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Original Article

Severity Assessment in CDKL5 Deficiency Disorder

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ABSTRACT

Background: Pathologic mutations in cyclin-dependent kinase-like 5 cause CDKL5 deficiency disorder, a genetic syndrome associated with severe epilepsy and cognitive, motor, visual, and autonomic disturbances. This disorder is a relatively common genetic cause of early-life epilepsy. A specific severity assessment is lacking, required to monitor the clinical course and needed to define the natural history and for clinical trial readiness.
Methods: A severity assessment was developed based on clinical and research experience from the International Foundation for CDKL5 Research Centers of Excellence consortium and the National Institutes of Health Rett and Rett-Related Disorders Natural History Study consortium. An initial draft severity assessment was presented and reviewed at the annual CDKL5 Forum meeting (Boston, 2017). Subsequently it was iterated through four cycles of a modified Delphi process by a group of clinicians, researchers, industry, patient advisory groups, and parents familiar with this disorder until consensus was achieved. The revised version of the severity assessment was presented for review, comment, and piloting to families at the International Foundation for CDKL5 Research-sponsored family meeting (Colorado, 2018). Final revisions were based on this additional input.
Results: The final severity assessment comprised 51 items that comprehensively describe domains of epilepsy; motor; cognition, behavior, vision, and speech; and autonomic functions. Parental ratings of therapy effectiveness and child and family functioning are also included.
Conclusions: A severity assessment was rapidly developed with input from multiple stakeholders. Refinement through ongoing validation is required for future clinical trials. The consensus methods employed for the development of severity assessment may be applicable to similar rare disorders.

Introduction

Pathologic mutations in cyclin-dependent kinase-like 5 (*CDKL5*)[1-5] result in CDKL5 deficiency disorder (CDD, OMIM 300203, 300672, also referred to as *CDKL5 disorder*, *CDKL5 syndrome*, and CDKL5). Previously considered a "Rett variant," this unique disorder[6,7] has overlapping features with many of the developmental encephalopathies, disorders defined by genetic or presumed genetic etiology, severe seizures, and intellectual or cognitive disability.[8] Incidence varies from ~1:40,000 to 1:60,000,[9-11] approximately one-half to one-third as common as Dravet syndrome (1:20,000-50,000)[12,13] or Rett syndrome (1:10,000 female births).[14] Thus CDD is a diagnostic consideration in young children with severe, early-onset epilepsy.

CDD is associated with high rates of severe epilepsy as well as cognitive, motor, visual, and autonomic disturbances.[4,15-22] Although surveys have reported the characteristics and frequency of CDD features,[6] no clinical severity assessment (SA) has integrated CDD's clinical manifestations. Assessments for Rett syndrome,[23-26] FOXG1,[27] tuberous sclerosis,[28] and other developmental epileptic encephalopathies[29,30] incorporate many CDD features, but none provide a focused or comprehensive assessment of patients with CDD. A specific severity CDD assessment targeting all clinical features is lacking and needed for clinicians to evaluate care, define natural history, inform specialist and therapeutic referrals, and with appropriate validation, to assess the outcomes of interventions in clinical trials. Given the recent initiation of human therapeutic trials (CBD,[31] ataluren ClinicalTrials.gov: NCT02758626, ganaxolone ClinicalTrials.gov: NCT03572933, TAK-935 ClinicalTrials.gov: NCT03694275) and the reversibility of symptoms in CDD animal models,[32] a validated assessment is urgently needed for CDD clinical trials.

We established a uniform clinical approach to patients as part of the International Foundation for CDKL5 Research Centers of Excellence (COE) at three sites (Children's Hospital Colorado/University of Colorado School of Medicine, Boston Children's Hospital, and Cleveland Clinic) and sites associated with the National Institutes of Health-funded Rett and Rett-Related Disorders Natural History Study (NHS) (U54 HD061222; ClinicalTrials.gov: NCT00299312/NCT02738281). Each site collects clinical or research data on patients with CDD. Application of scales and assessments developed for Rett syndrome were not adequate to capture unique features of CDD. The CDD Severity Assessment (CDD-SA) intends to capture unique features of CDD, such as epilepsy severity, cognition, motor and visual impairment, and specific aspects of movement disorder. This assessment needs to be comprehensive but efficient to administer. The assessment must capture the distribution of abilities of patients with CDD without saturating. Given the multiple stakeholders with overlapping goals for this type of assessment, we supplemented our clinical research infrastructure by recruiting into our group an international and multidisciplinary panel of clinicians, researchers, and industry professionals outside of the COE and NHS along with parents of patients directly involved in CDD patient advocacy groups. This collaboration provided input to develop and refine the CDD-SA as described here.

