

CDKL5 Current Knowledge, Gaps and Future Directions

Clinical Features

What is currently known¹

- CDD is a severe Developmental Epileptic Encephalopathy with onset in early infancy (A, B, C).
- Seizures are refractory although there may be an early honeymoon period in just under a half (B, C).
- Multiple seizure types, often with multiple phases, occur including epileptic spasms, tonic, myoclonic and generalised tonic-clonic seizures (B).
- Gross motor, fine motor and communication skills are all severely impaired with only a quarter of females able to take independent steps with males, if non-mosaic, even more impaired (B, C).
- Cerebral visual impairment (CVI) is present in at least three quarters of patients, and a possible early predictor of clinical severity (B).
- Gastrointestinal, respiratory, and musculoskeletal symptoms are similar in prevalence to other DEEs with hypotonia and sleep disturbances more prominent but movement disorders possibly less prominent (B, C).
- Seizures, developmental delay including communication, sleep and gastrointestinal problems have been expressed as of major concern by caregivers of individuals with CDD.
- More than 200 individual genetic variants and only a small number of recurrent variants have been identified in individuals with CDD. Truncations occur throughout the gene but missense variants only in the kinase domain (C).
- There is some evidence to demonstrate that those with late truncating mutations have better functional ability (C).

¹ Data informing our clinical knowledge of CDD has been derived to date from four sources: A) case reports and case series; B) a multi-centre clinic-based infrastructure; C) an international caregiver-report database; and D) clinical trials

What is not known and therefore needed

- Data on the evolution of electroclinical (EEG, evoked potentials) features which may be used for future development of biomarkers (B).
- Seizures are so frequent that accurate counting may be problematic; each seizure event may include distinct semiologies. Therefore, developing assessments that measure the impact of seizures on daily functions is needed (B, C).
- Evaluation of the nature and magnitude of sleep disturbances given their likely burden on the child and family (B, C).

- Investigation of the prevalence and clinical features of movement disorders, musculoskeletal issues and other comorbidities not yet characterised e.g., behavioural profile, cardiac rhythm abnormalities (B, C).
- Better understanding of the factors that predict phenotypic variability by pooling or harmonising data from multiple sources where practicable (B, C).
- Data on natural history and mortality including the rate of Sudden Unexpected Death from Epilepsy (B, C).

Clinical Management

What is currently known

- Minimal published research on efficacy of ASMs although several drugs in various stages of development (D).
- Polypharmacy is common but associated with negative impact on child quality of life (C).
- Purified CBD was associated with some improvement in seizure control in a small open-label study while in an observational study 49 of 70 caregivers expressed benefit from their child's use of a cannabis preparation (C, D).
- Use of ketogenic diet has been shown to provide some short term benefit for seizure control and has been recommended as an initial treatment of infantile spasms along with conventional first line treatment or if first line treatment failed (B, C).
- Improvements in seizure frequency, duration and intensity reported with VNS but no concomitant reduction in ASMs (B, C).
- Absence of research evaluating the impact of therapy on child development.

What is needed

- Replication of small studies showing benefit for particular ASMs initially through large scale observational studies accounting for age, seizure type and combinations of treatment used (B, C).
- Disease-specific clinical trials of new ASMs which like fenfluramine have shown efficacy in other disorders (D).
- Research to evaluate the impact of different therapy approaches on developmental progress (B, C).
- Pre-clinical research to identify potential disease-modifying treatments which go beyond only seizure control. Clinical assessments and biomarkers that are translatable from animal models to a human CDD population are also needed (B, C).
- Program of clinical trial readiness to ensure there are validated outcome measures available for the specific domains (including for quality of life) likely to be involved (B, C)

