

# CDKL5 Disorder

## A Guide for Professionals



Giving hope through research  
and support to those living with  
a CDKL5 Disorder

**CDKL5 UK** 

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# CDKL5 UK

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### Foreword

In the decade since gene changes in CDKL5 were first linked to Rett syndrome, much has been learnt about the CDKL5 disorder.

Whilst individuals with CDKL5 mutations share some clinical features with those with MECP2 mutations causing Rett syndrome, we now know that they should be considered to be distinct disorders. In addition to careful clinical delineation of the disorder, laboratory based research studies, and the development of a mouse model for Cdkl5 deficiency, will enhance our understanding of the biological processes contributing to the CDKL5 disorder, and which will hopefully ultimately lead to targeted therapies.

It is therefore very timely that the key clinical and genetic features of the CDKL5 disorder should be brought together into this information booklet, along with the current approaches to the management of the complications of the disorder; and details of local specialist services CDKL5 support organisations. We hope you will find this resource of value.

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## Introduction

This information leaflet is aimed at providing information to professionals who may be involved in the assessment, diagnosis and treatment of children with CDKL5.

This is not intended to be a comprehensive guide, but rather an introduction to the complex clinical features that children with a CDKL5 disorder may exhibit. Not all features described may be present, and as the condition was only recognised recently, there may be other clinical manifestations that become apparent as we learn more.

## What is CDKL5?

CDKL5 is a rare genetic condition that was first identified in 2004. It is caused by mutations in the CDKL5 gene that is found on the X-chromosome and it therefore affects mainly girls although boys can also be affected. It typically presents with epileptic seizures in the first few weeks or months of life followed by severe neurodevelopmental delay. Many children who are now known to have CDKL5 were previously thought to have a variation of another genetic condition called Rett syndrome (atypical Rett) because there were some similar characteristics. However, in 2012, the “CDKL5 disorder” became recognised as a distinct condition.

## How can CDKL5 disorders be recognised?

The most prominent feature of the CDKL5 disorder is early onset of seizures.

The onset of seizures can happen within the first hours, days, weeks or months. Children have been diagnosed with CDKL5 with seizures starting as late as 8 months and in some cases up to the age of two. Some mothers have described feeling seizures in the pre-natal period.

Seizures manifest as tonic seizures with myoclonic clusters and tonic / clonic seizures. They generally happen in sleep at the onset of seizures, but as time passes they may appear during waking hours as well. It is common for these first seizures not to be detectable on EEG, and some children may initially be diagnosed with Benign Sleep Myoclonus, or Sandifer Syndrome. It is important to note that the absence of seizure activity on EEG does not necessarily exclude the presence of CDKL5 related seizure activity.

Children undiagnosed, are often given an electro-clinical diagnosis of Ohtahara Syndrome, Lennox Gastaut Syndrome or West Syndrome, some also may have a diagnosis of Leigh’s encephalopathy or other mitochondrial diseases. These syndromes have many different genetic causes including CDKL5. The CDKL5 disorder mainly affects girls, however, it should not be excluded as a diagnosis in boys as there are a number that have been diagnosed worldwide.

For additional symptoms please see the Clinical Symptoms A-Z from page 3 onwards.

## CLINICAL SYMPTOMS

# A to Z

### Abdominal Distension

This can be due to aerophagy, which commonly accompanies the abnormal breathing. Very severe cases may be helped by percutaneous gastrostomy, while other cases may also be helped by medication.

### Aerophagia

Air swallowing can be significant and can interfere with eating and full respiratory effort.

### Altered Pain Response

Inappropriate pain responses are very common in people with CDKL5. This can manifest itself in a number of ways. Parents report that children and adults bite themselves, may tolerate blood tests and lumbar punctures without showing the pain responses that a child of normal development might experience. However, they may cry appropriately when they take a “bump” for example. Altered pain response should be an important consideration when assessing someone with CDKL5 in a clinical setting, such as an emergency department, because although they may appear pain free, this may not always be the case. It has also been reported that some children who have experienced extreme pain, may not always appropriately respond to high dose opiates, and that alternative medication would need to be considered.