Methods

Clinically obtained or research subject data available under institutional review board (IRB) approvals (COMIRB 13-2020, 15-2332, Cleveland Clinic IRB 14-478, need Boston COE IRB P00016602, and UAB NHS parent IRB F150518001) of 111 unique patients with CDD were reviewed. Based on these data, review of available scales, and the literature noted above, an initial CDD-SA was developed by the principal investigator (PI; T.A.B.) and presented at the annual CDKL5 Forum meeting (Boston, November 2017). This was followed by an open forum allowing input from stakeholders for feedback and queries. Revisions were made based on this input. We questioned whether the CDD-SA should be for clinical or research purposes, the potential domains to assess, the optimal type(s) of response scale to use, and the time frame of evaluation that is assessed (e.g., birth to present, prior six months to present, last month to present, and last week to present). Domains considered to be relevant included overall severity of disorder, epilepsy, cognition, motor function, vision, autonomic disturbances, and movement disorders. Response scales that were considered included five-point scales (evaluating frequency or

severity of a feature), Likert scales (evaluating the appropriateness of a statement), and global impressions of severity or change (caregiver and clinician global impression scales). We agreed that a clinical component provided by an examination was needed to complement and inform caregiver-reported observations, leading to parent and clinician sections of the CDD-SA.

The CDD-SA was then iteratively evaluated through four cycles of anonymous modified Delphi[33] comment and consensus by an international panel of clinicians, researchers, industry, patient advisory groups, and parents familiar with CDD (Fig). The group grew in numbers from those initially present at the Boston LouLou Foundation CDKL5 Forum to the full CDD-SA advisory group (SAAG, Table 1). Each CDD-SA version was e-mailed to the group and returned to the PI with comments and suggested changes. The number of questions in each domain, the specific items in each domain, and the wording of items were debated and modified to accurately reflect the experiences of each group of contributors. The number of items began at 24 and converged by the third round to approximately 50 items, similar to the final. The feasibility of applying the CDD-SA in a clinical setting led to a reduction of items in each domain. The PI reviewed all comments, developed an independently ascertained best consensus from suggested changes, revised the CDD-SA, and returned this to the review group with prior anonymous comments to provide historical background from the previous CDD-SA version. This allowed the group to understand the rationale for emerging consensus and provide commentary as to whether the emerging consensus was tracking with the intended changes to the CDD-SA. Although this was not a survey-based approach like a traditional Delphi process, the overall method of eliciting feedback and creating consensus was similar. The number of participants remained consistent throughout the review period, with no dropouts, providing a representative stakeholder input. The penultimate CDD-SA version was presented by the PI at the International Foundation for CDKL5 Research annual meeting to parents of over 100 patients with CDD (Denver, June 2018) for review, comment, and trial. All families present were provided access to the CDD-SA, and comments were solicited and received for a duration of four weeks after the conference. Two families (whose children were not managed by the PI) agreed to trial the CDD-SA at the meeting; the time to administer the CDD-SA was measured and collected. The final revision of the CDD-SA was based on this additional input to result in the current CDD-SA (see Supplementary file). There was full consensus by SAAG members on the final CDD-SA.

Results

After multiple revisions by the SAAG, the domains selected were epilepsy, cognition and motor, vision and autonomic function. Movement disorders were included within the motor domain. Clinical examination components were separated from the parent report section within the cognition, motor, vision, and autonomic domains. This allowed a combination of parent or caregiver report and a clinician-completed portion based on physical examination findings. Parental components would be completed before the clinical examination; the time to complete this component has not yet been captured. In a pilot clinical examination, the parent portion was reviewed and the clinical portion was completed in 30 minutes by each of the two volunteer families.

Use of a global impression of severity[24] was rejected by the SAAG because these impression scales may rate self (caregiver)-described and patient-specific features that limit comparisons between patients. Thus the clinical value of a global impression of severity may not translate to research settings and could be a limitation in that context. The five-point scale (0 = normal, 5 = most severe), similar to that used in the Rett syndrome Motor-Behavioral Assessment,[25] was selected, with higher scores indicating more severity. Likert scales were added, as a compromise to deletion of the global impressions scale, for ratings of overall child improvement and parent or caregiver resilience and adaptability (−5 = worse, 0 = no change, 5 = best possible) and evaluation of therapies (−5 = worse, 0 = no change, 5 = best possible).

