptoms associated with CDD and its genetic cause are different from those of Rett syndrome, and CDD is now considered a separate condition.

How frequent are seizures typically in CDD?

Seizures may become very frequent with multiple events per day.

How may seizures change over time?

The types of seizures can change with age, and they usually follow a predictable pattern. Seizures occur daily in most affected children. However, there may be periods of seizure freedom.

What other problems apart from Epilepsy, affect people with CDD?

The number of symptoms your child will experience, and the degree to which he or she experiences them, will be unique to your child. There is a wide spectrum in severity from moderately affected to profoundly affected. Most children with CDD have severe intellectual disability. The majority of CDD children are unable to walk, talk or feed themselves and many are confined to a wheelchair, but a significant proportion of children are able to walk independently. Some may have scoliosis (sideways curvature of the spine), visual impairment, gastrointestinal difficulties such as reflux and constipation, respiratory and sleep problems. Nearly all affected individuals have low muscle tone (hypotonia), and movement disorders can also be present.

What are the treatment options for CDD?

Seizures in CDD are difficult to treat with no single antiseizure medication (ASM) proven to be most effective in these children. However, some people do well on one ASM, while others need more than one medication or treatments. Steroid treatment and or the ketogenic diet (low carbohydrate high fat) have been used and been effective in some children. Vagus Nerve Stimulator (VNS) has been effective in some with CDD in addition to their ASMs..

Early intervention from Physiotherapy, Occupational therapy, Speech and language and dietician are recommended to maximize each child's potential.

What is the emergency protocol?

It is important that every child with CDD has an individualised seizure management plan (SMP) for seizures. Prolonged seizures may be dangerous to health and must be treated immediately.

What could I ask my doctor about?

- Safety advice
- Personalised seizure management plan
- Medication side effects & ongoing medicine management
- Genetic counselling
- Liaison with nursery/school
- Support/respite
- Sudden unexpected death in epilepsy (SUDEP)
- Early referral to Child Development centre .

Links

- CDD Orphanet summary
- CDKL5 Alliance website
- Loulou foundation: a private non-profit UK foundation dedicated to advancing research into the understanding and development of CDKL5
- CDKL5 Facebook group
- NHS Rare Disease Collaborative Network – CDKL5 (located at Bristol Children's Hospital)

CDKL5 ALLIANCE

Authors: Carol-Anne Partridge (CDKL5-UK) and Prof. Reetta Kälviäinen (Kuopio University Hospital, Finland).
The European Commission support for the production of this publication does not constitute endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

European Reference Network

Co-funded by the European Union