

## ORIGINAL ARTICLE

# A framework for understanding quality of life domains in individuals with the CDKL5 deficiency disorder

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The CDKL5 deficiency disorder (CDD) is a rare condition caused by spontaneous mutations on the *cyclin-dependent kinase-like 5 (CDKL5)* gene. It is a severe and complex disability that markedly affects the individual's health and wellbeing. This study aimed to identify the quality of life (QOL) domains important for individuals with CDD. Twenty-five parents of individuals registered in the International CDKL5 Disorder Database participated in semi-structured telephone interviews to explore areas that supported or challenged their child's QOL. Rett syndrome (RTT) is another severe genetically-caused neurodevelopmental disorder but is generally less severe than CDD. Qualitative data were analysed using directed content analysis, based on previously identified QOL domains for RTT that related to health and wellbeing, daily activities and community immersion and services. Each of the domains identified for RTT was represented in the CDD dataset overall and when the dataset was divided into three age groups: 3–5 years old; 6–18 years old; and older than 18 years. This is the first study to conceptualise factors important for individuals with CDD. Findings from this study will guide health professionals and other service providers who support individuals with CDD and will offer insight into choosing appropriate QOL instruments when measuring outcomes for this group.

**KEYWORDS**

CDKL5 deficiency disorder, epileptic encephalopathy, intellectual disability, qualitative research, quality of life

## 1 | INTRODUCTION

The CDKL5 deficiency disorder (CDD) is a rare, neurodevelopmental condition that is characterised by early-onset epilepsy and severe physical and intellectual impairment. Additional comorbidities include gastrointestinal problems, respiratory complications, cortical visual impairment and sleep disturbances (Mangatt et al., 2016). CDD is caused by a spontaneous mutation on the *cyclin-dependent kinase-like 5 (CDKL5)* gene. Because of its overlapping clinical presentation, CDD was initially considered to be an early-onset variant of Rett syndrome (RTT), another severe neurodevelopmental disorder caused by mutations on separate gene. Since 2013, however, it has been considered to be an independent condition because the majority of diagnosed individuals do not meet the clinical criteria for RTT (Fehr et al., 2013).

**ABBREVIATIONS:** aa, amino acid; CDD, CDKL5 deficiency disorder; CDKL5, Cyclin-dependent kinase-like 5; QOL, Quality of Life; RTT, Rett syndrome.

Early-onset epilepsy is the cardinal feature of the disorder and may alert clinicians to perform genetic testing using gene panels or sequential single-gene testing in order to confirm a diagnosis (Trump et al., 2016). Seizures usually appear in the first 3 months of life, are frequent in occurrence and refractory to treatment despite the use of multiple medications (Fehr et al., 2016). Additional treatments such as the ketogenic diet may therefore be used, but this also only appears to have short-term efficacy with a median duration of use of 17 months (Lim et al., 2017).

Developmental milestones are significantly delayed (Fehr et al., 2015) and most affected individuals cannot walk, verbally communicate or self-feed (Fehr et al., 2016). In the absence of knowledge concerning the clinical features, natural history and burden of the disorder, the International CDKL5 Disorder Database was established in 2012 to collect clinical information relating to individuals diagnosed with CDD as well as their family health and wellbeing (Mori et al., 2017).

Individuals affected by CDD face considerable barriers to their physical, psychological, and social wellbeing, thereby limiting everyday activities and restricting community participation. Therefore, it is vital to systematically identify areas that are important to the quality of life (QOL) of individuals with the disorder. QOL refers to the individual's perception of different aspects of their life and examines their satisfaction from a holistic perspective (Verdugo, Schalock, Keith, & Stancliffe, 2005). Areas important for other intellectual disability populations such as RTT (Epstein et al., 2016), Down syndrome (Murphy et al., 2017), cerebral palsy (Davis et al., 2017), and autism spectrum disorder (Epstein et al., 2017) have previously been identified through parent-reported observations. They include good physical health, opportunities for social interaction, and time spent outdoors in nature. However, QOL has not been systematically explored in CDD, which is typically more severe than the aforementioned conditions. From what is currently known about the natural history of CDD, it is feasible that the QOL domains important for children with CDD may be similar to those important for adults with CDD.

