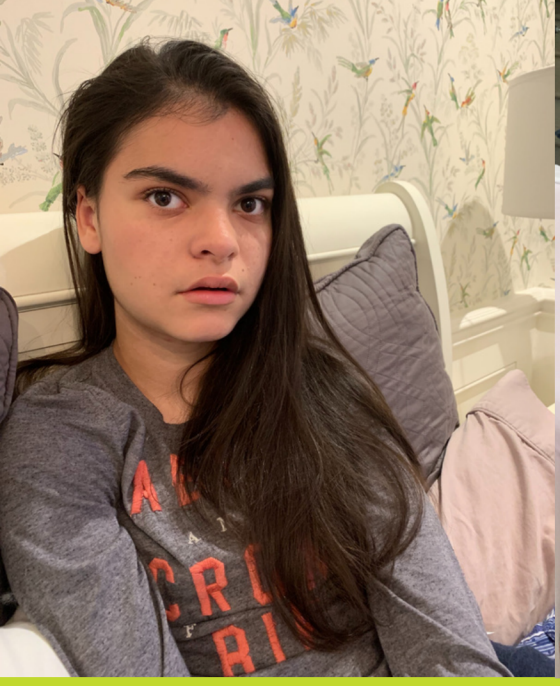
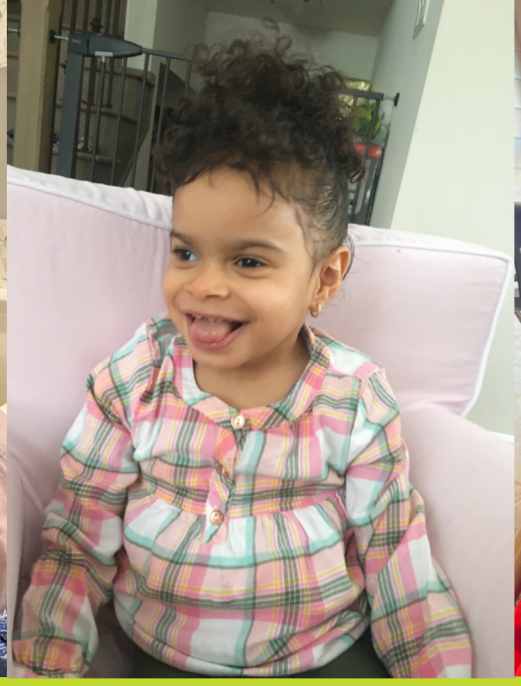
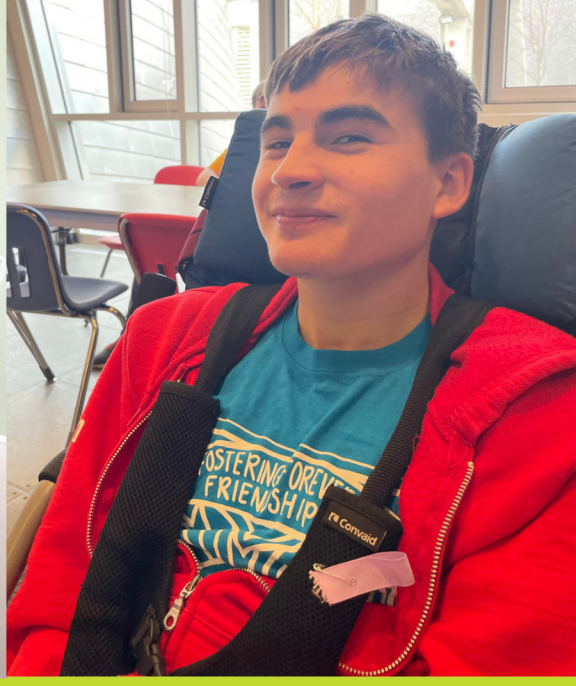
