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Topical Review

Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review

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ABSTRACT

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental encephalopathy caused by pathogenic variants in the gene *CDKL5*. This unique disorder includes early infantile onset refractory epilepsy, hypotonia, developmental intellectual and motor disabilities, and cortical visual impairment. We review the clinical presentations and genetic variations in CDD based on a systematic literature review and experience in the CDKL5 Centers of Excellence. We propose minimum diagnostic criteria. Pathogenic variants include deletions, truncations, splice variants, and missense variants. Pathogenic missense variants occur exclusively within the kinase domain or affect splice sites. The CDKL5 protein is widely expressed in the brain, predominantly in neurons, with roles in cell proliferation, neuronal migration, axonal outgrowth, dendritic morphogenesis, and synapse development. The molecular biology of CDD is revealing opportunities in precision therapy, with phase 2 and 3 clinical trials underway or planned to assess disease specific and disease modifying treatments.

Introduction

Pathologic variants in cyclin-dependent kinase-like 5 (*CDKL5*)[1-5] cause CDKL5 deficiency disorder (CDD; OMIM 300203, 300672), a developmental encephalopathy.[6] Developmental encephalopathies share common constellations of features that extend beyond traditional criteria of autism spectrum disorder or intellectual disability such as treatment-resistant epilepsy, movement disorders, and autonomic dysfunction. Pathologic variants in *CDKL5* cause early life epilepsy in one in 40,000 to 60,000 live births,[7-9] half to a third as prevalent as Dravet (1:20,000 to 50,000)[10,11] or Rett (1:10,000 females)[12] syndrome. Common features include infantile-onset refractory epilepsy, hypotonia, developmental delay, intellectual disability, and visual impairment.[13-15] CDD is an X-linked disorder that affects females more than males (~4:1) (Olson et al., unpublished data, 2018) as males with germline variants have no normal CDKL5 gene and may not survive fetal life. CDD was initially identified as the early seizure variant of Rett syndrome, but only 23.7% of females and no males with CDD met criteria for typical or atypical Rett syndrome and diagnosis of atypical Rett syndrome is even rarer in recent clinical experience (Olson et al., unpublished data, 2018).[13,16]

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The literature on CDD includes case series and data from the International CDKL5 Disorder Database, based on caregiver questionnaires.[13,17-21] Prospective data collection is occurring through the Natural History Study for Rett and Rett-related disorders (U54 HD061222; ClinicalTrials.gov: NCT00299312/NCT02738281) and through a clinic-based study by the International Foundation for CDKL5 Research Centers of Excellence (COEs). Initial sites were Boston Children's Hospital, Children's Hospital Colorado, and Cleveland Clinic. The COEs provide comprehensive care and collaborate on research for CDD. The COEs have collected data on more than 93 individuals with CDD between 0 and 34 years to inform the typical features and spectrum of CDD (Olson et al., unpublished data, 2018).

CDKL5 protein and molecular biology

CDKL5 is a serine threonine kinase. The N-terminal catalytic domain starts in exon 2 and the long C-terminus may have a regulatory role.[22] CDKL5 is highly expressed in the brain, predominantly in neuronal nuclei and dendrites, with peak expression in early postnatal life, when symptoms typically begin.[23-26] The CDKL5 protein has roles in cell proliferation, neuronal migration, axonal outgrowth, dendritic morphogenesis and synapse development, and function in the adult brain.[27]

CDKL5 has multiple transcripts because of alternative splicing in mice and humans.[22] The primary brain isoform is hCDKL5_1.[22] Pathogenic missense variants occur exclusively within the catalytic domain except for the recurrent missense variant p.Val718-Met, which affects splicing.[28] A male individual mosaic for this variant followed in our COEs has a "typical" CDD phenotype but has walked independently since age two years. Somatic mosaicism in probands, perhaps more often in males, and presumed parental mosaicism is described; unaffected parents with a full germline *CDKL5* variant have not been described.[15,19,29-33] Thus parental testing is critical to assess variants of uncertain significance in *CDKL5*. There are neither biomarkers nor is there a functional assay for variants of uncertain significance, both would be beneficial to the field.

Currently, no evidence supports pathogenic variants in exons 20, 21, and 22, which are part of transcript isoform *hCDKL5_5*, or within exon 17, which is part of transcript isoform *hCDKL5_2*.[28] The pathogenicity of variants in the 5′ untranslated region remain uncertain except for deletions extending to include exons 1 and 2.[28] Deletions and truncating variants appear to nearly universally cause CDD.[28] *CDKL5* variants from individuals in the COEs are shown in Fig, on a schematic of the protein and on a three-dimensional model along with population variation.