Using an existing framework of QOL domains for RTT (Epstein et al., 2016), this study aimed to identify the domains important for QOL in individuals with CDD, determine whether differences exist between the domains important for children and adults, and compare these domains to those identified in individuals with RTT.

## 2 | METHODS

### 2.1 | Participants

Families were recruited from the International CDKL5 Disorder Database, a worldwide registry housed at the Telethon Kids Institute in Perth, Western Australia. To date, this database has recruited families from over 40 countries and has received data from nearly 350 families, with individuals with CDD ranging in age from 10 months to 35 years. For the current study, families were recruited provided the parent was fluent in English and their affected child had a pathogenic mutation on the *CDKL5* gene. Thereafter, sampling was purposive to enable optimal variability in clinical presentations by gender, mutation group, age (although restricted to 3 years or older), functional abilities and comorbidities. As previously (Fehr et al., 2015), we grouped individual *CDKL5* mutations based on predicted structural and functional consequences (Bertani et al., 2006). The groups comprised: (a) variants resulting in no functional protein (including variants causing loss of the functional components in the catalytic domain before amino acid [aa] 172 and full gene deletions); (b) missense/in-frame variants within the catalytic domain (includes missense variants within the protein's kinase active region or in-frame variants); (c) truncating variants located between aa172 and aa781 (includes any variants resulting in a truncation such as nonsense or frameshift variants potentially resulting in maintained kinase activity but loss of the C-terminal region); and (d) truncating variants occurring after aa781 (maintaining kinase activity and majority of the C-terminal region). For brevity, we will hereafter refer to the individuals with CDD as children, regardless of age.

**TABLE 1** Characteristics of the children with the CDKL5 deficiency disorder ( $n = 25$ )

Characteristics	$n$ (%)
<b>Age group</b>	
3–5 years	7 (28%)
6–18 years	12 (48%)
18 years and older	6 (24%)
<b>Gender</b>	
Female	20 (80%)
Male	5 (20%)
<b>Mutation group</b>	
No functional protein	7 (28%)
Missense/in-frame within the catalytic domain	9 (36%)
Truncations between aa172 and aa781 <sup>a</sup>	6 (24%)
Truncations after aa781 <sup>a</sup>	2 (8%)
Missing	1 (4%)
<b>Walking ability</b>	
No assistance	5 (20%)
With assistance	3 (12%)
Unable	17 (68%)
<b>Communication through words</b>	
Yes	4 (16%)
No	21 (84%)
<b>Current seizure frequency</b>	
Seizure-free <sup>b</sup>	2 (8%)
Monthly	2 (8%)
Weekly	2 (8%)
Daily, 1–5/day	9 (36%)
Daily, >5/day	10 (40%)
<b>Presence of gastrostomy</b>	
Yes	14 (56%)
No	11 (44%)
<b>Current use of ketogenic diet</b>	
Yes	5 (20%)
No	20 (80%)

<sup>a</sup> aa = amino acid.

<sup>b</sup> One child had the last seizure 6 months ago and the other had the last seizure 2 years ago.

A total of 25 semi-structured interviews were conducted with biological parents who resided in the United States of America ( $n = 18$ ), the United Kingdom ( $n = 3$ ), Australia ( $n = 2$ ), Ireland ( $n = 1$ ), and Canada ( $n = 1$ ). At the time of interviewing, their children (20 females and 5 males) were aged 3–35 years old with a mean age of 12.7 years. The *CDKL5* mutation of seven children was classified in the no functional protein group ( $n = 7$ ), nine had a missense/in-frame mutation ( $n=9$ ), six a truncation between aa172 and aa78 ( $n=6$ ) and two had a truncation after aa781 ( $n = 2$ ). Further information on child characteristics is presented in Table 1.