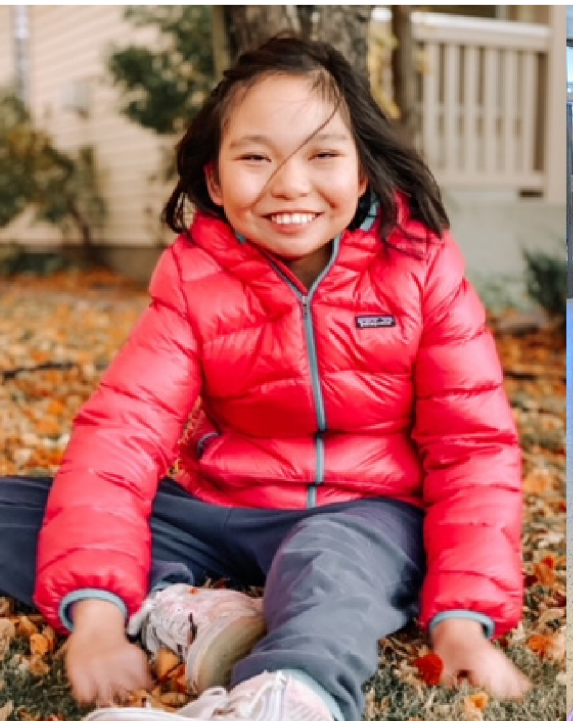
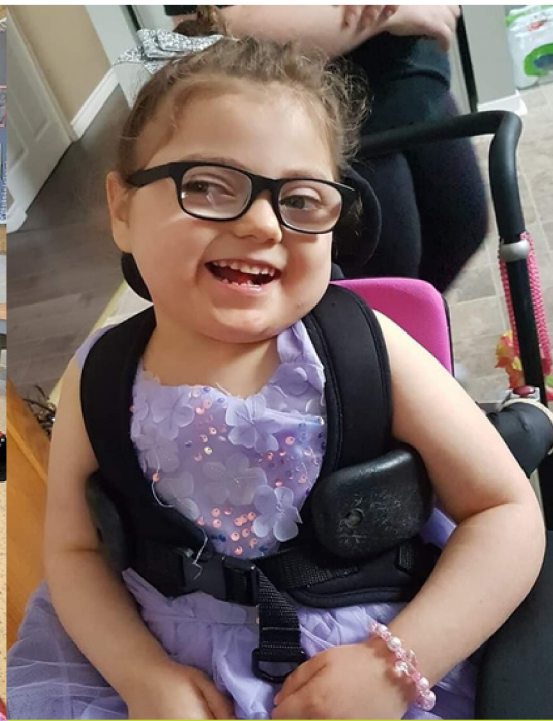