Individuals with *CDKL5* duplications show variable penetrance of macrocephaly and learning disability without epilepsy or magnetic resonance imaging abnormalities.[35] Neighboring genes are rarely affected in these duplications. This contrasts with other genetic developmental encephalopathies for which duplications cause a different disease than deletions (e.g., *MECP2* and *FOXG1* disorders).[28,36-39] More comprehensive phenome-genome studies of *CDKL5* duplication are needed to determine if these duplications are clinically pathogenic.

Molecular studies in rodent models have identified several signaling pathways that are altered in CDD, including protein kinase B (AKT) and mechanistic target of rapamycin (mTOR), AKT and glycogen synthase kinase-3 beta (GSK-3b), and brain derived neurotropic factor and Ras-related C3 botulinum toxin substrate 1 (Rac1) and the netrin G1 ligand and postsynaptic density protein 95 interaction.[23,24,26,27,40,41] However, these rodent models demonstrate a behavioral phenotype but lack spontaneous seizure activity.[41-43] Dendritic outgrowth and spine development are inconsistently altered in cellular CDD models.[41] Mouse model data suggest that CDKL5 expression modulates postsynaptic localization and composition of N-methyl-D-aspartate receptors.[44] CDKL5 influences MeCP2 activity, possibly explaining overlapping features of CDD with Rett syndrome, although the relevance of this *in vitro* data remains uncertain.[27] Additional CDKL5 substrates include DNA methyltransferase 1, amphiphysin, netrin G1 ligand, histone deacetylase 4, microtubule associated protein 1S, rho guanine nucleotide exchange factor 2, and microtubule-associated protein RP-EB family member 2 (EB2).[45,46] A recent review summarized the molecular features of CDD.[27]

Epilepsy and treatment

Refractory epilepsy severely impacts quality of life and neurodevelopment.[14,34] Median age of epilepsy onset is six weeks with 90% onset by three months.[13,14] Eighty percent of children with CDD have daily seizures and 20% have weekly to monthly seizures.[47] Fewer than half (43.6%) of caregivers reported more than 2 months of sustained seizure freedom.[14,34] Among individuals with more than two months of seizure freedom (N = 71 of 163 families reporting information on seizure freedom), in three quarters of families able to provide additional information this honeymoon period had a median duration of six months (range 2.5 months to six years) and median onset of two years.[14] In the COE cohort, 9% of families reported a seizure-free period of one to three months, 12% three to six months, 11% six to 12 months, and 13% more than 12 months. This honeymoon period typically occurs in the first two years of life, although some have seizure-free periods later in childhood or into their teenage years (Olson et al., unpublished data, 2018).

Three proposed epilepsy stages in CDD include (1) early onset, at times pharmacoresponsive, (2) epileptic encephalopathy, and (3) refractory multifocal and myoclonic epilepsy.[48] Infantile spasms are the initial seizure type in 23% and present at any point in 81% of individuals with CDD (Olson et al., unpublished data, 2018).[49] Evolving epilepsy tends to be generalized or mixed focal and generalized with spasms, tonic, and tonic-clonic seizures most common (Olson et al., unpublished data, 2018).[49] Complex seizure semiology with multiple phases per seizure is common (56%) (Olson et al., unpublished data, 2018),[49] including a novel seizure pattern: hypermotor-tonic-spasms sequence.[16,50-53] Autonomic changes can be seen intermixed with any of these seizure types, including pupillary dilatation, facial flushing, irregular respirations, apneas, or hyperventilation (Olson et al., unpublished data, 2018). Although for many individuals refractory epilepsy continues long term, our experience suggests that rare individuals outgrow their epilepsy in childhood and one individual did not have epilepsy onset until age nine years (*de novo* c.1675C>T; p.Arg559Ter) (Olson et al., unpublished data, 2018).

