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The Development, Content and Response Process Validation of a Caregiver-Reported Severity Measure for CDKL5 Deficiency Disorder

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S. Ziniel has no COI.

A. Mackie has no COI.

J. Saldaris has no COI.

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Abstract

Background—CDKL5 Deficiency Disorder (CDD) is a severe X-linked developmental and epileptic encephalopathy. Existing developmental outcome measures have floor effects and cannot capture incremental changes in symptoms. We modified the caregiver portion of a CDD clinical severity assessment (CCSA) and assessed content and response-process validity.

Methods—We conducted cognitive interviews with 15 parent caregivers of 1-39-year-old children with CDD. Caregivers discussed their understanding and concerns regarding appropriateness of both questions and answer options. Item wording and questionnaire structure were adjusted iteratively to ensure questions were understood as intended.

Results—The CCSA was refined during three rounds of cognitive interviews into two measures: (1) the CDD Developmental Questionnaire – Caregiver (CDQ-Caregiver) focused on developmental skills, and (2) the CDD Clinical Severity Assessment – Caregiver (CCSA-Caregiver) focused on symptom severity. Branching logic was used to ensure questions were age and skill appropriate. Initial pilot data (n=11) suggested no floor effects.

Conclusions—This study modified the caregiver portion of the initial CCSA and provided evidence for its content and response process validity.

Keywords

CDKL5 deficiency disorder; caregiver-report; validation; outcome measure; severity; developmental attainment

1. Introduction

CDKL5 Deficiency Disorder (CDD) is a severe developmental and epileptic encephalopathy characterized by refractory seizures with onset in the first months of life (Leonard et al., 2022; Moseley et al., 2012). Motor development is impaired with most patients unable to attain independent walking and pincer grasp. Similarly, communication is severely impaired with approximately 20% of patients achieving at least a single word of verbal communication (Fehr et al., 2016; Fehr et al., 2015). In addition to epilepsy and developmental impairment, patients with CDD have a variety of additional health challenges including gastrointestinal problems such as constipation and reflux, dysautonomia, cortical visual impairment, movement disorders, dysregulated sleep, and behavioral challenges (Fehr et al., 2016; Hagebeuk et al., 2013).

Increasing development of novel disease modifying therapeutics necessitates outcome measures that capture symptoms additional to seizure frequency. However, the severity of developmental impairments and broad range of symptoms in CDD (Demarest et al., 2019b; Fehr et al., 2015; Mangatt et al., 2016) reduces the utility of most existing clinical trial outcome measures. Furthermore, different treatments can only be compared if instruments are available to measure the breadth of outcomes that are important to patients and their families. The CDD Clinical Severity Assessment (CCSA) was developed in 2019, through an international multi-stakeholder panel who participated in a modified Delphi process. This was the first attempt to develop a comprehensive scale capturing the diverse challenges of CDD. This initial assessment included clinician- and parent-reported items for functional abilities, comorbidities, and neurologic impairments of CDD (Demarest et al., 2019a). It was then developed further as two separate measures because of differing sources of information (caregiver vs clinician). The CDD Clinical Severity Assessment – Clinician (CCSA-Clinician) has demonstrated content validity for assessing patient characteristics that are directly observable by a clinician within a typical clinical setting (Saldaris et al., 2021). The revised and content-validated CCSA-Clinician includes 29 items measuring dimensions of functional abilities and neurologic impairment and validation is ongoing.

This paper aims to describe the development and modification of the caregiver-reported items in the CCSA, and initial evaluation of content and response process validity and structural characteristics through cognitive interviews. Initial pilot data were collected from participants once the items were finalized as a preliminary assessment of score distribution.

2. Materials and methods

This study was approved by the University of Colorado IRB (COMIRB 18–1598). Consent was obtained remotely during the cognitive interviews using an electronic signature. All

cognitive interviews with caregivers were completed through a video interface between June 2020 through March 2021.