CDKL5 DEFICIENCY DISORDER

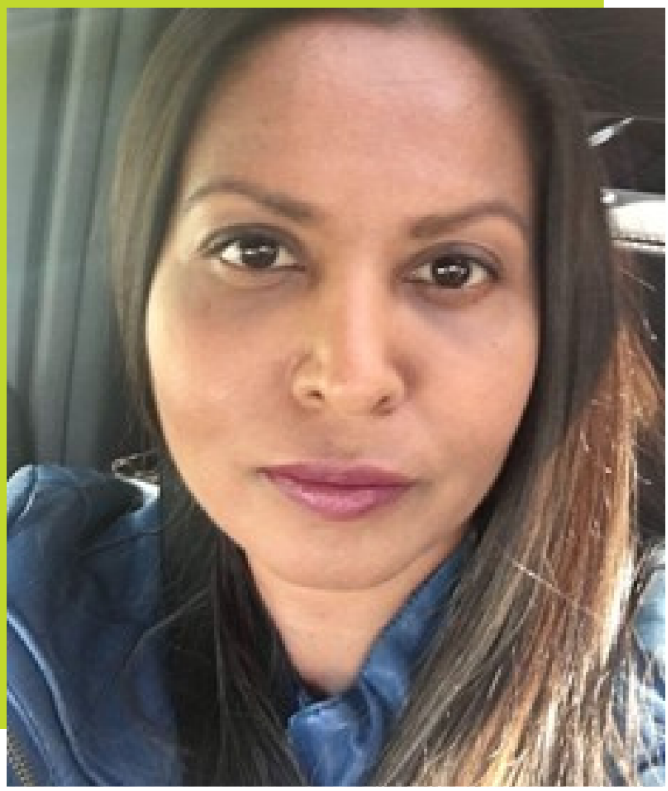
Parent Handbook

CDKL5 CANADA





Foreword



Sangeeta Staley

Founder & Past President

CDKL5 Canada

CDKL5 Deficiency Disorder (CDD) is a rare x-linked genetic disorder resulting in drug resistant epilepsy and other comorbidities notably scoliosis, gastrointestinal issues and cortical visual impairment (CVI). However, seizures are the most prominent feature that begin in infancy, which is a crucial time in a child's development.

In 2004 my daughter Tia was born. She started to display seizure-like activities around four months of age, but I suspect they were present much earlier on, because seizures can take many forms, such as absence seizures, infantile spasms, tonic-clonic and more. The search for a diagnosis began but proved unsuccessful as CDD was classified as an early-onset seizure variant of Rett Syndrome (RTT), as a result she was duly diagnosed as atypical RTT. Today we know it is an independent entity resulting from a mutation in the cdkl5 gene with its own distinct characteristics.

There is important research being conducted in Canada and worldwide into the discovery of treatments and ultimately a cure for the disorder. However, while we wait for those treatments, it is important we continue to provide the best care for our loved ones in order for them to have their best quality of life. In 2011 when my daughter was diagnosed, there was very little information available, but today we know much more. The aim of this handbook is to provide information about the disorder, and to aid you while you navigate this journey, it is not a comprehensive guide, nor is it a substitute for medical advice. We hope you find it useful.

Table of Contents

What is CDKL5?

CDKL5 Deficiency Disorder (CDD) is a rare developmental epileptic encephalopathy caused by mutations in the CDKL5 gene, and this can manifest in a broad range of clinical symptoms and severity. The hallmarks are early-onset, intractable epilepsy and neurodevelopmental delay impacting cognitive, motor, speech, and visual function. Although rare, the occurrence is believed to be ~1:40,000-75,000 live births, making it one of the most common forms of genetic epilepsy.

The CDKL5 gene provides instructions for making proteins that are essential for normal brain and neuron development. CDKL5 stands for cyclin-dependent kinase-like 5, and this protein acts as a kinase, which is an enzyme that changes the activity of other proteins by adding oxygen and phosphate atoms (a phosphate group) at specific positions. Researchers have not yet determined which proteins are targeted by the CDKL5 protein.

CDKL5 Deficiency Disorder was first identified in 2004. The CDKL5 gene is located on the X chromosome, which is one of the sex chromosomes. Females have two X's, and males have one X and one Y chromosome. Because of its location, CDD predominantly affects girls but many cases have been identified in boys.

What is CDKL5 Canada?

CDKL5 Canada is a Canadian registered charitable organization. It was founded in 2012 by Sangeeta Staley who served as President for 10 years. The organization is run by a volunteer working Board of Directors, many of whom are CDKL5 parents.

Our Misson

To pursue research into finding a cure and treatments for CDKL5 disorder and to raise public awareness of the disorder, while providing support to those affected by CDKL5 in Canada.

Vision & Values

We are committed to funding innovative research to find a cure for CDKL5 disorder. We believe in the power of collaboration and helping to unite efforts in curing this devastating disease. And we are dedicated to raise vitally needed public awareness, to advocate, and to provide support and information to all who deal with the hardships of this disorder.