Electroencephalographs at onset ranged from hypsarrhythmia to mild abnormalities but more abnormalities in background rhythms and epileptiform activity develop over time.[15,17,19,48,52,54,55] Early mild abnormalities that sometimes precede a diffuse encephalopathy included focal delta slowing in the posterior head regions and intermittent generalized slowing.[56] Some individuals have hypsarrhythmia and evolution often includes focal or generalized slowing, focal and generalized epileptiform activity, and in some cases pseudoperiodic epileptiform discharges.[15,17,19,48,52,54,55] Infantile spasms can occur, however, in the absence of hypsarrhythmia, including with a normal electroencephalograph or rare epileptiform activity (Olson et al., unpublished data, 2018).[56] Burst suppression is rare and atypical for neonates with CDD.[52]

Data on the efficacy of seizure therapies are limited. A review of antiseizure medication response in 39 individuals with CDD found

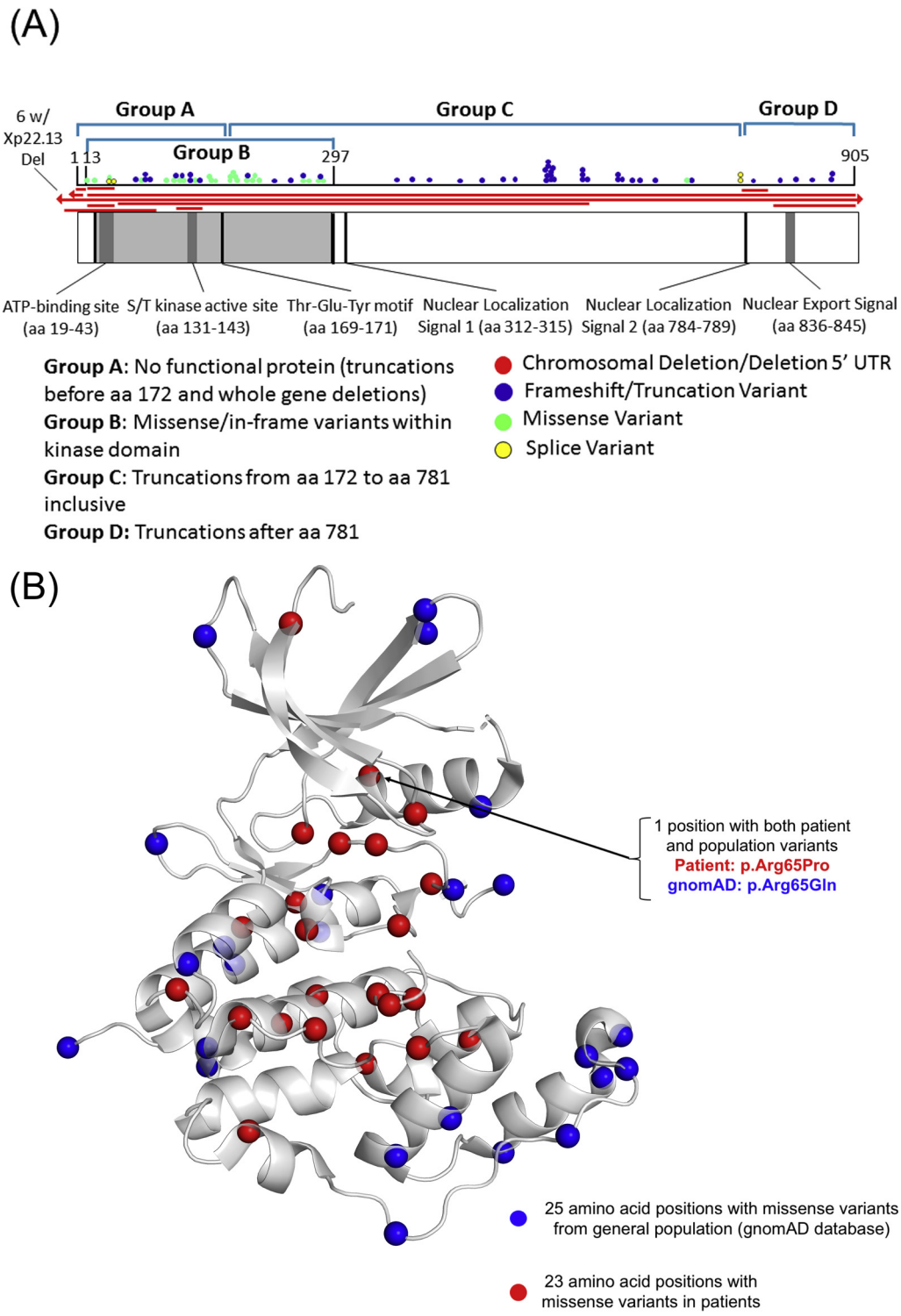

FIGURE. (A) A schematic of the CDKL5 protein with variants from individuals with CDD evaluated in the CDKL5 Centers of Excellence (COEs). *CDKL5* gene image adapted from prior publication.[34] (B) Three-dimensional protein structure of the *CDKL5* gene (Protein Data Bank ID: 4bgq) along with position of population variation (blue spheres) from gnomAD database and variants from the COEs (red spheres). (C) Highlight of variants in functional domains in the CDKL5 protein. The missense variants in *CDKL5* identified in affected individuals are mapped on the three-dimensional protein structure (protein data bank id: 4bgq) as red spheres (total 23 positions). The yellow-colored region is a nucleotide binding region (aa. 19 to 72), and we observed the disease-associated variant p.Tyr24Cys in this region. The cyan-colored site is a proton acceptor active site (aa. 135), and we observed the disease-associated variant p. Asp135Gly in this site. The green-colored region is a functionally essential DFG motif (aa. 153 to 155), and we observed the disease-associated variant p. Asp153Val in this region. The pink-colored region is the morphology (information content) or consensus sequence of phosphotyrosine Y171 (part of Thr-Glu-Tyr motif) (aa. 164 to 178), and we observed the disease-associated variants p.Trp176Arg, p.Tyr177His, and p.Arg178Gln in this region. DFG, asp-phe-gly.