2.1 Participants

Participants were parents or guardians of CDD patients, over 18 years old and English speaking. They were recruited from an established cohort of patients at the CDKL5 Center of Excellence at Children's Hospital Colorado as well as some referrals nationally through the International Foundation for CDKL5 Research (IFCR). We used purposive sampling in recruiting participants aiming for maximum variation regarding age, comorbidities, and developmental skills seen in CDD, evaluated using the 16-point CDD Developmental Score (Brock et al., 2021).

2.2 Preparation of draft instrument

The initial caregiver instrument contained the caregiver questions of the CCSA (Demarest et al., 2019a). This version included 87 items that were organized into the following sections: history of medications and therapy; information about the frequency and intensity of different types of seizures in the past 30 days; cognition, behavior, vision, and speech in the past 30 days; the child's ability to complete tasks that assess gross and fine motor function and developmental milestones communication, cognition and social functional skills; autonomic functions in the past 30 days; and lastly, overall impressions of changes in the child's health from caregivers. It was first reviewed by a survey methodologist (SZ) and the study team, and item wording was changed to better conform with common best practices for questionnaire design since the instrument elicited caregiver-reported information (Artino et al., 2018; Gehlbach and Artino, 2018). For example, we revised the language to include lay rather than clinical terms, defined terms where necessary and included time frames for recollection of behaviors or symptoms. We split double-barreled items into component items. The instrument was then programmed into REDCap hosted at the University of Colorado for cognitive interviews (Harris et al., 2019; Harris et al., 2009).

2.3 Validation processes

Cognitive interviews are a qualitative technique essential for establishing content and response process validity (Peterson et al., 2017). All interviews were completed by one interviewer (AM) who had experience with semi-structured interviewing and was specifically trained to conduct cognitive interviews for this study. Cognitive interviews allow researchers to gauge if respondents understand items in the same way they were intended (Willis and Artino, 2013). In addition to neutral probes and follow-up questions after each item, we used the "think-aloud" technique. Respondents were asked to think out loud while they were answering each item which provided information into the various stages of how respondents form their answer to each of the items. Questions asked how participants understand specific terms, how they recalled or retrieved relevant information from memory and how motivated they were to do so, how they used response options to judge which of the retrieved information might be relevant, and if they adjusted the information before they reported it due to social desirability (Ziniel et al., 2019). During the interview, the interviewer audio-recorded and took notes on participant feedback to each item as well as any suggestions on how to improve it. Non-verbal reactions such as hesitating with an

answer, taking a long time to answer, or any facial expressions were also noted to help identify the difficulty of items. After each round of cognitive interviews, the study team met to discuss the comments, reactions, and suggestions from the participants and how to address them. These changes were then implemented prior to the subsequent round of cognitive interviews. Recruitment for additional rounds of cognitive interviews was stopped once cognitive interview participants did not offer any further suggestions on how to change the instruments and our interviewer was certain the items were understood in the way they were intended.

Establishing content validity is a critical portion of the outcome measure development processes that ensures that the overall conceptual framework, item content and structure of the outcome measure are relevant, comprehensive, and comprehensible to the population of interest and meet the Food and Drug Administration (FDA) requirements for development of outcome measures (U.S. Department of Health and Human Services et al., 2009). This foundational step precedes quantitative testing of reliability, validity, and responsiveness to change. Content validity had already been established by the expert panel through the modified Delphi process (Demarest et al., 2019a) and we now sought to establish content validity of the two caregiver-reported measures by caregivers with a CDD patient themselves (Magasi et al., 2012). At the end of each section as well as each instrument we asked the caregiver if all aspects of their experience regarding the domain had been covered or if any item included wasn't relevant to their child. We asked 11 experts in CDD to provide feedback on the final instrument.

