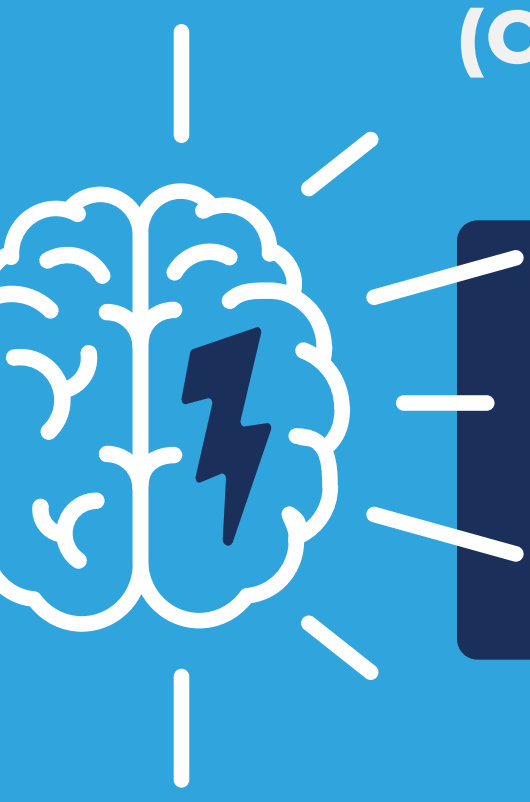
CDKL5 Deficiency Disorder (CDD)



CDD is a rare, genetic, developmental and epileptic encephalopathy caused by a mutation in the cyclin-dependent kinase-like 5 (*CDKL5*) gene[1]

INCIDENCE

CDD is one of the most common genetic epilepsies; about half the incidence of Dravet Syndrome due to *SCN1A* mutation[2-4]

Occurs in **1 in ~40,000** live births[4]

Approximately 90 to 100 newborns with CDD in the United States per year[4,5]

X-linked disorder impacting females more than males (4:1)[6]

ETIOLOGY

Most cases result from de novo mutations in the *CDKL5* gene; >265 pathogenic variants are known[6]

CDKL5 is a serine-threonine protein kinase highly expressed in the brain[6] that regulates a variety of neurodevelopmental processes, including:

- Neuronal maturation and migration[7]
- Synaptic plasticity[8]
- Dendritic spine development[9]

Protein function is affected by missense, frameshift, splice, and nonsense mutations[6,10]

CDD CLINICAL CHARACTERISTICS

CDD was initially identified as the early-onset seizure variant of Rett Syndrome[11]

EPILEPSY

Often, the first overt symptom of CDD is the onset of epileptic seizures, typically within the first few weeks to months of life[1,6]

6 weeks
Median time of seizure onset[1,12]

3 months
90% of patients experience a seizure[1,11]

6 months
97% of patients experience a seizure[6]

More than 98% of patients experience epileptic seizures[6]

Up to 80% have daily seizures[6,13]

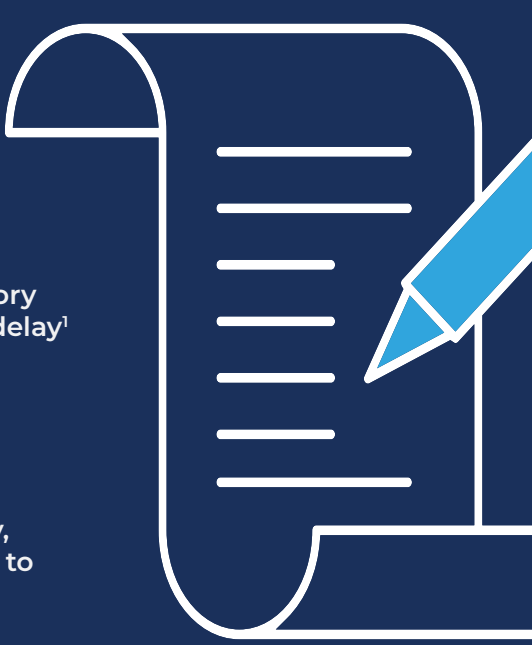
Approximately 84% have treatment-resistant, refractory seizures[14]

Seizures evolve over time across 3 stages[1,15]:

- Early epilepsy
- Epileptic encephalopathy
- Late resistant multifocal and myoclonic epilepsy

- Infantile spasms are an early manifestation in some patients and occur in most patients at various stages of CDD[1]
- Complex seizure semiology is common in later stages with a unique seizure pattern of hypermotor-tonic-spasm sequence[1]

SUMMARY



- CDD is an epileptic encephalopathy characterized by early-onset, refractory epilepsy and severe developmental delay[1]
- CDD is caused by a mutation in the *CDKL5* gene and requires genetic testing for diagnosis[1,20]
- Seizures in CDD are highly refractory, with limited or short-lived responses to many treatments[1]
- Consensus recommendations have been published to help standardize and guide medical care for patients with CDD[20]

References: 1. Olson HE, et al. *Pediatr Neurol*. 2019;97:18-25. **2.** Mei D, et al. *Mol Diagn Ther*. 2017;21(4):357-373. **3.** Wu YW, et al. *Pediatrics*. 2015;136(5):e1310-e1315. **4.** Symonds JD, et al. *Brain*. 2019;142(8):2303-2318. **5.** Osterman MJK, et al. *Natl Vital Stat Rep*. 2022;70(17):1-50. **6.** Jakimiec M, et al. *Brain Sci*. 2020;10(2):107. **7.** Fuchs C, et al. *Neurobiol Dis*. 2014;70(100):53-68. **8.** Ricciardi S, et al. *Nat Cell Biol*. 2012;14(9):911-923. **9.** Zhu Y-C, et al. *Proc Natl Acad Sci U S A*. 2013;110(22):9118-9123. **10.** Peikes T, et al. *Genet Genomics*. 2020;1(1):1-7. **11.** Fehr S, et al. *Eur J Hum Genet*. 2013;21(3):266-273. **12.** Mangatt M, et al. *Orphanet J Rare Dis*. 2016;11:39. **13.** Fehr S, et al. *Neurology*. 2016;87(21):2206-2213. **14.** Frullanti E, et al. *Int J Genomics*. 2019;2019:6956934. **15.** Bahi-Buisson N, et al. *Epilepsia*. 2008;49(6):1027-1037. **16.** Fehr S, et al. *Am J Med Genet A*. 2016;170(11):2860-2869. **17.** Loulou Foundation, International Foundation for CDKL5 Research. *The Voice of the Patient Report: CDKL5 Deficiency Disorder (CDD)*. June 17, 2020. **18.** Leonard H, et al. *Lancet Neurol*. 2022;21(6):563-576. **19.** Olson HE, et al. *J Neurodev Disord*. 2021;13(1):40. **20.** Amin S, et al. *Front Neurol*. 2022;13:874695.

BEYOND EPILEPSY: OTHER COMORBIDITIES OF CDD

All patients with CDD experience delayed psychomotor development and intellectual disability, but the extent of functional disability is variable and may depend on *CDKL5* mutation genotype[6,16]

Generalized hypotonia[6]
100%

Limited or absent speech[14]
83%

Global developmental delay[17]
100%

Visual impairment[6]
80%

Gastrointestinal & feeding problems[6]
87%

Sleep problems[14]
44%

Hand stereotypies[6]
86%

Respiratory disorders[6]
33%

DIAGNOSIS

- Early clinical signs of CDD include[18]:
  - seizures with multiple phases
  - prominent hypotonia
  - cerebral visual impairment
  - progressively worse encephalopathy

- Proposed minimal diagnostic criteria include[1]:
  - A pathogenic or likely pathogenic variant in the *CDKL5* gene
  - Motor and cognitive developmental delays
  - Early-onset epilepsy within the first year of life

CDD MANAGEMENT AND TREATMENT CONSIDERATIONS

Management is symptom-based and requires a multidisciplinary approach[6]

Levetiracetam, topiramate, clobazam, and phenobarbital were reported as the most frequently used ASMs in the United States to treat CDD-associated seizures[19]

Nonpharmacological seizure management methodologies, including ketogenic diet, vagal nerve stimulation, and corpus callosotomy, have shown variable results[1]

Consensus recommendations from an international and multidisciplinary panel of experts were published in June 2022 to propose clinical management recommendations[20]

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