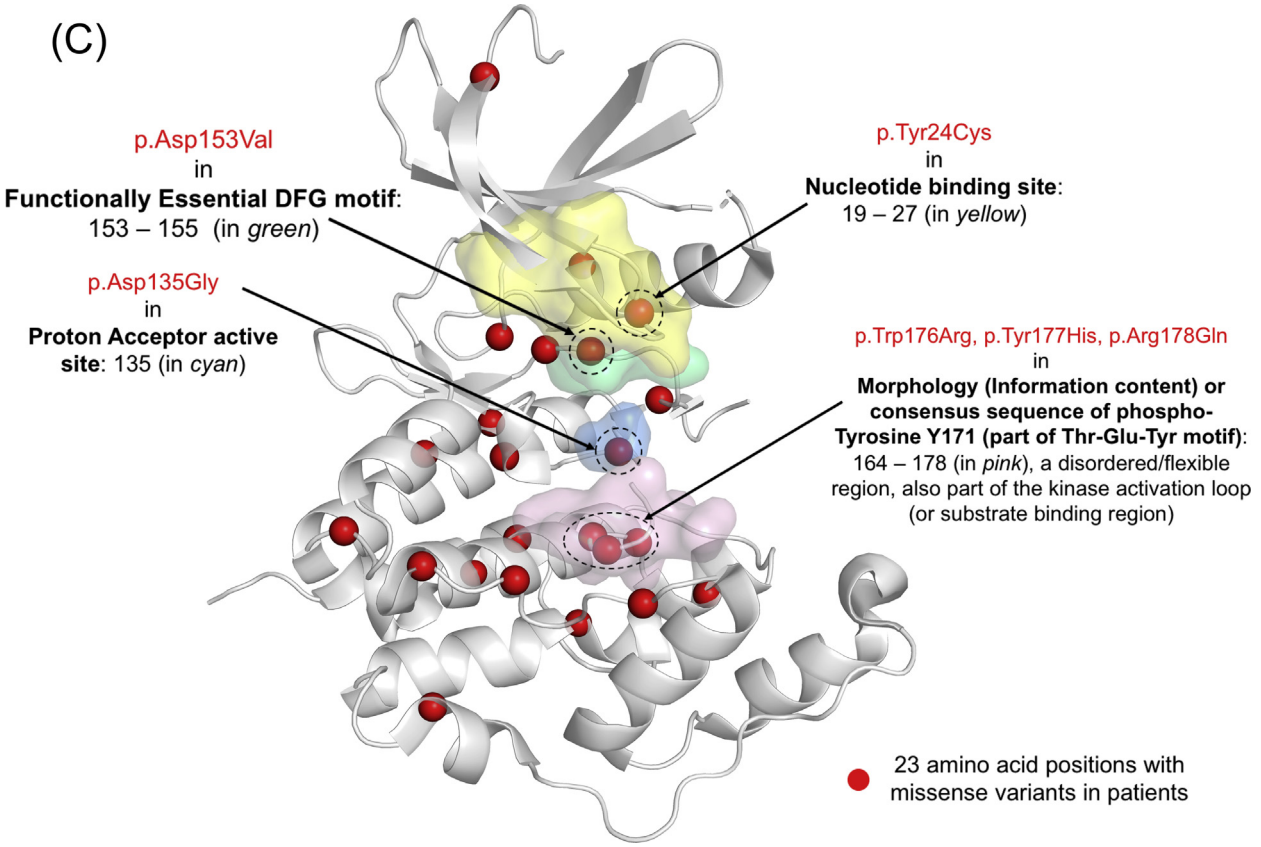

FIGURE. *Continued*

a responder rate (defined as 50% seizure reduction) to at least one antiseizure medication of 69% at three months, 45% at six months, and falling to 24% at 12 months.[57] Medications with the highest rates of seizure reduction at three months included felbamate, vigabatrin, clobazam, valproic acid, steroids, lamotrigine, and zonisamide.[57] The efficacy of each antiseizure medication showed large interindividual variability, with a maximum of 33%, except for felbamate with 3 of 3 responding at three months.[57] At 12 months, the responder rate dropped to 0% to 20% except for one of three (33%) still responding to felbamate.[57] Exacerbation of seizures occurred with at least one antiseizure medication in 31% of individuals, most often with carbamazepine (4/15 individuals).[57] Our approach in the COEs is to use broad-spectrum antiseizure medications especially when there are generalized seizure types. Overall, two of 39 individuals (5%) became seizure free for more than three years with antiseizure medication or ketogenic diet.[57] The most commonly used antiseizure medications in CDD were broad spectrum, including clobazam, valproate, topiramate, levetiracetam, and vigabatrin and 29.6% of individuals were treated with steroids or adrenocorticotropic hormone.[14] Another study of caregiver perceptions of treatment by survey of 44 caretakers of individuals with CDD reported subjective efficacy (not further defined) in more than two individuals to vigabatrin (12/23), clobazam (6/14), sodium valproate (5/27), and levetiracetam (3/27).[58] In the Boston Children's Hospital COE, greater than a 50% reduction in seizures types (excluding epileptic spasms) in more than one individual occurred with the following antiseizure medications: phenobarbital, clobazam, topiramate, rufinamide, and valproic acid (Olson et al., unpublished data, 2018).