Advantages and disadvantages of different data sources

- A) Case reports and small series provide in-depth clinical information about a limited number of patients but often cannot stratify their findings by gender or age group and rarely by genotype. Moreover, these patients may not necessarily be representative of the underlying population of CDD cases.
- B) Multicentre clinical studies have the advantage of aggregating data from multiple sites thereby building numbers while still retaining clinical detail. These can take the form of data collected in routine clinical care through the US Centers of Excellence (COE) or in a research infrastructure such as the US Natural History Study (NHS) which since 2013 has undertaken annual clinical evaluations on 72 individuals with CDD. These include structured clinical examinations, parent report, electrophysiological biomarkers and biobanking. Although there are many potential benefits from such a natural history study, disadvantages include cost, sustainability, geographical restrictions, and burden on families. Setting up both types of systems (COE and NHS) requires considerable time, funding and resources especially with respect to the ethical and governance requirements. Families attending such clinics may be more advantaged and again not necessarily representative of the underlying population.
- C) The ICDD is an international database established in 2012 in order to accrue numbers of cases not feasible from an individual country. Data on close to 400 individuals from over 50 countries has now been submitted. Although possibly representative of the children diagnosed in these countries these cases are not necessarily representative of all children with the disorder as diagnosis is a function of access to genetic testing which varies by country and socioeconomic circumstances. The advantages of this database are the much larger numbers. The disadvantages are that data are parent-reported so that certain clinical items are not available.
- D) Given the use of rigorous protocols and validated outcome measures clinical trials can provide best evidence of efficacy for new treatments but their implementation provides many challenges especially for an ultra-rare disorder. Clinical trials in CDD have the advantages of in-person clinician performed assessments, however the assessments are specifically tailored around the interventional end-points of the study, such as seizures. Access to data sets may be limited and available only after publication which often takes considerable time although ClinicalTrials.gov can be a helpful tool in determining the status of a specific trial.

Hypotonia	85%#	-	85%#	-	-	-	-	-	-	-	-	-	-	-	95%#	81%#	92%#	-	-	-	-	-	-	-	-	-	
Brain MRI																											
Normal	4%#	-	4%#	-	-	-	-	-	-	-	-	-	-	-	74%#	47%#	69%#	-	-	-	62%	25%	52%	-	-	-	
Brain atrophy	65%#	-	65%#	-	-	-	-	-	-	-	-	-	-	-	26%#	53%#	31%#	-	-	-	33%	75%	45%	-	-	-	
Other abnormality	31%#	-	31%#	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Gastrointestinal																											
Any	72%	-	72%	-	-	-	86%	89%	87%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Constipation	-	-	-	-	-	-	69%	83%	71%	-	-	-	-	-	48%	-	-	-	-	-	-	-	-	-	-	-	-
Reflux				-	-	-	65%	59%	64%	-	-	-	-	-	22%	-	-	-	-	-	-	-	-	-	-	-	-
Air swallowing	15%	-	15%	-	-	-	28%	24%	27%	-	-	-	-	-	40%	-	-	-	-	-	-	-	-	-	-	-	-
Gastrostomy ever	-	-	-	-	-	-	24%	58%	29%	-	-	-	-	-	31%	-	-	-	-	-	-	-	-	-	-	-	-
Sleep																											
Any	55%	-	55%	-	-	-	86%	94%	87%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Night waking	-	-	-	-	-	-	59%	53%	59%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Daytime napping	-	-	-	-	-	-	47%	44%	47%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bruxism	40%	-	40%	-	-	-	38%	50%	40%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Night screaming	-	-	-	-	-	-	23%	22%	23%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Night laughing	-	-	-	-	-	-	26%	33%	27%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory																											
Any	-	-	-	-	-	-	30%	50%	33%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperventilation	15%	-	15%	-	-	-	14%	13%	13%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Apnoea/breath holding	-	-	-	-	-	-	24%	44%	26%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pneumonia ever	-	-	-	-	-	-	17%	53%	21%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aspiration ever	-	-	-	-	-	-	18%	53%	23%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skeletal																											
Scoliosis	-	-	-	-	-	-	19%	31%	20%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular																											
Arrythmia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	38%	-	-	-	-	-	-	-	-	-	-	-	-

N.B. percentages are rounded to nearest percent, * Average age used instead of median age, # Liang et al.³⁹ study consists of an aggregation of case reports and case series reported in the literature and contains the subset of individuals from the Bahi-Buisson et al. study¹², ^Age at diagnosis of visual impairment was 2 years and above. [‡] Please note, individuals may be coded/diagnosed with more than one seizure type hence the total percentage for initial seizure types and seizure types may not add up to 100%. Additionally, not all publications used the same seizure classifications systems. The authors attempted to align all classifications with the most recent ILAE classification.

