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Research Paper

Beyond the Diagnosis: Evaluation of Quality-of-Life Measures and Family Functioning in SLC6A1-Related Neurodevelopmental Disorder

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ABSTRACT

Background: SLC6A1-related neurodevelopmental disorder (SLC6A1-NDD) is a rare genetic disorder linked to autism spectrum disorder, epilepsy, and developmental delay. In preparation for future clinical trials, understanding how the disorder impacts patients and their families is critically important. Quality-of-life (QoL) measures capture the overall disease experience of patients. This study presents QOL findings from our SLC6A1-NDD clinical trial readiness study and the Simons Searchlight SLC6A1-NDD registry.

Methods: We compiled QoL data from participants with SLC6A1-NDD enrolled in our clinical trial readiness study (n = 20) and the Simons Searchlight registry (n = 32). We assessed the distribution of scores on the Quality-of-Life Inventory-Disability (QI Disability), Quality of Life of Childhood Epilepsy (QOLCE-55), and Pediatric Quality of Life Inventory Family Impact Module (PedsQL-FIM) administered to caregivers.

Results: In our cohort of 52 participants, the mean QI Disability total score was 73 ± 12.3, the QOLCE-55 mean total score was 49 ± 17.1, and the mean total PedsQL score was 51 ± 17.6. Longitudinal QoL scores for a subset of participants (n = 7) demonstrated a reduction in the Family Relationship domain of PedsQL-FIM (Δ-10.0, $P = 0.035$). Bootstrap resampling of total scores displays nonoverlapping 95% confidence intervals for the 10th, 50th, and 90th percentiles on all three measures.

Conclusions: This is the first study to investigate QoL measures for SLC6A1-NDD. Findings suggest that scores within the 10th percentile's confidence interval could be clinically significant, referring to QI-Disability scores of <61, QOLCE-55 scores of <46, and PedsQL-FIM scores of <42. Future validation studies are needed.

Introduction

SLC6A1-related neurodevelopmental disorder (SLC6A1-NDD) is a rare genetic disorder caused by a loss of function in the *SLC6A1* gene. The *SLC6A1* gene encodes a voltage-dependent gamma-aminobutyric acid transporter (GAT1) that functions to reuptake the inhibitory neurotransmitter gamma-aminobutyric acid from the synaptic cleft into presynaptic neurons.[1] Loss of GAT1 disrupts neuronal excitatory and inhibitory signaling and has been linked with phenotypes of SLC6A1-NDD including developmental delay, seizures, epilepsy, attention-deficit/hyperactivity disorder, and/or autism spectrum disorder.[1-3] SLC6A1-NDD is frequently among the

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top genetic disorders identified in epilepsy and autism spectrum disorder databases,[1,4] but little is known about the impact of SLC6A1-NDD on the quality of life (QoL) of individuals and families affected by this rare condition. This is the first study that explores the impact of SLC6A1-NDD on the QoL of the individual and the family.

QoL is a multidimensional variable that encompasses a patient's satisfaction with life experiences and their overall disease experience beyond a medical diagnosis. QoL measures are often used to determine clinical improvement or decline from a patient perspective and can serve as a composite measure of change in clinical trials.[5] There are currently no established QoL measures to capture the experience of patients with SLC6A1-NDD, but several have been used in genetic neurodevelopmental disorders with a similar spectrum of clinical symptoms. Introduced in 2019, the Quality-of-Life Inventory-Disability (QI Disability) measure is one of the most well-studied QoL measures among patients with intellectual disability/developmental encephalopathies.[6] It is validated in several populations including Rett syndrome, Down syndrome, cerebral palsy, and autism spectrum disorder and recently has been studied in CDKL5 deficiency disorder.[6-8] In one study of the QI Disability among patients with developmental encephalopathies (n = 176), which included participants with SLC6A1-NDD (16%), scores of QoL measures were not related to seizure frequency and only partially overlapped with objective measures of disease severity.[9] Overall conclusions supported the use of QI Disability for further characterization of a patient's disease experience among patients with developmental encephalopathies. The most cited limitation of the QI Disability framework centers around its dependence on parent/proxy reports of patient QoL; however, caregiver distress has not been shown to mediate or moderate the QI Disability values.[10]

Another common QoL used in neurodevelopmental disorders is the PedsQL Family Impact Module (PedsQL-FIM), which is designed to assess the impact of a patient's diagnosis on family members. It has been studied among families of patients with Rett syndrome,[11] Prader-Willi syndrome,[12,13] Menkes disease,[14] and progressive neurological diseases such as metachromatic leukodystrophy and pontocerebellar hypoplasia type 2.[15] Findings suggest that caregivers can be significantly impacted by the child's disease burden, especially mothers,[15] and that scores on PedsQL-FIM can correlate with lower scores on other variations of the PedsQL.