### Apraxia

Apraxia results from dysfunction of the cerebral hemispheres, especially the parietal lobe, and can be present in people with CDKL5. Apraxia includes limb-kinetic apraxia (the inability to make fine, precise movements with an arm or leg), *(continued on p. 4)*

## How do you diagnose a CDKL5 disorder?

The CDKL5 disorder is now being diagnosed in children at a relatively early age. Next generation sequencing is the new genetic technology that is likely to be used to diagnose CDKL5 disorder in your patient. It may be referred to as a “gene panel” and it is basically a genetic blood test. Instead of looking for spelling mistakes or deletions/duplications in one gene, the test would screen a number of genes for changes that may be found in people with severe early epilepsy. It should identify both spelling mistakes and deletions or duplications within the genes tested. Those who have had negative CDKL5 gene sequencing in the past may need this new test to look for a deletion or duplication of CDKL5 and to consider whether the explanation for the child’s difficulties lies within one of the other epilepsy syndrome genes.

## Referral to Appropriate Specialists

If a child is diagnosed with CDKL5 disorder, then the family should be offered genetic counselling. This would provide the family with the opportunity to discuss their child’s conditions and to consider their reproductive options. The family should also be supported in obtaining appointments with a paediatric neurologist and with a consultant paediatrician, who will coordinate the local therapy team providing the therapists with advice to help them in supporting the child. The therapists who may be involved are likely to come from physiotherapy, speech & language therapy, occupational therapy and music therapy.

## SEIZURE TREATMENTS: Anti-Convulsant Medication

Seizures within the CDKL5 disorder are difficult to treat.

It is important to note that some people do very well on low dose mono-therapy, whereas some need adjunctive therapy. It is usual for a child to go through the whole range of medications. Physicians should work closely with families to ensure that appropriate dosing is maintained to ensure quality of life for not only the child but also the family and care givers. Long-term use can affect bone density and this should be a consideration as the child gets older; appropriate testing and measures for monitoring bone density should be applied.

## SEIZURE TREATMENTS: Steroid Treatment

Steroid treatments, including the use of Corticotropin (ACTH) or Methyl-Prednisolone has shown some efficacy for those that have Infantile Spasms as part of their seizure disorder. Although there is evidence, that some patients may have a modified hypsarrhythmia that might also respond to steroid treatment, as well as those where non-convulsive status is a problem.

## CLINICAL SYMPTOMS

# A to Z

### Apraxia continued...

ideomotor apraxia (the inability to make the proper movement in response to a verbal command), ideational apraxia (the inability to coordinate activities with multiple, sequential movements, such as dressing, eating, and bathing), verbal apraxia (difficulty coordinating mouth and speech movements), constructional apraxia (the inability to copy, draw, or construct simple figures) and oculomotor apraxia (difficulty moving the eyes on command). Apraxia may be accompanied by aphasia. Generally, treatment for individuals with apraxia includes physical, speech, or occupational therapy.

### Aspiration Pneumonia

This is due to poor co-ordination of the muscles involved in swallowing. The epiglottis should fold over the trachea, to prevent the food or fluid from being inhaled, but fails to do so. Careful assessment of swallowing by an experienced speech therapist is required. Positioning is key to enhance swallowing, as is the texture of the food and consistency of fluid.

### Autistic Features

Varying degrees of social interaction, such as avoidance of eye contact or perseverating on people or objects. Repetitive behaviours may occur such as stereotypies, manic walking and repeated manipulation of objects occur. Other features include difficulty in motor coordination and attention, and lack of safety awareness.

### Bone Density

Osteoporosis is not common in CDKL5. However, it should be monitored over time

## CLINICAL SYMPTOMS

# A to Z

### Bone Density continued...

by an endocrinologist especially if there is a suggestion of precocious puberty. Osteoporosis should be considered particularly in those who have never walked or who have sustained a fracture. Bone density is also affected by anti-convulsants. A DEXA bone density scan should be undertaken in the event of a fracture or to provide a baseline for future assessments.

### Breathing Irregularities/ Hyperventilation

Some people with CDKL5 experience varying degrees of breathing irregularities and these can occur during wakefulness and sleep. Central and obstructive apnoea can also occur.

### Bruxism

Tooth grinding can be severe and can also occur during sleep. Involving a specialist dentist is important to prevent tooth decay and enamel problems.