2.4 Preliminary pilot testing

Participants were offered the opportunity to complete the instruments again once they had been finalized simulating a real assessment and offer their feedback on the changes that had been made. The data collected from the administration of the finalized CCSA-Caregiver and CDQ-Caregiver was used to assess the general structure of scores produced by the instruments. We used violin plots to illustrate the median, interquartile range, minimum and maximum scores, and the density curves of the distributions of the subdomains and the overall score. Stata version 16.1 was used to compute all scores (Stata Statistical Software, College Station, TX USA) and the violin plots were produced using GraphPad Prism version 9.0.0 (GraphPad Software, San Diego, CA USA).

3. Results

3.1 Participants

We completed three rounds of cognitive interviews with 5 new participants in each round, for a total of 15 cognitive interviews. For one child both caregivers volunteered to participate in a cognitive interview, so the 15 cognitive interviews represent the experience of 15 individual caregivers of 14 children with CDD. Table 1 shows the demographic characteristics of the participants and their children with CDD. Most participants were female (86.7%), white (90%), non-Hispanic (90%), married (70%), and between 31 and 40 years old (60%) at time of child diagnosis. Half had a Bachelor degree (50%). Most of the children with CDD were female (85.7%), white (78.6%), non-Hispanic (85.7%), and had a

median age of 10.4 years. The mean CDD Developmental Score was 9 points (interquartile range: 5.75, 10.75, total possible score of 16 points). In addition to participating in a cognitive interview, 11 of the 15 cognitive interview participants (73.3%) volunteered to complete the finalized instruments simulating a real assessment.

3.2 Item development

Figure 1 describes the refinement of the initial instrument. The first round of five cognitive interviews revealed that caregivers felt that the survey with 87 items was very long, especially since all items were designed to be answered by all respondents. Caregivers whose children were at an age where certain developmental milestones could not have been attained felt that they should not be asked to answer these questions. Parents reported fatigue as well as frustration to have to answer these questions. We therefore determined for each of the five developmental subdomains of the instrument which questions were appropriate for children's different developmental age ranges and milestones. If the child was younger and/or had developed fewer skills, then fewer questions would be asked of a caregiver. During this first round, caregivers expressed problems with questions around the different types of seizures and how to count them. Specifically, caregivers were confused by questions about seizures whose definitions showed subtle distinctions, e.g. the definition of a cluster of jerks vs. a series of isolated jerks that should be counted separately.

After the second round of cognitive interviews, we separated items into two caregiver-reported measures: (1) the CDD Clinical Severity Assessment – Caregiver (CCSA-Caregiver) focusing on areas of function and impairment analogous to the CCSA-Clinician but based on caregivers' observation (Supplemental Material A), and (2) the CDD Developmental Questionnaire (CDQ-Caregiver) (Supplemental Material B). The CDQ-Caregiver seeks to expand on traditional developmental assessments to measure incremental, but important, developmental achievements in this severely impaired population. Respondents seemed to be able to focus better on symptoms on the one hand and developmental accomplishments on the other. Separating the items into two measures might also have an additional advantage allowing different intervals of assessment in a clinical trial, as symptoms may demonstrate change more rapidly than developmental achievements.

During this round of cognitive interviews -just as in the second round, caregivers provided additional comments on the phrasing of some questions and response options, and the think-aloud protocol revealed that some of the questions were still not completely understood as intended. Table 2 illustrates some of the issues that were uncovered because of caregivers thinking aloud while they were answering the questions or from further probing after a caregiver had provided a response. As mentioned before, caregivers had difficulties understanding key terms used to defining different types of seizures. In the original version of the questionnaire each type of seizure was defined in the question that asked about it, causing the respondents to skip around on the page and read the other definitions in an attempt to help them understand how to distinguish different types from each other. Once all definitions were put at the beginning of this section and simplified, respondents seem to have less difficulty categorizing the seizures their child experienced into the different types about which questions were asked. Throughout the first 10 cognitive interviews, caregivers

also indicated that response options were often overly complex and not well suited for some of the developmental statements (Table 2). A simplification helped to decrease the cognitive burden when assessing these response options and increased the clarity of the meaning of the items.