Finally, the Quality of Life of Childhood Epilepsy (QOLCE-55) measure of QoL has been studied extensively among patients with epilepsy and tends to show worse QoL scores among individuals with epilepsy and intellectual disability.[16,17] Seizure control can have a positive impact on QOLCE-55 subdomain scores in cognition and social activity compared with those with uncontrolled seizures.[18]

Although all three of these QoL measures have been studied in similar clinical contexts and patient populations, little is known about how these measures perform in the SLC6A1-NDD population. Because QoL measures are commonly used as clinical outcome measures in clinical trials, a deeper understanding of how SLC6A1-NDD impacts patients and caregivers is critically important. The aim of this article is to (1) describe the distribution of scores on QoL measures commonly used in neurodevelopmental disorders (QI-Disability, PedsQL-FIM, and QOLCE-55), (2) assess for correlation of total and subdomain scores across QoL measures, and (3) assess for changes in scores over time.

Methods

Data collection

Data were gathered from two primary sources: (1) the SLC6A1-NDD clinical trial readiness study conducted at UT Southwestern Medical Center (UTSW) and (2) the Simons Foundation Autism Research Initiative (SFARI) Base Simons Searchlight Collection Version 11.0. Variables of interest included the total and subdomain scores on available QoL measures and demographic data such as age, race/ethnicity, sex, and genetic variant pathogenicity. Patients with pathogenic variants, likely pathogenic variants, or variants of unknown significance (VUS) with clinical phenotypes consistent with SLC6A1-related disorder were included.[19] Both studies include longitudinal data collection. All available patient data were included in statistical analysis. Only the QI-Disability measure was available in the SFARI database. Research participant records were not linked between the two studies. This study received ethical approval from the UTSW institutional review board.

Quality-of-life measures

The QI-Disability, the PedsQL-FIM, and the QOLCE-55 were administered to caregivers annually. These measures are widely recognized for their reliability and validity in assessing QoL across a variety of domains relevant to patients with neurodevelopmental disabilities.

QI-Disability

The QI-Disability is a tool designed to measure the QoL in children with intellectual disabilities.[6,8] This tool consists of 32 items spread across six domains: Social Interaction, Positive Emotions, Negative Emotions, Physical Health, Leisure and the Outdoors, and Independence. Parents rate each item using a five-point Likert scale reflecting their child's well-being and enjoyment over the past month. Each response is transformed into a score ranging from 0 to 100, with higher scores indicating better QoL. Domain scores are determined by averaging the item scores within that domain, and the total score is computed by averaging all the domain scores.

PedsQL-FIM

The PedsQL-FIM is a 36-item tool designed to measure the impact of a child's chronic health condition on parents and family functioning.[20] This tool includes eight scales, six of which assess various aspects of parent functioning, including Physical, Emotional, Social, Cognitive Functioning, Communication, and Worry, and two that assess family functioning, namely, Daily Activities and Family Relationships. Parents respond to each item on a five-point Likert scale, with 0 indicating “never a problem” and 4 representing “always a problem.” The responses are reverse-scored and linearly transformed to a scale ranging from 0 to 100, where higher scores suggest better functioning or less negative impact. Scale Scores are calculated by summing the items and dividing by the number of items answered, accounting for any missing data. If more than half of the items in a scale are missing, the Scale Score is not calculated. The Total Scale Score, representing the overall impact on family life, is calculated by summing all 36 items and dividing by the number of items answered. The Parent Health-Related Quality of Life (HRQoL) Summary Score combines 20 items from the Physical, Emotional, Social, and Cognitive Functioning Scales. The Family Functioning Summary Score is based on eight items from the Daily Activities and Family Relationships Scales.