Madison
Bowmanville, Ontario

Clinical Symptoms A to Z

A Abdominal Distension

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

Aerophagia

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

Altered Pain Response

Inappropriate pain responses are very common in people with CDD. This can manifest itself in a number of ways. Parents report that children bite themselves, and may tolerate blood tests and lumbar punctures without showing the pain responses that a child of normal development may 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 CDD in a clinical setting (such as an ER), because although they may appear to be pain free, this may not always be the case. It is also reported that some children have experienced extreme pain, but have not appropriately responded to high dose opiates. In such cases, an 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 CDD. Apraxia includes limb-kinetic apraxia (the inability to make fine, precise movements with an arm or leg), 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

Aspiration pneumonia occurs when food or liquid is inhaled into the airways or lungs, instead of being swallowed. In CDD, this is due to poor coordination 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 the 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. Other features include difficulty in motor coordination and attention, and lack of safety awareness.

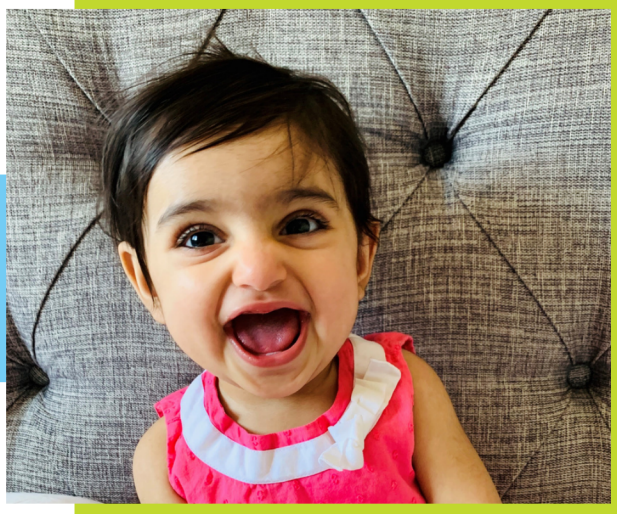
B

Bone Density

Osteoporosis is not common in CDD. However, it should be monitored over time 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 CDD experience varying degrees of breathing irregularities and these can occur during wakefulness and sleep. Central and obstructive apnea can also occur.



Arjoi
Brampton, Ontario

Bruxism

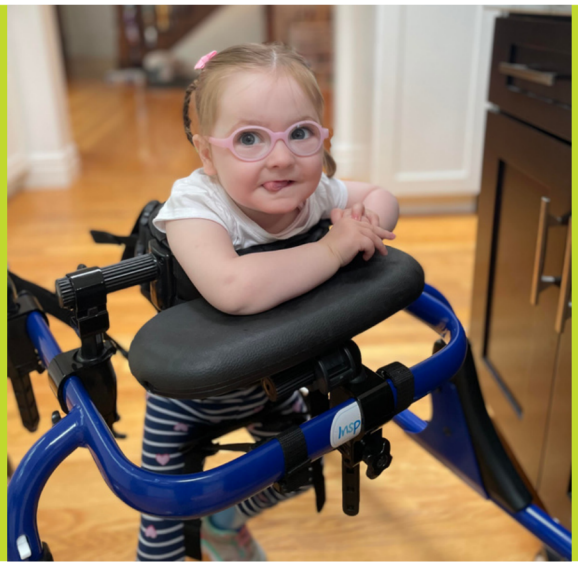
Tooth grinding can be severe and can also occur during sleep. Involving a dental specialist is important to prevent tooth decay and enamel problems.

C 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 water intake, which may be low.

Cortical Visual Impairment (CVI)

CVI is a form of visual impairment which is related to the brain rather than the eyes. The brain is having difficulties processing and interpreting the information that the eyes receive. For some people with CDD 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 CDD tend to have a distinctive sideways glance.