We also needed to change questions that were asking about negative behaviors, such as a child being aggressive or self-harming. Caregivers were adamant in their need to point out that the negative behaviors of their children weren't intentional but more a reflection of the underlying disease and felt that the item needed to reflect that for them to be comfortable to answer the item. We therefore added to these items the phrase "regardless of intent or purpose." Another common correction we needed to make was adding additional options or rephrasing the current response options because caregivers felt that the response options provided did not reflect the current reality and they could therefore not really answer the question.

The third round of cognitive interviews with caregivers yielded only small wording changes, ultimately discovering no further issues with the two instruments.

After the cognitive interviews with caregivers were complete, 11 experts treating patients with CDD and conducting research in this area provided feedback. We specifically asked them to review the items regarding their relevance and appropriateness for caregivers of children with CDD and comment on if each item as well as the instruments as a whole were consistent with their experience treating CDD patients. The experts confirmed that the items and instruments were relevant and appropriate and had only minor comments regarding potential alternative wording. No major changes were made to the two instruments.

3.3 Instrument scoring and structure

The 11 caregivers completing the final CDQ-Caregiver and CCSA-Caregiver commented on the improvements that had been made to the instruments and had no further suggestions. The final CCSA-Caregiver was divided into three subdomains for scoring purposes: (1) epilepsy symptoms, (2) cognitive, behavioral, and vision symptoms, and (3) autonomic symptoms. The final CDQ-Caregiver was separated into five subdomains: (1) gross motor skills, (2) fine motor skills, (3) receptive communication skills, (4) expressive communication skills, and (5) social and cognitive skills. Because of the branching logic implemented based on symptom severity, the maximum number of items to be administered from the CCSA-Caregiver range from 30 to 50; caregivers of the least symptomatic children only needed to answer 30 questions while caregivers of the most symptomatic children answered 50. The number of items from the CDQ-Caregiver to be answered by the caregiver depends on the age as well as the developmental status of the child with CDD and can range from a minimum of 16 items for 6-month-old patients to 66 items for patients over 60-month-old with more milestones attained. Figure 1 includes the minimum and maximum number of items for each of the subdomains. The response options of each item the respondent is administered are scored between 0 and 100, irrespective of the number of categories, with higher scores indicating less developmental attainment or higher severity. For example, the response options of a question from the severity assessment with four response options receive in ascending severity the scores 0, 33.3, 66.6, and 100. The average score of all

eligible items in a subdomain represents the domain score while the average of all domain scores constitutes the overall instrument score. Each instrument can also be summarized by an overall severity score and overall development score, respectively. Figure 2 displays the violin plots for the subdomain and overall score for the CCSA-Caregiver and the CDQ-Caregiver from the pilot testing. None of the distribution within each subdomain show clear floor or ceiling effects suggesting the instruments' abilities to assess a wide range of symptom severity and developmental milestones.

4. Discussion

This study refined the initial caregiver reporting section of the CCSA (Demarest et al., 2019a) into two separate instruments measuring caregiver-reported observations regarding a child's CDD: 1) the CDQ-Caregiver that focuses on assessing developmental attainment regarding gross and fine motor skills, receptive and expressive communication skills, as well as social and cognitive skills, and 2) the CCSA-Caregiver that captures the extent of clinical manifestations such as epilepsy symptoms, cognitive, behavioral, and vision symptoms, as well as autonomic symptoms. Both together reflect a comprehensive assessment of a child with CDD and are designed so that scoring can be combined for an overall representation of severity that is anchored to the CDKL5 disease concept model developed through the FDA Patient Focused Drug Development process (U.S. Department of Health and Human Services et al., 2009).