QOLCE-55

The QOLCE-55 is a proxy-report instrument developed to assess the HRQoL in children newly diagnosed with epilepsy.[21] The QOLCE-55 is composed of four subscales Cognitive, Emotional, Physical, and Social and is designed for children aged four to 18 years. This tool evaluates seven dimensions of HRQoL, including cognition, physical activities, social activities, emotional well-being, behavior, general health, and general QoL. These dimensions are

TABLE.
Demographics and Clinical Characteristics of the Participants in This Study, Including Gender, Age, Race, Ethnicity, and Genetic Variant Classification

Demographics: UTSW and SFARI			
Variable	Characteristics	Number of Participants (N = 52)	Percent
Gender M:F	27:25		52%: 48%
Mean age (years)	7.9		
Median age & range (min-max), (years)	6.5 (1.4-16.9)		
Race	White/Caucasian	35	67.3%
	More than one race	5	9.6%
	Asian	2	3.8%
	Missing	10	19.2%
Ethnicity (UTSW only)	Not Hispanic or Latino	18	90%
	Missing	2	10%
Genetic variant classification	Pathogenic	28	53.8%
	Likely pathogenic	15	28.8%
	VUS	8	15.4%
	Missing	1	1.9%

Abbreviations:
F = Female
M = Male
max = Maximum
min = Minimum
SFARI = Simons Foundation Autism Research Initiative
UTSW = UT Southwestern Medical Center
VUS = Variants of unknown significance

represented by 16 subscales, which are scored on a five-point Likert scale and then transformed to a score ranging from 0 (low functioning) to 100 (high functioning). The total QOLCE-55 score is calculated as the unweighted mean of the subscale scores.

Statistical analysis

Graphical measures and the Shapiro-Wilk test were used to assess the normality of subdomain and total scores of all three measures. Since many of the subdomain scores demonstrated a non-normal distribution, we performed nonparametric statistical methods to assess and compare score distributions. The Wilcoxon rank-sum test compared QoL subdomain scores within each measure and total scores between measures. To better understand the distribution of QoL scores within SLC6A1-NDD, we leveraged the bootstrap resampling technique[22] to develop reference ranges of QoL subdomain and total scores for each measure. The bootstrap resampling technique involves resampling the data with replacement, computing a statistic, and repeating the process many times to estimate the distribution of that statistic. This method was applied to the 10th, 25th, 50th, 75th, and 90th percentiles to estimate the 95% confidence intervals for each percentile; this provides a nonparametric estimation of the confidence intervals, which is equivalent to using confidence intervals from a t distribution on QoL data.[21] We also obtained Spearman rank order correlation coefficients to assess the correlations between subdomains and total scores on each QoL measure as well as correlations across total scores and analogous subdomains, where available, of the three QoL measures. We defined correlation coefficients as very weak (0.00 to 0.19), weak (0.20 to 0.39), moderate (0.40 to 0.69), strong (0.70 to 0.89), and very strong (0.90 to 1.00).[23] Finally, Wilcoxon signed-rank test compared QoL subdomain and total scores between two time points measured at one-year intervals. R 4.2.2 was used to perform all statistical analyses.[24] Statistical significance was assumed at the 0.05 level.

Results

A total of 52 age-eligible participants were included in the analysis (UTSW n = 20, SFARI n = 32) with an age range of 1.4 to 16.9 years (7.9 ± 4.4). Both cohorts were predominantly non-Hispanic Caucasian (UTSW: 85%, 17 of 20; SFARI: 56%, 18 of 32) with a male to female ratio of 10:10 and 17:15 in the UTSW and SFARI cohorts, respectively. In the UTSW cohort, most participants had likely pathogenic (35%, seven of 20) or pathogenic variants (45%, nine of 20) and only three had VUS (15%). In the SFARI cohort, most *SLC6A1* variants were pathogenic (59%, 19 of 32), followed by likely pathogenic (25%, eight of 32) and VUS (16%, five of 32) (see Table). The mean total scores were highest on the QI-Disability (73 ± 12.3), followed by the PedsQL-FIM (51 ± 17.6) and the QOLCE-55 (49 ± 17.1) (see Fig 1). The Wilcoxon rank-sum test revealed no significant score difference between the PedsQL-FIM and QOLCE-55 ($P = 0.83$), but a significant difference was found in comparison of each of these measures to the QI-Disability ($P < 0.001$).