### 2.2 | Procedure

A qualitative methodology explored both the positive and challenging aspects of the child's daily life. Semi-structured telephone interviews were conducted with parents at a mutually-agreed upon time and

informed verbal consent was provided by parents at the beginning of each interview. Interviews were recorded digitally and lasted approximately 45–90 minutes. The interview schedule previously adopted in other qualitative QOL studies (Davis et al., 2017; Epstein et al., 2016, 2017; Murphy et al., 2017) was used. This included questions on satisfying and challenging aspects of life and experiences that were observed to be important to the children (Epstein et al., 2017). Additional probing questions such as “how do you know?”; “what does this look like?”; and “can you give me a recent example?” were asked to identify observable behaviours that demonstrated aspects of the child's QOL. These probing questions aimed to ensure that parents were not inaccurately inferring emotions since the children were not likely to be able to communicate verbally to confirm parents' inferences of what they were thinking or feeling.

Recordings were transcribed verbatim and the transcripts were emailed to the parent interviewees to provide them with an opportunity to review, edit or add information to support the validity of their reports. This minimised data misrepresentation and ensured accuracy of the parents' narratives prior to data coding and analysis. This study was approved by the Human Research Ethics Committee at the University of Western Australia, Western Australia (RA/4/1/9108) and all participants provided informed consent.

### 2.3 | Data analysis

Directed content analysis was performed based on previously identified QOL domains important for children and adolescents with RTT (Epstein et al., 2016). To assist with data organisation and coding, NVivo 11 (11th Ed, QSE International Pty Ltd, Burlington, MA) software was used. As described by Hsieh and Shannon (2005), operational definitions for each domain were determined initially from the domain and domain element descriptions for RTT, (Epstein et al., 2016) including illustrative examples. The domain and its elements defined by the RTT framework were created as nodes and sub-nodes, respectively, in NVivo. For example, the “Physical health” domain (node) contained the sub-nodes “pneumonia,” “seizures,” and “scoliosis”. Interview transcripts were then imported into NVivo, the data was coded line by line, and each transcript was read and re-read to promote the primary researcher's familiarity with the content. Data was independently analysed and initially coded by one researcher (JT) and reviewed together with a fellow researcher (AE) who had a psychology background and extensive experience with qualitative methods and QOL data coding. Only data describing observable behaviours were coded into the corresponding nodes. Texts in each node were rechecked regularly to ensure the coding remained consistent between transcripts.

To address the trustworthiness of the data and provide a more complete understanding of code assignments, the primary researcher (JT) discussed coding throughout the analyses with the whole research team (JD, HL, and AE). Texts that could not be coded were iteratively discussed on an ongoing basis to determine whether they represented a new domain or a subcategory of an existing domain. The subjects were then divided into three age groups: 3–5 years old; 6–18 years old; and 18 years and older. The domains identified for each participant were described according to age group. During the

final phase of analysis, the research team discussed the interpretation of the data and consensus was reached.

## 3 | RESULTS

All qualitative data were coded into the QOL domain framework previously identified for children and adolescents with RTT (Epstein et al., 2016). New domains did not emerge in this study during data analysis. The ten domains and their domain elements identified as important in CDD are summarised below and sample quotes for each domain are presented in Tables 2–4.

### 3.1 | Health and wellbeing

“Physical health”: This domain described aspects of bodily health relating to comorbidities such as epilepsy, gastrointestinal disorders or poor sleep that impacted wellbeing. Seizures were extensively discussed because of their considerable effects on daily routines and activities. For instance, parents frequently reported that during periods of increased seizure activity, their child slept for most of the day and was unable to attend school, therapies or other activities. Seizures also often disrupted sleeping patterns at night. Side effects from seizure medication were also highlighted, which were associated with lethargy and reduced engagement in day-to-day activities.