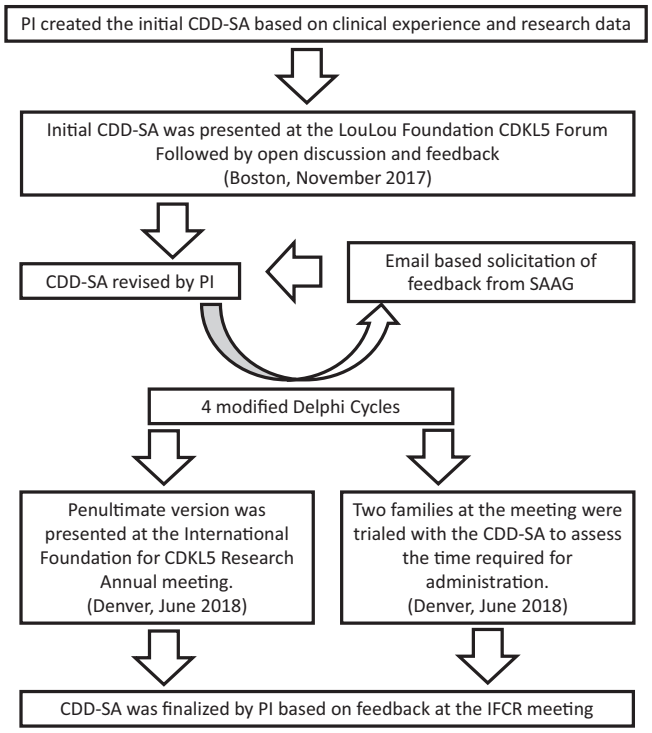

FIGURE. Modified Delphi process for CDD-SA development.

The SAAG determined that the CDD-SA evaluation time frame should reflect developmental and longitudinal changes.[20] Use of the birth-to-present questions was limited because they could reflect ceiling effects or static assessments that would be insensitive to change. Month-to-present time frames were considered most likely to reflect accurate changes, although week-to-present time frames could be substituted if a clinical trial required frequent assessments. As clinical assessments not part of a clinical trial may occur at half-yearly intervals, six-month to present time frames were also included.

TABLE 1.
CDD Severity Assessment Advisory Group; Affiliations for Nonauthors Noted

Sam Amin	Helen Leonard
Richard Chin	Eric Marsh
J Helen Cross	Lorraine Masuoka (Marinus)
Scott Demarest	Jeff Neul
Orrin Devinsky	Heather Olson
Jenny Downs	Axel Panzer
Katheryn Frame	Sumit Parikh
Jayne Gershkowitz (Amicus)	Carol-Anne Partridge
Femida Gwadry-Sridhar	Alan Percy
Joe Horrigan (Amo)	Elia M. Pestana-Knight
Amanda Jaksha	Sunny Philp (University of Birmingham, UK)
Walter Kaufmann	Robin Ryther (Washington University, USA)
Michael Johnson (Imperial College, UK)	Meghan Thorne-Miller (Roche)
Omar Khwaja	Karen Utley
Denise Lasbury (CDKL5-UK)	Judy Weisenberg
Dan Lavery (LouLou Foundation)	Ashley Winslow (LouLou Foundation)

TABLE 2.
Composition of the CDD-SA by Domain and Source of Data

Domain	By Caregiver	# Questions	By Clinicians	# Questions	Total # Questions
1. Epilepsy	Yes	15	No	0	15
2. Motor	No	0	Yes	13	13
3. Cognition and Vision	Yes	1	Yes	12	13
4. Autonomic	Yes	9	Yes	1	10
5. Overall	Yes	2	No	0	2
6. Therapies	Yes	1	No	0	1
7. Scale Scoring	No	-	Yes		
8. Visit notes	No	-	Yes		

The wording of the items was simplified during the iterations substantially, especially in the epilepsy domain given the complexities of classifying seizures. CDD is associated with multiple seizure types, including prolonged and atypical aura, epileptic spasms, tonic, tonic-clonic, myoclonic, and atypical absence.[18,19,22,34-36] Furthermore, a single seizure may involve multiple types that evolve, whereas other seizures can be challenging to characterize even by experts using video electroencephalography.[37] This feature of epilepsy associated with CDD makes traditional seizure counting difficult for parents and caregivers.[38,39] Rather, estimates of frequency and impact on function were agreed upon instead. Although this approach substitutes one subjective assessment for another, it becomes more patient centered.