### Cardiac Problems

Some people have experienced Long QT syndrome, which is more commonly associated with Rett Syndrome, abnormalities in heart rate such as tachycardia, and non-specific changes relating to T waves. It should be best practice to ensure that individuals with CDKL5 disorder have regular ECG's and echocardiograms.

### Constipation

Treat vigorously and actively with a view towards prevention. Bowel habits can change over time and can be a source of pain and discomfort. Even if dietary fibre is adequate, check the daily free water intake, which may be low.

## SEIZURE TREATMENTS: Ketogenic Diet

The ketogenic has been particularly successful for some people. Many families report an increase in awareness and alertness, as well as a decrease in seizure frequency. The ketogenic diet is a viable option for both people that feed orally, through a naso-gastric tube, or G Tube.

## Vagal Nerve Stimulation (VNS)

VNS is increasing in popularity. It has been particularly effective in treating CDKL5 related seizures. The settings vary with some people doing particularly well with rapid settings whilst others do well on lower settings.

## SEIZURE TREATMENTS: Neuro-Surgery

Neurosurgery can occasionally offer a method of seizure control when various other treatments have failed. In CDKL5 disorder the epilepsy rarely has a focus. If a seizure focus can be identified and is limited to one hemisphere of the brain it may be possible to provide surgical treatment. Eligibility for surgery can be determined by a PET scan or a SPECT scan to determine whether there is a focus.

## **THERAPEUTIC INTERVENTIONS:** **Hippotherapy / Equine Therapy**

The term “hippotherapy” means “treatment with the help of the horse”. Hippotherapy is a physical, occupational, and speech and language therapy treatment strategy that utilizes equine movement as part of an integrated intervention program to achieve functional outcomes. The movement provided by the horse is a multidimensional movement, which is variable, rhythmic and repetitive and is stimulating for the person living with CDKL5. Hippotherapy is an excellent tool for increasing trunk strength and control, balance, building overall postural strength and endurance, addressing weight bearing, and motor planning. This type of therapy may use a mechanical horse.

## **THERAPEUTIC INTERVENTIONS:** **Hydrotherapy**

Hydrotherapy is one of the most essential of the physical therapies for this group of profoundly disabled people. There are several reasons for the importance of this form of therapy, each of which relates to the nature of the disorder: CDKL5 produces a movement disorder which deprives the individual of the freedom to plan and carry out voluntary movement. This means that walking, if achieved, can be impaired. The difficulties which lead to the movement problem include fear which seems to be induced by perceptual difficulties. Although CDKL5 is not a progressive disease there is a liability to lose muscle bulk, strength and flexibility because of lack of use and the inability of the brain to coordinate the pathways involved.

## **CLINICAL SYMPTOMS**

# **A to Z**

### **Cortical Vision Impairment (CVI)**

CVI is a form of visual impairment which is related to the brain rather than the eyes. For some people with CDKL5 disorder this can be severe, though for some it does seem to improve over time. It is important to diagnose and to allow for therapeutic input from the appropriate specialists. Children with CDKL5 disorder tend to have a distinctive sideways glance.

### **Epileptic Seizures**

Seizures are almost always seen in CDKL5. Studies have suggested that children with a CDKL5 disorder exhibit 3 stages of epilepsy. Stage I is early epilepsy (onset 1-10 weeks) with a normal EEG despite frequent seizures. Stage II involves the development of epileptic encephalopathy (developmental epilepsy) with infantile spasms and hypsarrhythmia, being seen in about 50% of cases. Stage III appears as late, multifocal and myoclonic epilepsy, although this may not always be the case. Seizures are often difficult to control while puberty can bring about changes in seizure pattern and activity. Some become seizure free, though the neurodevelopmental issues remain profound.

### **Feeding Difficulties**

Dysphagia is common in CDKL5. Affected individuals may have difficulty with chewing, tongue movement, and swallowing. This may impair adequate nutrition or contribute to respiratory symptoms (aspiration, coughing, or choking during feeding). This may worsen with time with many affected individuals giving up eating altogether. Poor weight gain and episodes of aspiration require fluoroscopic examination and pH studies. In severe cases percutaneous

## **CLINICAL SYMPTOMS**

# **A to Z**

### **Feeding Difficulties continued...**

gastrostomy (PEG) should be considered. Persistent reflux may need medication or surgical correction.