Infantile spasms in individuals with CDD are often refractory to first-line therapies. From the parent-entered International CDKL5 Disorder Database, infantile spasms were reported in 33.8% of individuals.[14] In contrast, in the COE cohort of 93 individuals with data derived from physicians, spasms occurred in 81% (n = 75).[49] We hypothesize that the difference in prevalence may result from data collection methods and possible underdiagnosis of infantile spasms if not associated with hypsarrhythmia. Among 18 individuals in the COE cohort with detailed data, median spasm onset was age four months (two weeks to 36 months)[59]; spasms resolved in only three of 18 individuals (17%) with first-line treatments (adrenocorticotropic hormone or vigabatrin) for epileptic spasms, lower than the ~46% response rate at three months observed in infantile spasms cohorts.[59,60] Because CDD is often diagnosed before spasm onset and other seizure types often occur before spasms, such individuals with CDD are candidates for novel therapies.[15,48,59-62]

The ketogenic diet has modest efficacy in treating epilepsy in CDD. The largest cohort reported 104 individuals with CDD treated with median ketogenic diet duration of 17 months and reductions in seizure frequency in 61 of 104 (58.7%) individuals, consistent with data from the Boston Children's Hospital COE (Olson et al., unpublished data, 2018). Side effects of the ketogenic diet occurred in 31.7% of individuals.[63] A smaller cohort of 12 individuals with CDD reported that two (17%) had a significant reduction in seizures for more than six months and one (8%) for more than one year.[57] Behavior improvements were reported including improved alertness in 19 of 104 (18%) individuals on the ketogenic diet whereas worsening motor skills and social interactions were reported in 5.8%.[63] Ketogenic diet was most often discontinued because of lack of long-term efficacy. These retrospective observational reports did not provide data on diet ratios, ketone levels, efficacy for different seizure types, percent reduction in seizures, or duration of efficacy.

Notably, few individuals were treated with ketogenic diet in the first year of life and its efficacy and tolerability in this CDD group remain unknown.