Abbreviations: ICDD, International CDKL5 Disorder Database; F, female; M, male; freq, frequency; EoEE, early-onset epileptic encephalopathy; RTT, Rett syndrome; NSEE, nonspecific epileptic encephalopathy; ISSX, X-linked infantile spasms; HTSS, hypermotor-tonic-spasms sequence; GTC, generalized tonic-clonic;

Supplementary Table 2. Quality of Life Inventory-Disability (QI- Disability): Domains and Related Questions.¹

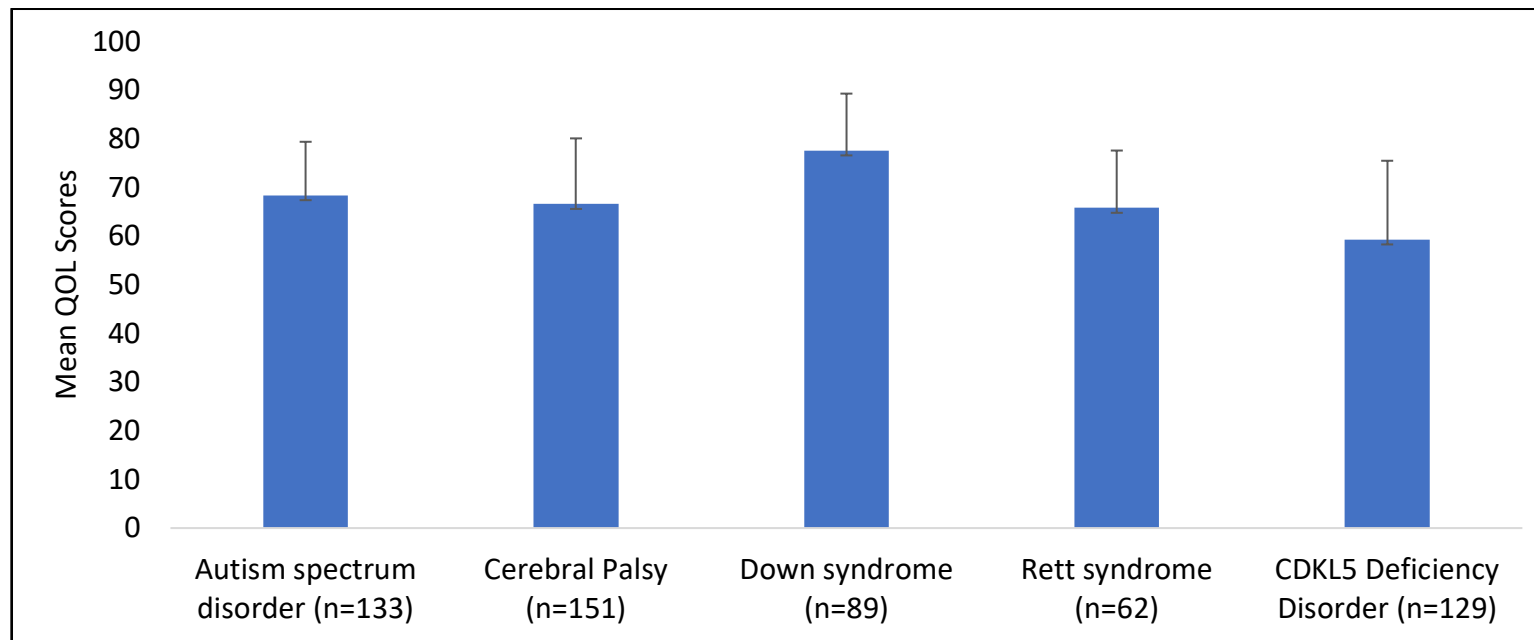
Domains of QI-Disability	No of items	Questions
Physical health	4	<p><i>Over the past month, how often has your child...</i></p> <p>Had enough energy to participate in routines and activities. Kept in good general health (e.g., avoided coughs, colds, fever). Slept well during the night. Been alert and aware during the day.</p>
Positive emotion	4	<p><i>Over the past month, how often has your child...</i></p> <p>Been in a good mood. Smiled or brightened their facial expression. Showed happiness through body language (e.g., making eye contact, body facing others). Showed cheeky or comical mannerisms (e.g., laughed, giggled).</p>
Negative emotion	7	<p><i>Over the past month, how often has your child...</i></p> <p>Been unsettled without an apparent reason. Showed aggression (e.g., hitting, kicking, using offensive language, being destructive). Appeared upset or angry (e.g., crying, screaming, moving, or stiffening the body). Become withdrawn with a low mood. Deliberately hurt themselves. Expressed discomfort with changes in routine (e.g., carers, school, out-of-home care). Showed signs of being anxious or agitated (e.g., teeth grinding, fast breathing, avoidance).</p>
Social interaction	7	<p><i>Over the past month, how often has your child...</i></p> <p>Expressed happiness when they were understood. Appeared relaxed when making eye contact. Initiated greetings with people verbally or nonverbally (e.g., eye contact). Enjoyed being included. Enjoyed the social experiences of meal times. Responded positively when others paid attention to them (e.g., your child smiled, showed interest). Showed pleasure or excitement when looking forward to activities (e.g., going to school, outings, events).</p>
Leisure and the outdoors	5	<p><i>Over the past month, how often has your child...</i></p> <p>Enjoyed moving their body (e.g., walking, swinging, swimming). Enjoyed feeling steady or stable during physical activities (e.g., sitting, standing, bike riding). Enjoyed physical activities (e.g., going out for a walk, swimming, swinging, dancing). Enjoyed going on outings in the community (e.g., shopping, party, sports, theatre). Enjoyed spending time outdoors (e.g., contact with water, grass, wind, sunshine).</p>
Independence	5	<p><i>Over the past month, how often has your child...</i></p> <p>Expressed their needs (e.g., hunger, thirst, toileting). Made their own choices for activities or things they enjoy (e.g., DVD's, toys). Helped to complete routine activities (e.g., dressing, feeding, chores around the house). Enjoyed making things with their hands—can be with help (e.g., building blocks, painting, cooking). Enjoyed using technology (e.g., computer, tablet, applications on phones)</p>