Ebba

St. John's, Newfoundland

E Epileptic Seizures

Seizures are almost always seen in CDD. Studies have suggested that children with CDD exhibit 3 stages of epilepsy. Stage 1 is early epilepsy (onset 1-10 weeks) with a normal EEG despite frequent seizures. Stage 2 involves the development of epileptic encephalopathy (developmental epilepsy) with infantile spasms and hypsarrhythmia, and is seen in about 50% of cases. Stage 3 appears as late, multifocal and myoclonic epilepsy, although this may not always be the case. Seizures are often difficult to control, and puberty can bring about changes in seizure pattern and activity. Some CDD individuals become seizure free, though the neurodevelopmental issues remain profound.

F Feeding Difficulties

Dysphagia is common in CDD. 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 orally altogether. Poor weight gain and episodes of aspiration may require fluoroscopic examination and pH studies.

Alivya
Calgary, Alberta

G Gastrointestinal

Constipation, diarrhea, 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 CDD. There is anecdotal evidence that individuals with CDD may be more susceptible to volvulus and intussusception.

I Impaired Sleep

This includes night terrors, inappropriate laughing, and jerking. Once awake, children with CDD can take a long time to fall asleep again due to irregular breathing patterns, seizure activity, and general restlessness. Many people with CDD will have significantly impaired sleep. They may have days and nights with no sleep. Parents often refer to their children as having “all night parties”. Many families use medication as a sleep aid in the form of melatonin or benzodiazepines.

M Mobility

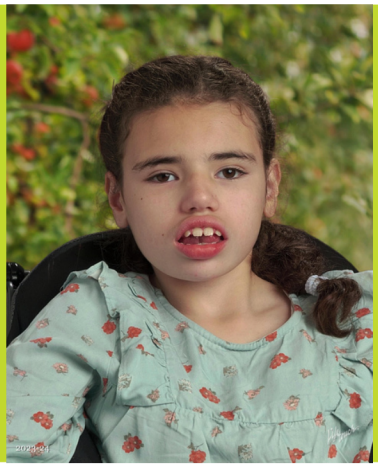
There is a wide range of abilities associated with CDD. Some patients will never walk, while others are able to walk. Some patients have almost no hand skills, while others perform some purposeful actions. Hypotonia is seen almost universally. Orthopedic surgeons should be consulted if there are problems such as scoliosis, hip alignment and joint laxity, which should be initially be screened for by the primary care physician. Physiotherapists are also very good at detecting problems that might be helped by an orthopedic specialist. These problems are easily detected by physical exam and radiographs.

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. Many parents report mood lability continuing on for days, with extreme shifts in the mood from elation to depression within the same day.

R Range of Motion

Contractures develop over time and are more likely to develop if the child has hypertonia as opposed to hypotonia, although they can be associated with both muscle conditions. Check for full passive range of motion. The practice model in most Canadian hospitals is consultative - meaning that a program of exercises is given to the caregiver and the child is seen for monitoring but not ongoing active therapy. If braces or splints are prescribed, they should be worn as prescribed and modified for comfort as the child grows. Your physiotherapist and orthotics specialists are your best advisors.



Gracie
Winnipeg, MB

S The Spine: Scoliosis/Kyphosis/Lordosis

The chance of developing scoliosis increases with age and approximately 8% of individuals with CDD will be at risk. There should be close monitoring of the spine for the development of any deformity. If detected, a referral to a spinal surgeon is recommended.

Stereotypies

A challenge for many children with CDD is repetitive and restricted behaviours (RRB). Some examples include continuously mouthing objects and hands, rocking, head swaying, hand flapping and clapping. Repetitive behaviour appears to represent a need for sameness and a resistance to novelty. Some children with CDD may resist obstruction or interruption of their rituals. Many professionals label RRBs as purposeless and maladaptive but some consider the person to be seeking sensory (self-) integration or pleasurable sensations, or creating a distraction from stress, or that the repetitive behaviour is being triggered by an underlying medical cause such as a neurological dysfunction. Hand stereotypies within CDD are very common. These manifest as finger tapping, hand mouthing, finger sucking and hand wringing. People with CDD may hand mouth during feeding, and arm splints may be a useful tool to enable more effective feeding. Many people with the disorder have non-functional hand use. However, therapy should be provided to encourage hand use.