“Body pain and discomfort”: This domain included episodes of agitation and periods of being unsettled because of physical discomfort. The child's responsiveness and engagement in daily activities was often compromised during such periods. For example, parents often observed their child becoming distressed when the temperature of their environment was too hot. In turn, this restricted opportunities to comfortably venture outside for walks or to a recreational pool, which were activities that their child otherwise enjoyed.

“Behavioural and emotional wellbeing”: This domain referred to emotional states, both positive and negative. Hypersensitivity was a frequently described element, which affected their life quality. For example, parents often described their child as being very sensitive to loud noises, such as those experienced in busy restaurants or closing of the cupboard doors. Some children were very easily agitated and took a long time to settle and calm.

### 3.2 | Daily activities

“Communication skills”: The ability to convey emotions and desires, both verbally and nonverbally, enabled individuals to express aspects of life quality. Communication aids, such as eye gaze technologies, choice boards, head switches, and other augmented communication systems were frequently used and enabled the children to make their needs known, which was noted to improve their life satisfaction.

“Movement and mobility”: Aspects of wellbeing such as contentment or enjoyment were often evident by observable use of motor and other functional skills. This domain included pleasure in movement, where parents noted behaviours of calmness or excitement when their child was able to move freely on the floor or when rocking their body in response to music.

**TABLE 2** Domains and elements identified for Rett syndrome within the “Health and wellbeing” category of domains (Epstein et al., 2016) and sample quotes illustrating their relevance to the CDKL5 deficiency disorder

Domain	Rett syndrome elements	CDKL5 deficiency disorder
Physical health	Enjoyment of food Respiratory infection Impacts of scoliosis Impacts of epilepsy Side effects of medications Periods of unwellness Periods of low energy/ poor sleep quality	<i>“She’s never been seizure-free so it’s never been totally controlled. If she’ll have one then she’ll sleep it off and we go about our day so that’s not bad. It’s when she has three during a day or something like that. We were having a hard time on our vacation because she was having it back-to-back... she had so many seizures that she just ended up sleeping in the hotel all the time and never really got to enjoy it so that can be a huge factor.”</i> (Female, 14 years old) <i>“I mentioned earlier about sleeping. She sleeps a lot. You know, she sleeps all night and then she goes from here at nine o’clock to day care. And the day care sends a note home every evening with what her day was like. And a lot of them will say, “She slept all morning and then after her peg [feeding tube], she slept all afternoon.”</i> (Female, 25 years old)
Body pain and discomfort	Regulating body temperature Gastrointestinal discomfort Prolonged sitting	<i>“We put her in the water and she reacts like it is burning her even though we are pretty sure it is not... She usually has a high pain tolerance, we think, but for some reason with water temperature, she does not like it... As soon as she is in it, she is fine but that initial touch of water, she wants to get out... She tenses up, crosses her legs together and kind of freaks out.”</i> (Female, 3 years old) <i>“She suffers a lot of pain, she’s also had a lot of physical issues with her this year... I didn’t quite work out what was wrong with her but she was really crying out in pain even if I put her music on or if I ran with her, she was crying out in pain so things like that, she feels uncomfortable.”</i> (Female, 19 years old)
Behavioural and emotional wellbeing	Bruxism Handwriting Self-injury Fear and anxiety Sensory hyper-sensitivity (e.g., excessive noise/light)	<i>“She complains more when she’s dissatisfied with what’s going on... if she’s drinking coffee, she’ll throw it. If she’s sitting at the dinner table, she’ll try to push it away. If we’re walking with her and doesn’t like it, she’ll try to push our arms off of her.”</i> (Female, 35 years old) <i>“Sometimes, it’s even little things. If somebody closes the cabinet door but it happens to be loud, he would jump and it might cause a seizure. If we’re in a restaurant or at a party and there’s a tonne of kids screaming, you know. I think it’s harder for him to understand kind of “Where am I? What’s going on?” And it seems chaotic to him. Sometimes, he seizes more in those environments.”</i> (Male, 3 years old)

“Stability of daily routines”: This domain referred to interactions with people with whom the individuals had been accustomed or during time spent within familiar environments. These environmental characteristics were observed to help children to better tolerate daily activities, including showering and teeth brushing. This familiarity also helped children anticipate and adapt to unexpected changes in schedules, which led to more relaxed and content behaviours.