### **Gastrointestinal**

Constipation, diarrhoea, intestinal gas and gastric reflux are all common problems. Constipation may not always be palpable, and should not be excluded until a bowel x-ray or ultrasound has been performed. Low gut motility, as well as slow gastric emptying, can also be evident with a child with CDKL5. There is anecdotal evidence that individuals with CDKL5 may be more susceptible to volvulus, and intussusception. Therefore with a rapid clinical deterioration with no apparent cause, there should be a high index of suspicion.

### **Impaired Sleep**

This includes night terrors, inappropriate laughing and jerking. Once awake, children with CDKL5 can take a long time to fall asleep again due to irregular breathing patterns, seizure activity and general restlessness. Many people with CDKL5 disorder will have significant impairment of sleep; they have days and nights with no sleep, but can also go for a couple of days where they sleep continuously. Many families use medication in order to aid sleep in the form of melatonin or benzodiazepines.

### **Mobility**

There is a wide range of ability; some affected patients will never walk, whilst others walk. Some have almost no hand skills while others perform some purposeful actions. Hypotonia is seen almost universally. *(continued on p. 8)*

## **THERAPEUTIC INTERVENTIONS:** **Music Therapy**

Music therapy has enormous value in aiding communication skills, improving gross and fine motor skills, helping with attention and general motivation and emotional well-being. It can also reduce stereotypies and functional use of hands can be developed. Music can also be used to help relax and calm.

### **Occupational Therapy**

We strongly recommend that the individual's overall 24 hour postural management should be considered carefully and reassessed at regular intervals. Individuals should be fully assessed for each piece of equipment that will promote functional hand use and sensory input encouraged to improve overall quality of life.

## **THERAPEUTIC INTERVENTIONS:** **Physiotherapy**

This is important in ensuring good postural management to influence scoliosis and joint deformities, develop or maintain transitional skills, increase motor ability, stimulate hand use, improve body awareness, reduce muscle pain and increase protective responses. Intensive physiotherapy programmes have also been used to good effect: Spider Therapy; TheraSuit Therapy; Universal Cage Therapy; and neuro-developmental Treatment (NDT Bobath).



## **THERAPEUTIC INTERVENTIONS: Speech & Language**

Supporting communication skills for people with CDKL5 is vital to improve concentration and develop effective communication methods. Speech and language therapists also have a responsibility to identify eating difficulties and provide advice about the texture of food and drink, adapted utensils, altering the pace of eating as dysphagia and aspiration pneumonia are common problems. The role of interactive eye gaze technology in facilitating communication for people with CDKL5 is uncertain but looks promising for some affected individuals. This may also prove useful in the assessment of cognitive function.

## **THERAPEUTIC INTERVENTIONS: Vision Therapy**

Vision Therapy is an individualized program designed to correct visual-motor and perceptual-cognitive deficiencies. Children affected by CDKL5 disorder show a range of characteristics and thus vision teaching strategies need to be assessed considering the uniqueness of each child. Vision Therapy offers comprehensive procedures designed to enhance the brain's ability to control hand-eye coordination problems and improve visual perceptual difficulties, such as:

- eye alignment,
- eye tracking and eye teaming,
- eye focusing abilities,
- eye movements,
- visual processing

## **CLINICAL SYMPTOMS**

# **A to Z**

### **Mobility continued...**

It is important for the child to be seen regularly by orthopaedic specialists and physiotherapy. They need assessments for scoliosis, hip alignment and joint laxity.

### **Mood Lability / Involuntary Behaviours**

Many families report inconsolable crying, laughing and erratic behaviour for no apparent reason. Although as the child gets older the families are able to interpret the crying as being related to pain, gelastic seizures, or sub-clinical seizure activity. A person reporting to medical services with severe crying should receive full work-up to exclude illness or possible gastrointestinal obstruction. Mood lability has been reported by parents, as going on for days with extreme shifts in the mood from elation to depression within the same day.

### **Range of Motion**

Contractures develop over time. Check for full passive range of motion. Reduction in Occupational and Physiotherapy services over time can lead to lack of awareness of this complication.