- Downs J, Jacoby P, Leonard H, Epstein A, Murphy N, Davis E, Reddihough D, Whitehouse A, Williams K. Psychometric properties of the Quality of Life Inventory-Disability (QI-Disability) measure. *Qual Life Res* 2019; **28**: 783-94

Supplementary Table 3. Preclinical outcome measures from preclinical trials and corresponding potential clinical outcome measures.

Preclinical Trial	Preclinical Outcome Measures								
	Hindlimb claspings	Rotorod	Repetitive behaviour	Learning and memory	Hyperactivity	Breathing pattern	Visual responses	Socialization	Seizure latency
GSK3b inhibitor ⁸²	✗	✗	✗	✓	✗	✗	✗	✗	✗
Protein replacement ⁸³	✓	✗	✓	✓	✓	✓	✓	✗	✗
Memantine ⁸⁴	✗	✗	✓	✓	✗	✗	✗	✓	✗
IEM 14606 ⁸⁵	✗	✗	✗	✓	✗	✗	✗	✓	✓
Sertraline ⁸⁶	✗	✗	✓	✓	✓	✗	✗	✗	✗
Gene replacement ⁸⁷	✓	✓	✓	✓	✓	✗	✗	✗	✗
Green tea ⁸⁸	✓	✗	✓	✓	✗	✗	✗	✗	✗
Potential Clinical Outcome Measures	Hindlimb claspings	Rotorod	Repetitive behaviour	Learning and memory	Hyperactivity	Breathing pattern	Visual responses	Socialization	Seizure latency
CCSA	✓	✓	✓	✓	✓	✓	✗	✓	✗
CSBS-DP	✗	✗	✗	✓	✗	✗	✗	✗	✗
QI-Disability	✗	✗	✗	✓	✗	✗	✗	✓	✗
VEP	✗	✗	✗	✗	✗	✗	✓	✗	✗
Resting state EEG	✗	✗	✗	✗	✗	✗	✗	✗	✓

Supplementary Figure 1: Total Quality of Life (QOL) scores in children with CDKL5 Deficiency Disorder¹ and other Intellectual Disabilities (Autism Spectrum Disorder, Cerebral Palsy, Down syndrome, Rett syndrome).²



1. Leonard H, Junaid M, Wong K, Demarest S, Downs J. Exploring quality of life in individuals with a severe developmental and epileptic encephalopathy, CDKL5 Deficiency Disorder. *Epilepsy Res.* 2021;169:106521.
2. Williams K, Jacoby P, Whitehouse A, Kim R, Epstein A, Murphy N, et al. Functioning, participation, and quality of life in children with intellectual disability: an observational study. *Dev Med Child Neurol.* 2021;63(1):89-96.

Supplementary Figure 2: A framework of likely observations contributing to the diagnosis of CDKL5 Deficiency Disorder.