Palliative surgeries for refractory epilepsy include vagus nerve stimulation and corpus callosotomy. Among 220 individuals with CDD with parent-entered data, 17% had a vagus nerve stimulation implanted and 69% of parents reported reduced seizure frequency.[64] These data are consistent with a case report of benefit[65] and Boston Children's Hospital COE reports improvement in five of six individuals (Olson et al., unpublished data, 2018).[66] There are no reports of response to corpus callosotomy in the literature and limited experience in the COEs but no response in one individual (Olson et al., unpublished data, 2018). In the International CDKL5 Disorder Database at least seven of 10 individuals had some improvement in seizures after corpus callosotomy of whom two had a longer than six-month period of seizure freedom (Leonard et al, unpublished data, 2018).

Development

All individuals with CDD have severe global developmental delays and intellectual disability, although regression is rare except with worsening of seizures or epileptic encephalopathy.[13,15,17-19,67-70] Individuals with CDD achieve gross motor milestones at a slowed pace compared with normal. Assessing in girls for whom there are more data, independent walking was attained by 22% to 23%, raking grasp by 49% by five years, and pincer grasp by only 13% at any time point.[34,68] Using time to event analysis, just under half of individuals could babble by six years (43/97 or 44%), and just under a quarter of subjects could speak single words by age seven years (17/105 or 16%).[34] Spoken language, signs, or abstract symbols were produced by 26% of females with CDD (0% of males) and 7.5% of females with CDD spoke in sentences.[68] The most common communication modalities were body language, facial expressions, and simple sounds and gestures.[68] Use of nonverbal communication devices such as switches and eye gaze technology-based communication is often limited by cortical visual impairment, but can be used by some individuals with CDD (Olson et al., unpublished data, 2018). Autistic features are commonly reported but autism spectrum disorder is infrequently diagnosed because of global developmental impairments.[2,15,17-20,70-72] A diagnosis of autism spectrum disorder has been observed rarely in the COEs.[59] Overall, males were reportedly more severely affected than females, although our COE experience does not suggest a striking difference in phenotype (Olson et al., unpublished data, 2018).[13,34] Males can have a milder phenotype (Olson et al., unpublished data, 2018).

Movement disorders

Hand stereotypies were reported in 80% of individuals, and 59% of females and 12.5% of males achieve functional hand use, which may be limited by stereotypies.[13] The hand stereotypies that we have observed are more consistent with self-stimulatory behavior versus the type of hand stereotypies observed in Rett syndrome (Olson et al., unpublished data, 2018). Repetitive leg crossing is also commonly observed (Olson et al., unpublished data, 2018). We lack data on other movement disorders although the COEs have observed episodic or persistent, and occasionally severe, choreoathetosis, akathisia, dystonia, and parkinsonian features (Olson et al., unpublished data, 2018). Movement disorders may worsen when individuals achieve temporary seizure control (Olson et al., unpublished data, 2018). At times this may be attributed to polytherapy with antiseizure medications, improving with reduction in number of antiseizure medications (Olson et al., unpublished data, 2018).

Physical examination findings

Hypotonia is a nearly universal feature.[14,15] Cortical visual impairment is common, occurring in at least 75% of individuals (Olson et al., unpublished data, 2018), with reports of poor eye contact and lack of visual tracking with an otherwise normal ophthalmologic examination.[15-17,19,34,69,70] Rotatory and horizontal nystagmus, dysconjugate gaze, abnormal fixation, and reduced or absent optokinetic nystagmus response are features observed in individuals with visual impairment. Microcephaly and deceleration of head growth occurs in fewer than 10% of individuals.[13,15,17-20,69,70] Subtle dysmorphic features include deep set eyes, broad or high forehead, prominent lips, deep philtrum, puffy phalanges, and tapered fingers.[13,15,19,67,70,71] Movement disorders have also been observed as mentioned previously.

Neuroimaging

Neuroimaging has not yet been systematically reported in individuals with CDD, although case reports document normal brain anatomy or less often, show cortical atrophy or T2 fluid-attenuated inversion recovery hyperintensities in the white matter.[15,17-19,48,52,54,55,67,69,70,72,73]

Neuropathology findings

There is very little literature describing the neuropathologic findings in individuals with CDD. One case report described the brain as the sole organ with abnormalities in a postmortem examination.[74] In addition to brain and cerebellar atrophy and ventricular enlargement, microscopic examination of the brain revealed gliosis in the cerebral cortex with preservation of the hexalaminar layers, neuronal heterotopias in the white matter of the cerebellar vermis, and gliosis of the cerebellar cortex with loss of Purkinje cells and axonal torpedoes.[74] Perivascular lymphocytes and axonal swelling in the anterior horn were the main findings in the spinal cord.[74] This child had a pathogenic splice variant c.2277-2A>G, predicted to destroy the splice acceptor site of exon 16.[74]