### 3.3 | Community immersion and services

“Social connectedness”: This domain referred to relationships with others within social settings such as at home, school, or within local community programs, where children demonstrated their enjoyment through smiling and laughing. These expressions were particularly observed during time spent with family members and support workers (e.g., therapists, hired carers). Parents reported that their children recognised the voices of familiar people, often turning their head in their direction and smiling or reaching out toward the familiar person, deriving enjoyment from these interactions.

“The natural environment”: Individuals were often observed to be settled and content when surrounded by elements in nature and the outdoors, which appeared to improve their life quality. This included time spent with animals as well as excursions to the beach or a park. Peaceful behaviours were commonly detected when children were engaging with their natural environments, while agitated or unsettled mannerisms became less prevalent.

“Variety of activities”: There appeared to be value in involvement in different interactive activities including community programs or family driven endeavours such as walks in the park and visiting the zoo. Frequently described activities were at home pursuits such as looking at books, listening to music, and watching TV, as well as time spent in the water, which included swimming and when taking a bath. The parents noted their child fully engaged with the activity at hand as well as demonstrating enjoyment by smiling.

“Provision of targeted services”: This domain included the availability and accessibility of support services staffed by appropriately trained health professionals, therapists, teachers and aides, who were willing to provide high quality, holistic and long-term care. Access to suitable equipment (e.g., wheelchairs, specialised beds), as well as provision of home modifications (e.g., widening of door frames) was considered important in facilitating increased comfort and QOL for the children. Parents noted that regular communication with service providers was imperative to ensure timely attention to their child’s needs and typically resulted in observable improvement of overall health outcomes.

### 3.4 | Domains across ages

The ten domains identified for RTT (Epstein et al., 2016) were represented in each of the three age groups for this study (Table 5), providing evidence that the domain structure was consistent across the CDD cohort irrespective of age.

**TABLE 3** Domains and elements identified for Rett syndrome within the “daily activities” category of domains (Epstein et al., 2016) and sample quotes illustrating their relevance to the CDKL5 deficiency disorder

Domain	Rett syndrome elements	CDKL5 deficiency disorder
Communication	Eye contact Facial expressions Body language Communication aids Can make needs known	<p><i>“Her new ability to communicate is contributing a lot to her happiness. We got her a Tobii eye gaze system about three years ago and she is fairly proficient at it, it's quite wonderful to watch her engage with people... So the other morning, my grandson and I are having a conversation while I was feeding her breakfast. I was feeding her favourite thing, she loves the stuff but she looked at her eye gaze system and said “I want to stop” and I went “what do you want to stop?” and she looks over at the food and I'm like “okay so you want me to stop feeding you?” and she turned to look at the thing and said “I want to stop” again and I was like “oh, wait a minute, my grandson and I were talking, she wants us to stop talking” and then she said “That's so cool”</i></p> <p>(Female, 25 years old)</p> <p><i>“This therapist is like ‘no, you have to do it now’ and she doesn't want to do it now. She doesn't really respond well to that, she'll just shut down. She doesn't respond and she's always tired when the person comes over or when she sees her at school. When she starts shutting down, you can totally see it because she will just stop moving, stop kicking her legs, she won't play with her hands and she would just sit there.”</i></p> <p>(Female, 6 years old)</p>
Movement and mobility	Opportunities for movement Mobility aids Pleasure in movement	<p><i>“I think she gets really frustrated when she can't crawl down her little incline floor or she doesn't move across it and she tries and tries to do it but... she'll stop and put her head down and kind of pout”</i></p> <p>(Female, 4 years old)</p> <p><i>“When she's happy, because when she's at home, she's just happy to walk around the house. I have a big house, she just goes everywhere, just going into one room and then comes and then she lies down and things like that. If we're in the restaurant, she can stand there for a long time... That's when she's most happy when she's walking and exploring by herself.”</i></p> <p>(Female, 6 years old)</p>
Stability of routines	Familiar activities Predictable routines Consistent carers	<p><i>“Normally, when it's not so hot or cold, we try to do a walk in the evening. She responds very positively to that. Around this time of the night, she will go towards the door. She knows the pair of shoes that I wear when we go, and she will get excited and go grab the doorknob and she's ready to go. She really likes her walks.”</i></p> <p>(Female, 7 years old)</p> <p><i>“He likes a certain cup because he's used a certain cup style forever. And just now, I am starting to try to get a more adult kind of cup for him. He likes a certain straw and so, he'll put the straw in his mouth but then he'll be like ‘No, that's not mine’ and then he'll just push it back to me.”</i></p> <p>(Male, 17 years old)</p>