The clinical portion was based on features typically evaluated during an examination by a pediatric neurologist. However, certain CDD-SA components would likely add time to the routine visit, especially if that clinical visit includes a discussion of clinical decision making. Regardless of the country and practice considerations, the CDD-SA had to provide relevant data that could be assimilated and utilized at a clinical visit. The final domains and details of the examination were considered recommendations: clinicians would tailor their approach such that not every item within their usual assessment would necessarily be included for all visits or all patients, although the items seek to limit clinician-to-clinician variability. It can be challenging to assess the breadth of features and the functional impact of movement disorders within a clinical visit. Also, any clinical examination is a snapshot in time and may not assess some areas captured for which extended observation by a parent or caregiver may be more informative. There are similar challenges when assessing cognition and vision in patients with CDD who are often nonverbal and have some degree of visual impairment. Cognition assessment is limited by both examination time and CDD features to assessing choice and visual attention in the CDD-SA.

In summary (Table 2 and Supplementary file), the final CDD-SA comprised the following four domains: (1) epilepsy; (2) motor; (3) cognition, behavior, and vision; and (4) autonomic, which are nearly equally weighted with similar maximum scores (69, 65, 65, and 44, respectively) on items that mostly were scored on a 0 to 5 range. Impressions of overall improvement, parent or caregiver resiliency, and therapy utility were each given a -5 to 5 Likert scale. An optional part of the CDD-SA was medical decision making. Although no points were assigned to each intervention, the goal was to provide a formulaic framework to track the impact of these when the CDD-SA is used in a primarily clinical setting. Secondary scoring of data to reflect impact could be developed based on features such as patient discomfort and invasiveness, financial impact, impact to parent or caregivers, etc.

Discussion and conclusions

Using a modified Delphi process, we developed a new clinically relevant and easily administered SA for CDD (CDD-SA). With ongoing natural history studies such as the National Institutes of Health-funded NHS and current and planned drug trials specifically for patients with CDD, our CDD-SA offers the ability to capture aspects of this disorder that may change with time or in response to interventions. In the first instance, we have provided some evidence for its content validity, basing the CDD-SA on available literature, the clinical and research experience of an international panel of experts, and the live experience of our parent participants. We achieved a consensus across a broad spectrum of international clinicians from multiple specialties and subspecialties, parents, lay organizations, and industry professionals to develop this CDD-SA.

A limitation of the process was the lack of a framework with an objective “gold standard” to validate our CDD-SA. Furthermore, both the stakeholders and the PI could neither reliably determine the relative value of specific recommendations nor the validity of the scale to measure the feature of interest. Bias by the PI in adjudicating disagreements and alternative views could be an inherent limit of this process but was countered by extensive expertise of the investigators and the live experiences of families in the consultation process. The SAAG input helped ensure the comprehensive and disease-appropriate nature of the CDD-SA, and it is unlikely that the primary domains will need major alterations in the future. The SAAG-approved SA is being applied in CDD COE and can be applied in other clinical and research settings; this will provide the basis for future validation that will include some refinement of necessary items and language. In addition, qualitative data are needed to validate parental interpretations of questions and refine future versions to determine the sensitivity of the CDD-SA. A quantitative dataset with a large sample size will be necessary to determine change with interventions and evaluate interrater reliability, factor analyses, stability, and responsiveness over time.

We propose that our clinical assessment will have immediate utility with clinicians who see children with CDD. The CDD-SA is freely available for general use. This methodology could be applied to the development of clinical assessments for other rare genetic disorders, and the framework could potentially serve as an early foundation to other constituent organizations. Key aspects that allowed this to happen included an initial framework (COE and NHS) that standardized the identification of clinical features relevant to CDD. Next, those that were outside of the COE and NHS were included in the process. The support of patient advocacy groups and associated parents or caregivers provided mission-critical context. Finally, a willingness to collaborate by the SAAG despite many other commitments and time constraints allowed the process to move forward.

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Supplementary data

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