Using cognitive interviews, we revised the instruments and established their content validity from a caregiver perspective consistent with FDA guidance (U.S. Department of Health and Human Services et al., 2009). In addition, we also asked experts in CDD to review the measures for relevance and appropriateness of content. The cognitive interviews with caregivers also allowed us to assess response process validity, ensuring that questions, answer options, and instructions are understood in the same way they were intended by the measure designers. The participants in these interviews were specifically recruited to represent experiences within the spectrum of severity seen in CDD as well as different levels of education. After three rounds of cognitive interviews and iteratively restructuring the measures, deleting, and adding items, as well as changing item wording, we reached two instruments that caregivers felt comfortable to complete. Data from a pilot sample of caregivers showed no clustering of scores at the ends of the scale, a problem previously encountered by other similar measures (Demarest et al., 2019b). More specifically, existing parent-reported measures of developmental functioning and/or delay are not adapted to identify small but clinically important changes regarding the development of gross and fine motor function, and communication, behavioral, and social skills in children with CDD (Sparrow et al., 2016; Squires and Bricker, 2009). These measures have also demonstrated poor performance and significant floor effects in similar populations with developmental and epileptic encephalopathies (Berg et al., 2022). Other, more in-depth, tests that could be more amenable to assess developmental functioning in this population, are mostly designed to be administered by clinicians, nurses, or occupational therapists and focus more on screening for developmental delay in motor function, language, and cognition than on measuring change over time (Bayley and Aylward, 2019; Ellison et al., 1985; Frankenburg et al., 1992).

The separation of the severity and developmental attainment items into two different instruments provides several advantages. For caregivers, the grouping of items in two different instruments seems to bring more cohesion among the question and make more sense since as on the one hand they are reporting developmental attainment and on the other more clinical symptoms. Having two instruments also allows them to be administered in different time intervals since changes to clinical symptoms would be likely to occur more rapidly (e.g. after a change in medication) than changes in development.

A limitation of this study is that the final instruments were only administered in a small sample and therefore conclusions cannot be drawn regarding other aspects of validity. Additional interviews with caregivers whose children are not receiving care at the hospital where the cognitive interviews were conducted might have provided further comments regarding the phrasing of the items. Some domain scores, specifically the Social & Cognitive Skills Domain and the Expressive Communication Domain of the CDQ-Caregiver, also showed skewed distributions. However, given that for both domains the complete range of scores is represented, this could be an effect of the small sample size and the characteristics of the patients regarding these domains. Finally, despite our effort to capture a range of caregiver and patient characteristics, it is possible that our interview samples had some bias. For example, our sample comprised mainly relatively affluent, white, and well-educated caregivers. In addition, we also only included parents as participants but intended these instruments to be applicable to other non-parent primary caregivers of CDD children such as grandparents with custody.

Ultimately, the CCSA-Caregiver and CDQ-Caregiver provide complementary data to the CDD Clinical Severity Assessment that is completed by a clinician (CCSA-Clinician) (Saldaris et al., 2021). The CCSA-Clinician focuses on the assessment of functional abilities and neurologic impairments in the moment from a clinical perspective while the caregiver-reported instruments provide information about CDD symptoms and developmental attainments that necessitate observations over a longer time period.

Future work will need to establish the validity of the CCSA-Caregiver and CDQ-Caregiver in a larger sample to evaluate the structural, reliability, and psychometric, properties of these measures. Any future studies should focus on including participants of lower socioeconomic status, ethnic and racial minorities, and non-parental primary caregivers. Validation of a Spanish translation of these instruments will also help in reaching a wider patient population. This ongoing work will establish the final outcome measures and their readiness for use in future clinical trials.