### 3.5 | Comparison to existing RTT QOL theoretical framework

While the ten domains were consistent with those identified for RTT, there were some differences in domain elements, possibly because CDD is generally more severe than RTT. For RTT, the domain “variety of activities” included the element “motivation to engage” and the domain “behavioural and emotional wellbeing” included the element “fear and anxiety.” These elements were not observed in CDD.

## 4 | DISCUSSION

This is the first study to identify QOL domains important for children with CDD. Directed content analysis based on a previously identified framework of QOL domains for RTT (Epstein et al., 2016) was performed and the domains identified for CDD aligned with this framework with no new domains emerging. The domains were also found to be relevant to individuals across childhood and adulthood. These findings provide valuable information for professionals and families supporting individuals affected by CDD to assist the development of strategies to improve wellbeing and QOL.

Overall, physical health was primarily affected by seizures. Severe epilepsy is a hallmark for individuals with CDD (Fehr, Wong, et al., 2016) and was extensively discussed by the parents. Most subjects (19/25) in this study experienced daily seizures, and periods of heavy

seizure loads were often linked to longer recovery times that was often associated with sleeping all day. Consequently, children were unable to attend therapy, school or outings, programs and activities that were important for facilitating cognitive engagement, physical activity and social inclusion. The sequelae associated with the refractory nature of the epilepsy were described by parents as being a substantial challenge for their children's QOL. Consistent with the current literature (Fehr, Wong, et al., 2016; Lim et al., 2017), many children in this study had tried multiple therapies including anti-epileptic medications, formulations of medical cannabis, the ketogenic diet and the vagus nerve stimulator but efficacies were generally minimal. One family resorted to a corpus callostomy surgery for their 6-year-old daughter after exhausting most available options, and their child's seizures (20–30 major seizures/day) adversely affected her daily life including multiple hospitalisations.

Comorbidities such as gastrointestinal problems and sleep dysfunction are common in CDD (Mangatt et al., 2016) and further compound the poor health status. Constipation and gastric reflux were associated with discomfort and pain, which meant that the individual could not fully participate in school, therapies, or daily routines. This highlights the requirement for comprehensive care and in particular, the imperative for additional research on therapies especially to reduce refractory epilepsy.