V Vasomotor Disturbances

Vasomotor disturbance is often characterized by changes in skin temperature and color. In CDD patients, 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 CDD may still have cold extremities.

Seizure Treatments

Anti-Convulsant Medications

Seizures within CDD are difficult to treat. It is important to note that some people do very well on low dose mono-therapy, whereas others need adjunctive therapy. It is usual for a child to go through a whole range of medications. Physicians should work closely with families to ensure appropriate dosing is maintained to ensure quality of life not only for the child, but also for the family and caregivers.

Ketogenic Diet

The ketogenic diet has been particularly successful for some patients, especially when used as an early form of treatment. 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, as well as those who use a naso-gastric tube or G-tube.

Vagus Nerve Stimulation (VNS)

VNS involves the implantation of a small electrical device (similar to a pacemaker) under the skin on the upper chest. The device connects to the vagus nerve, which runs from the brainstem to the abdomen. VNS sends regular, mild electrical pulses to the nerve, which carries the pulses to the brain. This can help to prevent or shorten the length of seizures.

Neurosurgery

Neurosurgery can occasionally offer a method of seizure control when various other treatments have failed. In CDD, 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.

Infantile Spasms

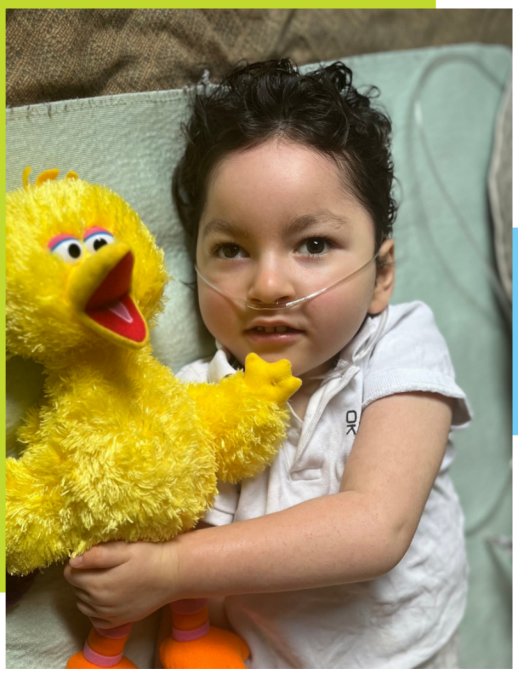
If a family has concerns that their child has developed Infantile Spasms, it is important to record and bring them to a physician for diagnosis as quickly as possible. An EEG can identify hypsarrhythmia or modified hypsarrhythmia to confirm diagnosis. Early diagnosis and treatment is key. Infantile Spasms can cause babies to stop developing as expected and can have a negative effect on the child's brain.

What do they look like?

Infantile spasms look like short tensing or jerking episodes that involve your baby's abdomen (belly), head, neck, arms and/or legs. The spasms only last for one to two seconds and usually happen one after another (in a cluster) every five to ten seconds. They look less intense then a typical seizure but are significantly more damaging.

Treatment

The standard treatments are Vigabatrin, or steroids, including the use of ACTH injections or high dose oral Prednisolone. These three methods have shown some efficacy for those that have Infantile Spasms as part of their seizure disorder. Families should discuss the possible side effects that accompany these treatments to determine which is the best treatment option for their child.