5. Conclusion

This study refined the caregiver portion of the initial CCSA into two measures, the CCSA-Caregiver and the CDQ-Caregiver, that can be administered independently and create flexibility of administration intervals. Cognitive interviews and additional expert review of the CCSA-Caregiver and CDQ-Caregiver provided satisfactory evidence for both content, and response process validity. Data from a small sample of caregivers showed no clear floor effects on any of the subdomains of the measures. As a next step, both measures will be

psychometrically validated to establish readiness for their use in clinical trials for CDKL5 Deficiency Disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Study data were collected and managed using REDCap electronic data capture tools hosted at University of Colorado Denver – Anschutz Medical Campus (Harris et al., 2019; Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

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Abbreviations:

CDD	CDKL5 deficiency disorder
CCSA	CDD Clinical Severity Assessment
IRB	Institutional Review Board
CDQ	CDD Development Questionnaire
FDA	Food and Drug Administration

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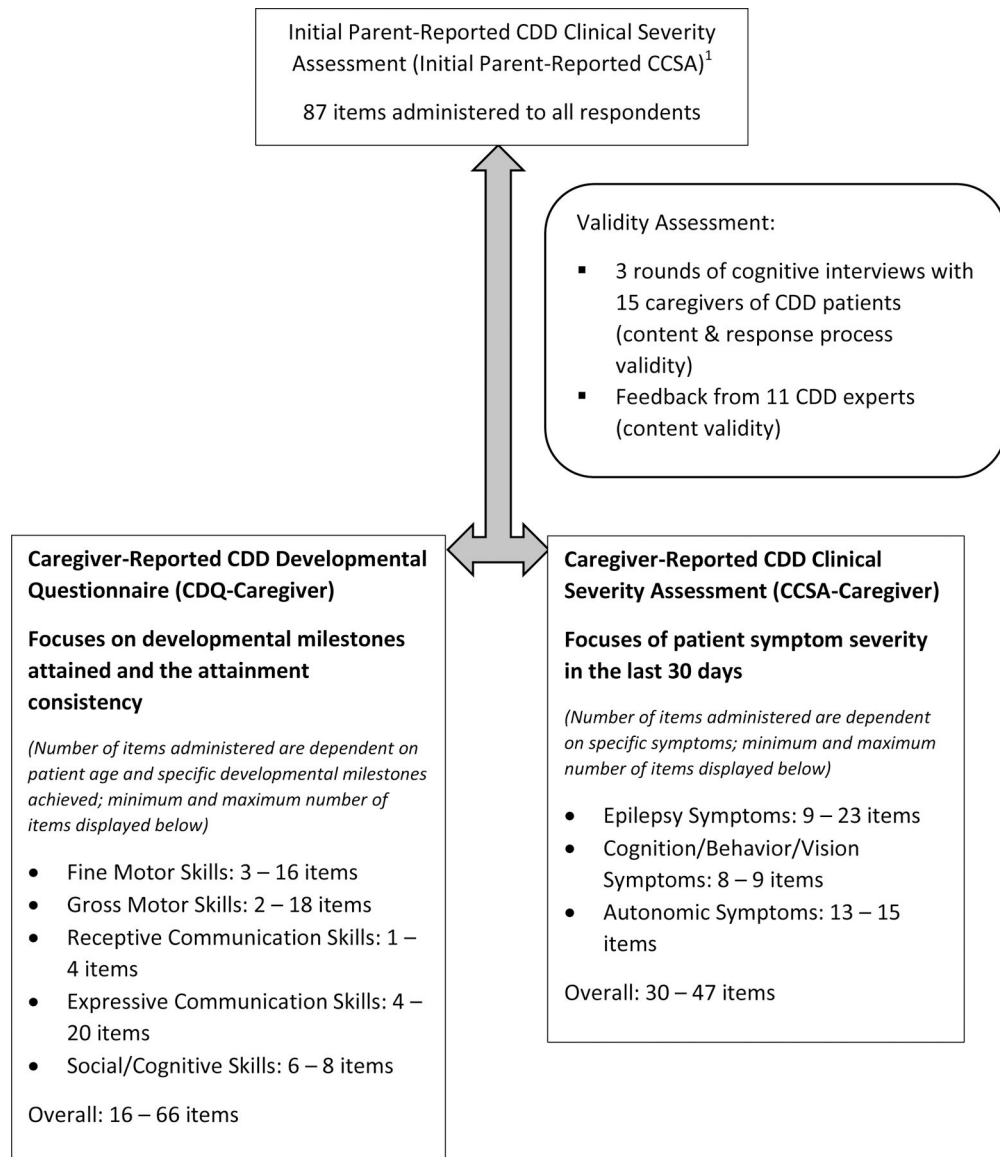