Other comorbidities

Gastrointestinal symptoms were reported by parents in up to 86.5% in the International CDKL5 Disorder Database (122/141), most often constipation (70.9%), reflux (64.1%), or air swallowing (27.1%).[13,47] Orthopedic complications of hypotonia include scoliosis (68.5% by 10 years).[13,47] Dysphagia is common and may require gastrostomy. Although 79.3% of individuals with CDD in the International CDKL5 Disorder Database fed orally and 20.7% were exclusively fed by gastrostomy or nasogastric tube, some required supplemental tube feedings and only 5.3% were able to eat and drink independently.[47] Notably, ~33% of individuals treated with the ketogenic diet had a gastrostomy; a similar percentage, 11 of 36 (31%) individuals, had gastrostomy in a caregiver survey of individuals with CDD.[63] Sleep difficulties are very common, reported by parents in over 85% of individuals, sometimes dubbed “all night parties.”[13,47] Night waking was reported in 72 of 123 (58.5%) individuals.[47] The odds of sleep problems were highest in the five to 10 year age group compared with those aged less than five years.[47] Using the Child Health Sleep Questionnaire, the team at Children's Hospital Colorado found significantly abnormal sleep maintenance and duration.[75] Abnormal sleep duration was reported in 63% of individuals with CDD compared with age-based norms, and the mean scores for waking once per night and more than once per night were increased (2.45 and 2.25, respectively, $P < 0.001$ for both).[75] Breathing abnormalities include hyperventilation reported

in 13.6% of individuals, breath holding in 26.4%, and aspiration in 22.6%.[47] Parents have expressed concerns about cardiac arrhythmias, and one study by caregiver survey reported arrhythmia in 11 of 29 individuals with CDD who underwent electrocardiogram.[58] Arrhythmias have not, however, been confirmed in the COEs, and this is an area of current investigation (Olson et al., unpublished data, 2018). Sudden unexpected death in epilepsy may occur but in large cohorts the frequency of CDD is much lower than Dravet syndrome or *SCN8A*-related epilepsy given the frequencies of these disorders.[76-78] However, the high seizure frequency and severity suggest that individuals with CDD are at high risk of sudden unexpected death in epilepsy, with daily and often nocturnal tonic or tonic-clonic seizures.[79] Metabolic abnormalities are rare; a boy with CDD had transient methylmalonic acidemia but the concurrence may be coincidental.[80]

Clinical criteria

We propose minimum CDD diagnostic criteria to include a pathogenic or likely pathogenic variant in the *CDKL5* gene along with motor and cognitive developmental delays and epilepsy with onset in the first year of life. We recognize that some patients with CDKL5 deficiency may be atypical and not meet these formal criteria. Table includes a list of common clinical features and what we determine to be the minimum diagnostic criteria.

Genotype-phenotype correlations

Genotype-phenotype correlations are limited. Compared with individuals with truncating variants, those with pathogenic missense variants in the adenosine triphosphate binding site had a milder disorder, some with ability to walk unaided, better hand use, and less refractory epilepsy.[4] One individual in the COE cohort with a missense variant, p.Tyr24Cys, in the adenosine triphosphate binding site has refractory epilepsy but is making more developmental progress than most individuals with CDD and lacks cortical visual impairment. Another study found that females with late truncating variants after amino acid 781 had better gross motor, hand function, and communication milestones than earlier truncating variants.[34,68] Seizure frequency was lower in individuals with truncating variants between amino acids 172 and 781 compared with those with no functional protein (incidence rate ratio 0.57; 95% confidence interval 0.35 to 0.93).[14] The influence of somatic CDKL5 mosaicism on clinical phenotype is unknown.

Clinical trials and treatments suggested from animal studies

The ultimate goal of understanding the genetics and molecular biology of CDD is to establish precision therapies, targeting the underlying biologic pathways, although the complex biology of CDD makes this challenging. This may include small molecules or perhaps genetic or genomic treatment approaches. The hope is that these therapies may be more effective than currently available treatments.