Rohan
Edmonton, AB

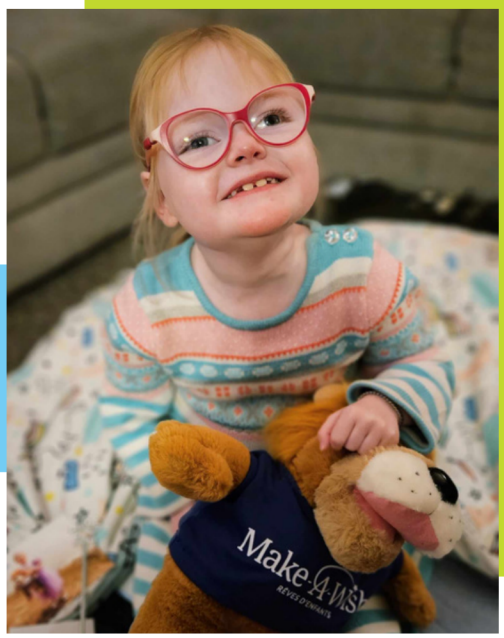
Therapeutic Interventions

Health & Social Care

The spectrum of disability and health needs vary widely with CDD. The conditions can be life shortening due to complications associated with, but not limited to, the seizure disorder, orthopedic, GI issues, and autonomic dysfunction. These may require long term care and attention. Families should work with their primary healthcare physician or specialists to access support services in their community for medically fragile and/or developmentally challenged individuals. These services may vary from province to province.

Physiotherapy

Physiotherapy should be started as early as possible and will continue to play an important role throughout the lives of people with CDD. It is important to develop and maintain transitional skills, increase motor ability, stimulate hand use, improve body awareness, reduce muscle pain, increase protective responses and ensuring good postural management to prevent scoliosis and joint deformities,



Lyla
Halifax, Nova Scotia

Occupational Therapy

Occupational Therapy is helpful for people with physical, sensory, or cognitive difficulties. Using everyday exercises and activities, Occupational Therapists (OTs) can help reduce barriers by working on skills such as functional hand use and improved hand-eye coordination. OTs can also fit individuals for specialized equipment to help build independence such as wheelchairs, splints, standers, gait trainers, and bathing equipment.

Speech & Language Therapy

Supporting communication skills for people with CDD is vital to improve concentration and develop effective communication methods. Speech and Language Therapists (SLPs) also have a responsibility to identify eating difficulties and provide advice about the texture of food and drink, adapted utensils, and altering the pace of eating.

An Augmentative and Alternative Communication (AAC) Specialist may also be considered. They can recommend methods of communication which can be used by people with CDKL5 disorder who have little or no speech. They would also be helpful in assessing if a tool such as interactive eye gaze technology is a possibility.

Vision Therapy

Vision Therapy is an individualized program designed to correct visual-motor and perceptual-cognitive deficiencies. Prior to an intervention plan, it is critical to determine how a child sees; once that is understood, an intervention plan can be developed.

People with CDD show a range of visual characteristics; therefore, various teaching strategies need to be assessed. Cortical Visual Impairment (CVI) is very common in CDD, and children can present with visual behaviours such as light gazing, difficulties looking at a distance, delayed responses in looking at an object, and showing a strong preference for looking at one side or another. 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, eye focusing abilities, eye movements, and visual processing.

Liv
St. Catherine's, Ontario

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 CDD. Hippotherapy is an excellent tool for increasing trunk strength and control, balance, building overall postural strength and endurance, addressing weight bearing, and motor planning. In addition, it is a therapy that children often enjoy.

Music Therapy

Music therapy is the use of music to promote healing and enhance quality of life. There is some evidence that music therapy can reduce pain, stress and provide an overall sense of well-being. It may also reduce stereotypies and aid in relaxation.

Hydrotherapy

Hydrotherapy is a physical therapy that can be very beneficial to people with CDD. The four key features of hydrotherapy are buoyancy, water resistance, hydrostatic pressure and water temperature. Hydrotherapy can also increase the metabolic rate, increase digestion activity, boost the immune system, improve skin and muscle tone, and encourage relaxation.