### **The Spine: Scoliosis / Kyphosis / Lordosis**

The chance of developing scoliosis increases with age, although statistics are not yet available as to the precise risk. There should be close monitoring of the spine for the development of a deformity. If detected then referral to a spinal surgeon is recommended.

### **Stereotypies**

A challenge for many children with CDKL5

## **CLINICAL SYMPTOMS**

# **A to Z**

### **Stereotypies continued...**

is repetitive and restricted behaviours (RRB). Some examples are continuously mouthing objects and hands, rocking, head swaying, hand flapping and clapping, also common in autism and Rett Syndrome. Similar to obsessive compulsive disorder (OCD), repetitive behaviour appears to represent a need for sameness and a resistance to novelty in which some children with CDKL5 may resist obstruction or interruption of their rituals. No one really knows why they happen and there is little consensus about treatment. However, most professionals label RRBs as purposeless and maladaptive. Alternative views consider the person may be seeking sensory (self-) integration or pleasurable sensations, or creating distraction from stress, or that the repetitive behaviour is being triggered by a possible underlying biomedical cause such as neurological dysfunction. Hand stereotypies within CDKL5 are very common. These manifest as finger tapping, hand mouthing, finger sucking and hand wringing. People with CDKL5 may hand mouth during feeding therefore, arm splints may be useful to enable effective feeding.

Many people with the disorder have non-functional hand use. However, therapy should be provided to encourage hand use.

### **Vasomotor Disturbances**

Sympathetic tone is high, due to poor autonomic restraint. Treat the skin gently, encourage activities using the whole body, and ensure that hands and feet are kept warm even in the summer. Even with warm clothing the person with CDKL5 may still have cold extremities.

## **THERAPEUTIC INTERVENTIONS: Health & Social Care**

The spectrum of disability and health needs vary widely with people with CDKL5. However, they are almost always exclusively classified by health, social and education specialists as having Profound and Multiple Learning Disabilities (PMLD). CDKL5 is a life shortening condition, due to the nature of the complications of the seizure disorder, orthopaedic considerations and autonomic dysfunction. Therefore the family should be supported to access the appropriate health and social care package to meet the family's needs. Some people with CDKL5 will access Continuing Health Care services, and some will meet the criteria for Hospice Care. Families requesting Hospice care for respite should be fully supported to access this.

## **Professionals**

Throughout their life-time, a person living with CDKL5 may need the help of many medical specialists. If a child presents and is diagnosed early, then a complete clinical work-up should be adopted. Medical and Allied Health specialists currently involved with individuals who have a CDKL5 disorder include:

- Paediatrician
- Geneticist
- Spinal Surgeon
- Endocrinologist
- Neurosurgeon
- Community Children's Nurse
- Neuropsychologist
- Physiotherapist
- Dietician
- Speech and Language Therapist
- Paediatric Neurologist
- Gastroenterologist
- Orthopaedic Surgeon
- Cardiologist
- General Surgeon
- Educational Psychologist
- Occupational Therapist
- Social Worker

## **CLINICS / SPECIALIST**

### **Testing in United Kingdom**

#### **Genetics Laboratory**

Institute of Medical Genetics  
University Hospital of Wales  
Heath Park, Cardiff CF14 4XW

#### **West of Scotland Genetic Services**

Level 2B, Laboratory Medicine  
Southern General Hospital  
Govan Road, Glasgow G51 4TF  
Tel: 0141 354 9330

### **Clinicians with a specialist interest**

#### **Dr Hayley Archer / Professor Angus Clarke**

Institute of Medical Genetics  
University Hospital of Wales  
Heath Park, Cardiff CF14 4XW

#### **Ass Prof Sameer Zuberi / Dr John Tolmie**

Epilepsy Genetics Clinic  
Fraser of Allander Neurosciences Unit  
Royal Hospital for Sick Children  
Glasgow G3 8SJ

## **Access to clinics**

People with CDKL5 need a well coordinated local team that meet their needs. Occasionally, parents / carers may find it helpful to access a specialist clinic for advice. The question being asked will determine which clinic would be most appropriate to refer to.

Dr Hayley Archer and Professor Angus Clarke often see families for information and advice, but cannot usually offer regular follow-up to NHS patients from outside Wales; in that case, they liaise with local services and suggest appropriate investigations and other referrals for the management of specific complications.



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