Using n = 54 data points (n = 48 unique individuals) for QI-Disability, n = 22 (n = 16 unique individuals) for QOLCE-55, and n = 27 (n = 20 unique individuals) for PedsQL-FIM, bootstrap resampling for total scores revealed nonoverlapping confidence intervals for the 10th, 50th, and 90th percentiles for all three QoL measures (see Fig 2). The QI-Disability measure shows distinct separation between all percentiles at or below the 75th percentile. On the QI-Disability measure, scores of 53 to 61 fall into the 10th percentile, 69 to 77 are in the 50th percentile, and 83 to 95 are in the 90th percentile. On the QOLCE-55 measure, scores of 12 to 46 fall into the 10th percentile, 47 to 56 are in the 50th percentile, and 57 to 76 are in the 90th percentile. On the PedsQL-FIM measure, scores of 7 to 42 fall into the 10th percentile, 44 to 56 are in the 50th percentile, and 58 to 73 are in the 90th percentile.

The lowest scores on each measure were the Physical subdomain for QOLCE-55 (28.2 ± 16.7), the Worry subdomain for PedsQL-FIM (27.2 ± 18.2), and the Negative Emotions subdomain for QI-Disability (58.0 ± 21.4). The Wilcoxon rank-sum test revealed that only the Negative Emotions subdomain was significantly lower than the other subdomains on the QI-Disability ($P < 0.01$), but there was no other significant difference between subdomain scores on each respective measure. The highest scores on each measure were the Social subdomain for QOLCE-55 (74.1 ± 29.3), the Cognitive subdomain for PedsQL-FIM (61.5 ± 24.4), and the Positive Emotions subdomain for QI-Disability (81.9 ± 15.9). The Wilcoxon rank-sum

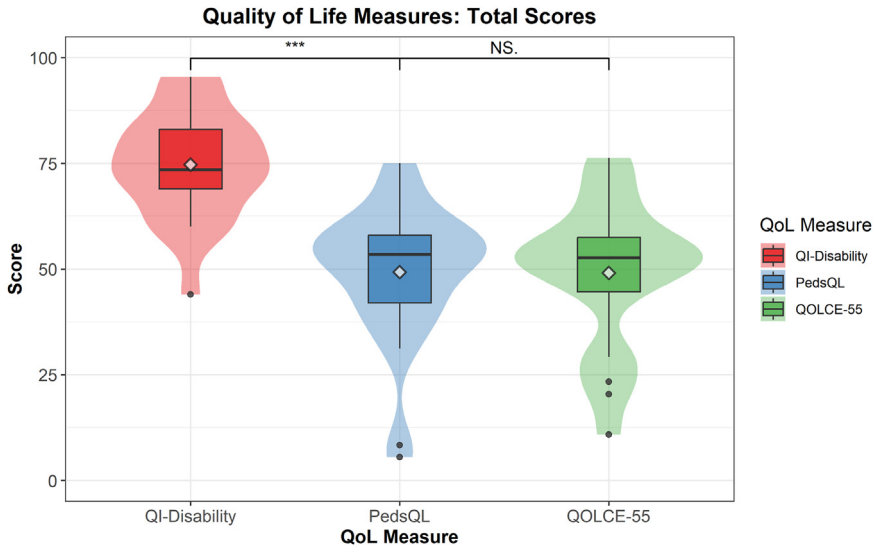

FIGURE 1. Box-and-violin plot of the total scores from the QI-Disability, PedsQL-FIM, and QOLCE-55 QoL measures, ordered from highest to lowest mean score. Mean values are provided by the gray diamonds. Wilcoxon rank-sum test shows a significant difference between QI-Disability and the other two measures. QoL, quality of life; QI-Disability, Quality-of-Life Inventory-Disability; PedsQL-FIM, Pediatric Quality of Life Inventory Family Impact Module; QOLCE-55, Quality of Life of Childhood Epilepsy. The color version of this figure is available in the online edition.

test revealed that only the Social subdomain was significantly higher than the other subdomains on the QOLCE-55 ($P < 0.025$).