Massage Therapy

Massage therapy involves manipulation of the superficial layers of muscle and connective tissue. Full body massage may be beneficial, as well as hand massage because of the lack of hand use. Muscle atrophy (wasting) caused by forced inactivity can be delayed by massage. Massage therapy helps to improve muscle tension and pain, increase flexibility and mobility, reduce pain and stiffness in muscles and joints, promote relaxation, maintain range of motion, and stimulate the lymphatic system throughout the body.

Clinics & Specialists

Clinicians with a Specialized Interest

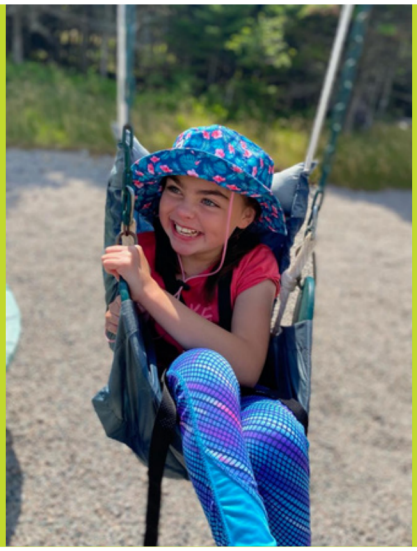
Dr. Laura McAdam, MSc, MD, FRCP(C)

Holland Bloorview, Kids Rehabilitation Hospital
150 Kilgour Road, Toronto Ontario Canada M4G 1R8
Tel 416 425 6220 | Toll free 800 363 2440
lmcadam@hollandbloorview.ca

Specialists

Throughout their life-time, people living with CDD may need the help of many medical specialists. If a child is diagnosed early, then a complete clinical work-up should be adopted.

Summary of Potential Referrals:
Paediatrician
Paediatric Dentist
Paediatric Neurologist
Geneticist
Gastroenterologist
Orthopaedic Surgeon
Cardiologist
Neurosurgeon
General Surgeon
Public Health Nurse
Neurosychologist
Educational Psychologist
Physiotherapist
Occupational Therapist
Dietician
Speech and Language Therapist
Social Worker



Jordan
St. John's, Newfoundland

CDKL5 Registries

What is a CDKL5 Registry?

A CDKL5 registry is an official record of CDKL5 patients. By joining a CDKL5 registry, we can accurately track and safely share data with researchers and pharmaceutical companies who are interested in hosting clinical trials. Registries are especially important for rare diseases because there are so few cases and often hospitals don't have a recording system in place.

Link Canada

Link Canada is our Canadian registry which helps us to organize the CDKL5 community in Canada. As parents of CDKL5 children, we want to have access to new drug therapies, treatments, and clinical trials. Your information will be used for the sole purpose of organizing the community, and will assist in facilitating research and trial opportunities. A parent, guardian or caregiver can register an individual by visiting our website at www.cdkl5canada.ca. Find it under the Families tab, under Link Canada.

International CDKL5 Registry

The International CDKL5 Registry is a joint effort funded and supported by the LouLou Foundation and the Orphan Disease Centre at the University of Pennsylvania's Perelman School of Medicine. In addition to collecting data for research and pharmaceutical development, the registry advances scientific knowledge by sharing de-identified (anonymous) data with researchers from around the world. This is a larger, more in depth registry that includes patient history, symptoms, and treatments, and requires additional surveys over time to track progression of the disease and to increase understanding of CDD symptoms.

CDKL5 Affiliated Organizations

CDKL5 Canada
www.cdkl5canada.ca
Natalie Ladly nladly@cdkl5canada.ca

CDKL5 Alliance
Umbrella group representing many patient and non-profit organizations from around the world
www.cdkl5alliance.org

LouLou Foundation
www.louloufoundation.org
Daniel Lavery dlavery@louloufoundation.org

International Foundation for CDKL5 Research (IFCR)
www.cdkl5.com
Karen Utley kutley@cdkl5.com

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