Figure 1: Refinement, Validity Assessment and Final Composition of the Caregiver-Reported CDD Developmental Questionnaire (CDQ-Caregiver) and Clinical Severity Assessment (CCSA-Caregiver)

¹Demarest S, Pestana-Knight EM, Olson HE, et al. Severity Assessment in CDKL5 Deficiency Disorder. *Pediatr Neurol.* Aug 2019;97:38-42.

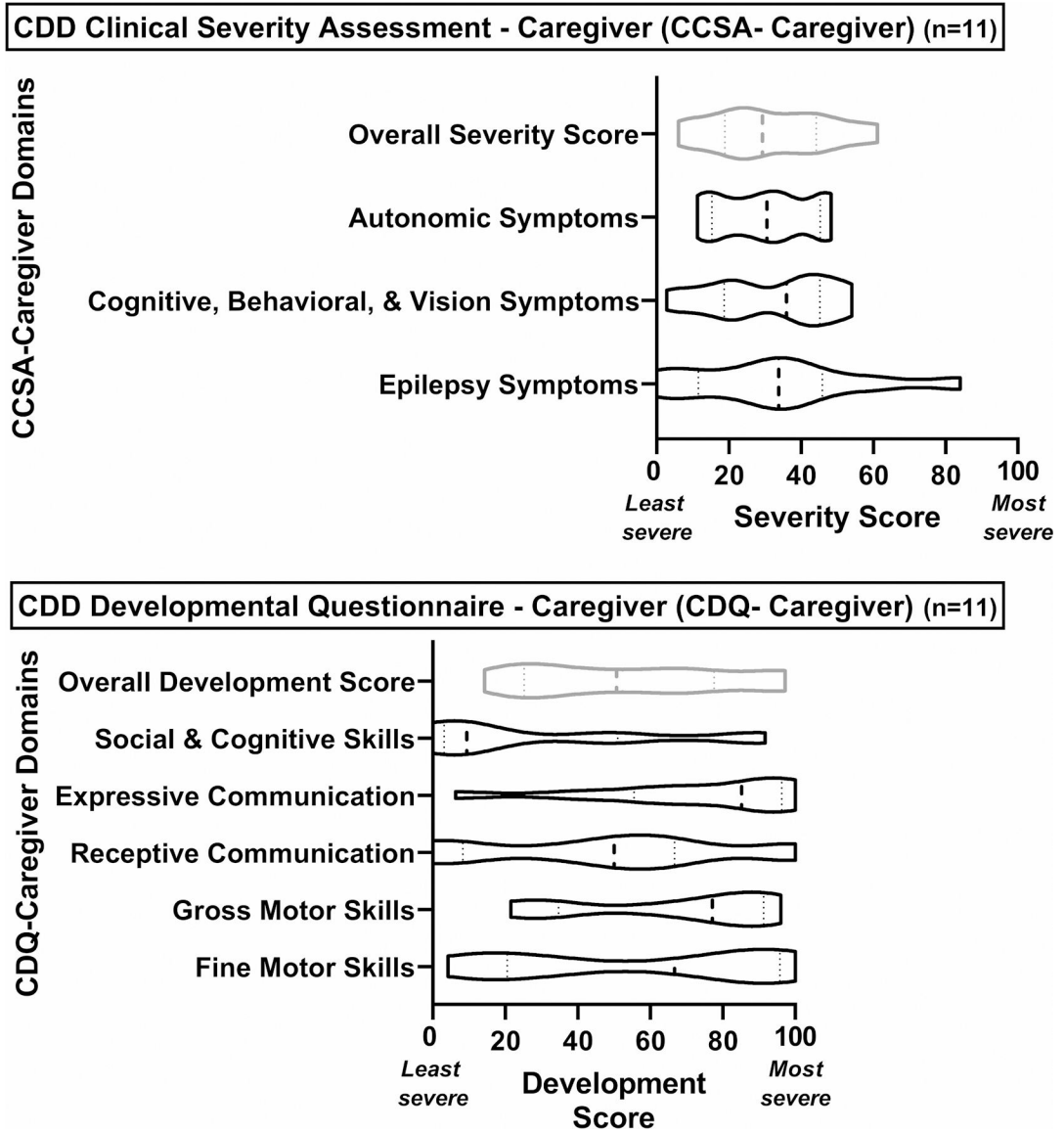


Figure 2:
Violin Graphs of Domain Scores of CDD Clinical Severity Assessment – Caregiver (CCSA – Caregiver) and CDD Developmental Questionnaire – Caregiver (CDQ – Caregiver) (n=11)

Table 1:

Characteristics of Cognitive Interview Participants and Patients

Characteristics	Percentage/Median (Interquartile Range)
Cognitive Interview Participant (Caregiver) ¹	
Gender (n=15)	
Female	86.7%
Male	13.3%
Race (n=10)	
American Indian or Alaska Native	10.0%
White	90.0%
Ethnicity (n=10)	
Hispanic or Latino	10.0%
Not Hispanic or Latino	90.0%
Relationship Status (n=10)	
Divorced	20.0%
Married	70.0%
Other	10.0%
Number of Dependents in Household (n=10)	
1	40.0%
2	60.0%
Age at Child's Diagnosis (n=10)	
25–30	10.0%
31–40	60.0%
41–50	20.0%
60+	10.0%
Highest Level of Education (n=10)	
Bachelor's degree	50.0%
High school diploma or equivalent degree	20.0%
Post-secondary degree	30.0%
Household Income (n=10)	
\$40,000 - \$59,999	10.0%
\$60,000 - \$79,999	20.0%
\$80,000 - \$99,999	10.0%
\$100,000 - \$129,999	40.0%