Most children in the study were nonverbal (21/25), instead utilising body language, vocalisations and facial expressions as their main



**TABLE 4** Domains and elements identified for Rett syndrome within the “Community immersion and services” category of domains (Epstein et al., 2016) and sample quotes illustrating their relevance to the CDKL5 deficiency disorder

Domain	Rett syndrome elements	CDKL5 deficiency disorder
Social connectedness	Inclusiveness in social settings Responsiveness in social settings Enjoyable time with family members and other familiar people	<i>“And you can just tell that he recognizes people. There was a woman in the grocery store and she would talk to him all the time. We hadn't been in that particular store for three to six months and she went up and started talking to him and you could tell that he recognized her. She could even tell and she didn't have much experience being around people like him but his eyes lit up and he just perked right up and had a big smile on his face and you could tell he remembered her.”</i> (Male, 21 years old)
Nature and outdoors	Exploration of plant life Sensation of land elements and weather patterns Time spent with animals (including pets and wildlife)	<i>“She loves being outside... she loves the stars, she loves the sun, she'll always find the sunny spot in the house, she loves the trees and the movement of trees... like if we go for a walk outside, she'll look at the trees and try and touch the leaves.”</i> (Female, 11 years old)
Variety of activities	Motivation to engage Responsiveness to music and entertainment Responsiveness to music to soothe when upset Enjoys a range of activities	<i>“She just stares at it [the movie screen], she gets in a trance when she watches it. She likes Disney cartoons so we play them for her on her computer, close to her face and she just totally watches it. She'll still make noises or kick around if there's a musical and songs. We've taken her to the theatre and she laughs when other people laugh at the same time so that was fun to see her that interactive. It just captures her, the colour, the sounds, the lights and the music.”</i> (Female, 14 years old)
Provision and access to services	Informed service providers Accessibility of services Individualised programs Continuity of care Accessibility to equipment Availability of respite services	<i>We're waiting on the bed, that's been denied twice now. A hospital bed, yes. With the hospital bed, you can adjust the bed into whichever angle, she's better for her eating and her breathing. It's not too high and she doesn't eat on the wheelchair because it's too much pressure on her stomach. Now, on the bed, on the hospital bed, you can put it in a certain angle that is better for her, it doesn't have that pressure but she's not lying flat either. With the regular bed, I would have to put pillows but she doesn't have any head control or trunk control so she will just fall to the side. It got denied again today so I'm applying again, first thing tomorrow.</i> (Female, 3 years old)

**TABLE 5** Frequencies of domains coded for individuals in each of the three age groups

Domain	Age group (years)		
	3–5 (n = 7)	6–18 (n = 12)	>18 (n = 6)
Behavioural and emotional wellbeing	7/7	11/12	4/6
Body pain and discomfort	4/7	7/12	5/6
Physical health	7/7	12/12	5/6
Communication	5/7	12/12	4/6
Movement and mobility	4/7	10/12	5/6
Stability of routines	4/7	12/12	4/6
Social connectedness	6/7	12/12	4/6
Nature and outdoors	3/7	8/12	1/6
Variety of activities	7/7	12/12	6/6
Provision and access to services	5/7	7/12	5/6

methods of communication. Therefore, children relied heavily on the ability of their primary caregivers to recognise subtle changes in behaviour and vocalisations as a mechanism for their child to make their needs known. This was an area also explored in the QOL study for individuals with cerebral palsy and comorbid intellectual disability (Davis et al., 2017). Communication aids such as choice boards and eye gaze technologies assisted individuals to converse with others and enabled valuable interactions with others. However, the communication impairments remained a substantial barrier in this disorder.

For instance, an eye gaze system may not be suitable for individuals who have cortical visual impairment or strabismus (Borgestig, Sandqvist, Parsons, Falkmer, & Hemmingsson, 2016; Wilkinson & Mitchell, 2014), both of which can occur in CDD (Bahi-Buisson et al., 2008). Several parents also mentioned a tendency for the child to “shut down,” depicting antisocial behaviours by putting their head down, shutting their eyes or being unresponsive to external stimulus (e.g., not answering to their name). While these could have been seizures or nonepileptic paroxysmal events such as those that occur in RTT (Glaze, Schultz, & Frost, 1998), parents specifically observed their child's avoidance of particular social interactions. Behaviours such as these are common for nonverbal and nonmobile individuals with intellectual disability (Molteno, Molteno, Finchilescu, & Dawes, 2001).