An open-label phase 2 clinical trial of cannabidiol in CDD and three other early life genetic epileptic encephalopathies suggested improvement in frequency of motor seizures more than three seconds in duration.[81] The CDD group had a median reduction in motor seizures from median 66.4 per 28 days (interquartile range 25.9 to 212.0) to 35.8 (interquartile range 8.9 to 141.6) at 12 weeks, with stable frequency at 48 weeks.[81]

A phase 2 randomized, placebo-controlled crossover study of ataluren, a medication that targets pathogenic nonsense variants in other genetic diseases, is in process in CDD (NCT02758626), but results are not yet available. Another phase 2 trial is being initiated for TAK-935, a novel medication that modulates the N-methyl-D-aspartate receptor system (NCT03694275).

Ganaxolone, a synthetic methyl derivative of allopregnanolone, is a neurosteroid for which there have been previous trials in the epilepsies including for infantile spasms, status epilepticus, and protocadherin 19-related epilepsy. A phase 2 open-label clinical study is completed, and a phase 3 randomized, placebo-controlled study is ongoing in CDD (NCT03572933). CDKL5 regulates the interaction of IQ motif containing GTPase activating protein 1 with microtubule plus end tracking protein cytoplasmic linker protein 170 (CLIP170), disrupting microtubule dynamics in CDD.[82] Pregnenolone, another neurosteroid, restores microtubule association of CLIP170 in CDKL5-deficient neurons, rescuing morphologic defects.[82]

Molecular pathway abnormalities in CDD rodent models suggest additional possible therapies. Dysregulation in the GSK3-beta pathway in *Cdkl5* knockout mouse model led to treatment with a GSK3-beta inhibitor, tideglusib.[40] Treatment during the juvenile period improved hippocampal development and hippocampus-dependent behaviors, whereas treatment in adult mice was not beneficial. Reduced expression of the GluA2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor was identified in *CDKL5* knockout mice.[83] Treatment of the mice with the antidepressant tianeptine normalized the expression of membrane-inserted α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors containing GluA2.[83] Treatment of rodents with IGF-1, which activates the AKT/mTOR pathway, rescued dendritic spine instability.[84]

Protein substitution therapy has been evaluated in animal models with promising results, although feasibility and timeframe to bring this approach to human trials are uncertain.[85] Novel therapeutic approaches including genome editing, RNA-based therapeutics, and gene therapy are being strongly considered.

Conclusions

The typical individual with CDD, defined by having a pathogenic gene variant that impairs CDKL5 function, is characterized by onset of treatment-resistant epilepsy and severe cognitive and motor developmental delays. Epilepsy usually begins in the first three months of life and includes tonic seizures, epileptic spasms without hypsarrhythmia, a seizure-free honeymoon period around one to two years old that may last up to 12 months, followed by multiple (2+) seizure types including sequences of mixed seizure type; cortical visual impairment associated with rotatory or horizontal nystagmus, dysconjugate gaze, and abnormal fixation; and global motor delays with hypotonia and severe impairment of hand function. Permanent regressions or progressive deterioration of neurological function is rare. Other commonly associated features

TABLE.
Common Clinical Characteristics and Proposed Minimal Diagnostic Criteria

Common Clinical Characteristics	Proposed Minimal Diagnostic Criteria
• Epilepsy, early onset, and refractory • Severe global developmental delay • Intellectual disability • Hypotonia • Cortical visual impairment • Sleep disturbance • Dyskinetic movements • Autonomic and breathing disturbances • GI disturbances (reflux, constipation) • Dysphagia	• A pathogenic or likely pathogenic variant in the *CDKL5* gene • Motor and cognitive developmental delays • Epilepsy with onset in the first year of life

of individuals with CDD include dyskinetic movements, sleep disturbances, autonomic and breathing disturbances, and gastrointestinal disturbances. We propose minimum CDD diagnostic criteria as mentioned previously recognizing that some individuals with CDKL5 deficiency may be atypical and do not meet these formal criteria.

CDD is an epileptic encephalopathy, defined by the International League Against Epilepsy as a disorder in which "the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these may worsen over time."[86] The transient regressions that occur in CDD are consistent with this definition although there is undoubtedly a developmental component as well. Future studies of the natural history of CDD will better define the role of seizures, interictal epileptiform activity, and antiseizure medications as factors that may adversely affect these children. We hope that increased preclinical studies to define the molecular consequences of impaired CDKL5 and advances in novel, targeted drug development and molecular biology and genetic approaches will radically transform the prognosis for children with CDD.

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