\$150,000 or greater	20.0%
Child Demographics ²	
Gender (n=14)	
Female	85.7%
Male	14.3%
Race (n=14)	

Characteristics	Percentage/Median (Interquartile Range)
Other	14.3%
Unknown	7.1%
White	78.6%
Ethnicity (n=14)	
Hispanic or Latino	7.1%
Not Hispanic or Latino	85.7%
Unknown	7.1%
Age at time of parent interview (n=14)	10.4 (4.2, 15.3)
Severity Scale³(16-Point Scale) (n=10)	9 (5.75, 10.75)

¹Demographic characteristics of the parents were collected from the participants that completed the final instrument.

²The children's characteristics were extracted from the medical record with the permission of the parents.

³Brock D, Fidell A, Thomas J, Juarez-Colunga E, Benke TA, Demarest S. Cerebral Visual Impairment in CDKL5 Deficiency Disorder Correlates With Developmental Achievement. *J Child Neurol*. Oct 2021;36(11):974-980.

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Phase of Question-Answering Process	Issue	Quotation	Original Version	New Version
	Problems matching response to available response option	<i>“So, when the word used, like always, never, that to me limits me, because I’m like no its not never or is not always.”</i>	<ol style="list-style-type: none"> 1. Always able to do 2. Often able to do 3. Sometimes able to do 4. Never able to do 	<ol style="list-style-type: none"> 1. Usually able to do 2. Often able to do 3. Sometimes able to do 4. Not currently able to do