“Variety of activities” was a domain explored by all parents in this study. They observed that their children appeared to be more focused and attentive when listening to music or being read to, and were often smiling and laughing when watching TV, suggesting that these tasks were key interests, similar to the components of QOL in RTT and Down syndrome (Epstein et al., 2016; Murphy et al., 2017). When compared to individuals with RTT (Epstein et al., 2016) who were reported to enjoy at-home and out-of-home pursuits, individuals with the CDKL5 disorder predominantly were observed to enjoy at-home activities. Many parents also noted their child to be hypersensitive to noise with limited tolerance of crowds, busy restaurants and other settings that might overstimulate them. These situations could lead to

negative behaviours such as agitation, self-injury, or “shutting down,” which restricted the social settings in which their children could comfortably participate, especially when others were unfamiliar with the characteristics of the disorder. Together with global developmental delay (Fehr et al., 2013), severe physical disability (Fehr, Downs, et al., 2016), and refractory epilepsy (Fehr, Wong, et al., 2016), each or all of these factors could pose substantial barriers to participating in out-of-home settings.

However, most individuals had an affinity with water activities, often observed during hydrotherapy, recreational swimming and bath time, irrespective of gross motor abilities in a disorder where the majority are unable to walk (Fehr et al., 2015; Fehr, Downs, et al., 2016). Parents reported manifestations of calmness (e.g., lying on a floatation device) or excitement (e.g., laughing and splashing in the pool) while their child engaged in these activities. Moreover, these responses have been observed in other groups with severe disability including cerebral palsy (Davis et al., 2017), RTT (Epstein et al., 2016), and Angelman syndrome (Williams et al., 2006).

The QOL domains important to individuals with CDD were represented in the RTT theoretical framework (Epstein et al., 2016) and new domains did not emerge during the data analysis conducted for this study, despite CDD being generally more severe than RTT. However, there is considerable clinical overlap between these two disorders in terms of functional abilities (e.g., nonverbal and difficulties in mobility) and comorbidities (e.g., gastrointestinal complications and lower respiratory tract infections; Mangatt et al., 2016). Hence, daily life may be similarly affected. This suggests that the RTT theoretical framework may also be applicable to other severe disability groups. Additionally, QOL domains were represented across the three age groups. Our previous findings suggest that skill levels are similar from childhood into adulthood (Fehr, Downs, et al., 2016). Hence, despite age, interests and enjoyment of life were generally consistent over time and a measure of QOL for children with CDD would still be appropriate for adults.

Because CDD is associated with severe cognitive impairment and restricted expressive communication skills (Fehr et al., 2015), the individual's ability to reflect inwardly, think abstractly and express feelings is limited. As these are important aspects to evaluate QOL, interviews were proxy-reported by parents who were also the primary caregivers. Probing questions such as “how do you know this?” determined the parents' rationale for their descriptions, while asking “what does that look like to an outside observer?” and “why do you think that is?” avoided parents' subjectivity and reduced the possibility of inferring emotion from their child. Only observable actions and behaviours as described by parents were coded. Most of the parents interviewed were mothers (23/25) and we acknowledge that fathers may have different perspectives.

This is the first study to investigate QOL in CDD and our data provides insight into important complexities and intertwined aspects of daily life. Our comprehensive framework will help to inform counselling for families soon after diagnosis, and will have utility in guiding families, health professionals, and other service providers on how to plan ongoing support and management. By exploring the personal impacts of poor health in CDD, our data illustrates the critical need for new and effective therapies, particularly for the management

of refractory epilepsy to improve wellbeing and enhance participation in the community. Finally, our QOL framework informs choice of a relevant QOL measure that would be suitable for CDD, to ensure valid assessment of ongoing management and new therapies.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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