All subdomains displayed moderate to strong correlations with their respective total scores on each QoL measure ($\rho = 0.53$ to 0.90), including the HRQoL and Family Functioning score on the PedsQL-FIM (see supplementary figures). Total scores across all QoL measures were moderately correlated with each other ($\rho = 0.59$ to 0.65). When comparing analogous subdomain scores across measures, all positive and negative emotional subdomain scores had moderate to strong correlations ($\rho = 0.51$ to 0.84). The cognitive and physical subdomain scores on QOLCE-55 and PedsQL-FIM displayed weak correlations ($\rho = -0.05$ to 0.25). All social subdomain scores demonstrated weak correlations ($\rho = 0.07$ to 0.37) (see Fig 3).

Within the UTSW sample, longitudinal data were obtained approximately 12 months apart (QOLCE-55 and QI-Disability n = 6, PedsQL-FIM n = 7). The Wilcoxon signed-rank test revealed no significant score difference between the two time points, with the

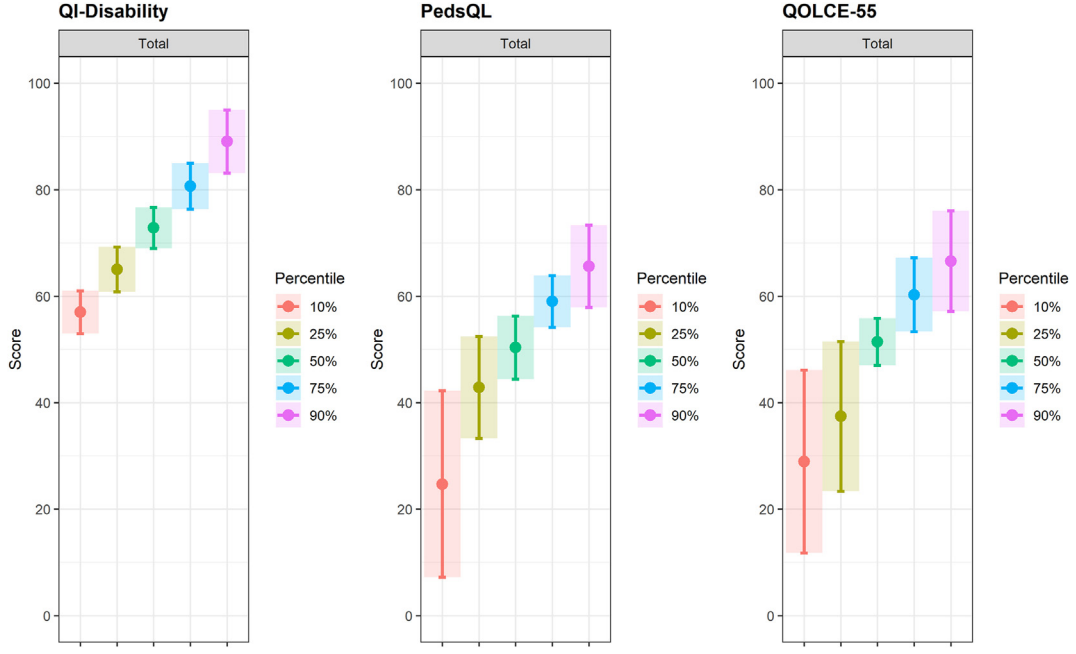

FIGURE 2. Error bar plot of the total scores from the QI-Disability, PedsQL-FIM, and QOLCE-55 QoL measures, ordered from largest to smallest number of data points. Upper and lower limits of the error bars represent the 95% confidence interval of the 10th, 25th, 50th, 75th, and 90th percentiles of the total scores. The confidence intervals do not overlap for the 10th, 50th, and 90th percentiles on all three QoL measures. With the largest cohort of participants, all the confidence intervals on the QI-Disability do not overlap with the exception of the 75th and 90th percentile. QoL, quality of life; QI-Disability, Quality-of-Life Inventory-Disability; PedsQL-FIM, Pediatric Quality of Life Inventory Family Impact Module; QOLCE-55, Quality of Life of Childhood Epilepsy. The color version of this figure is available in the online edition.

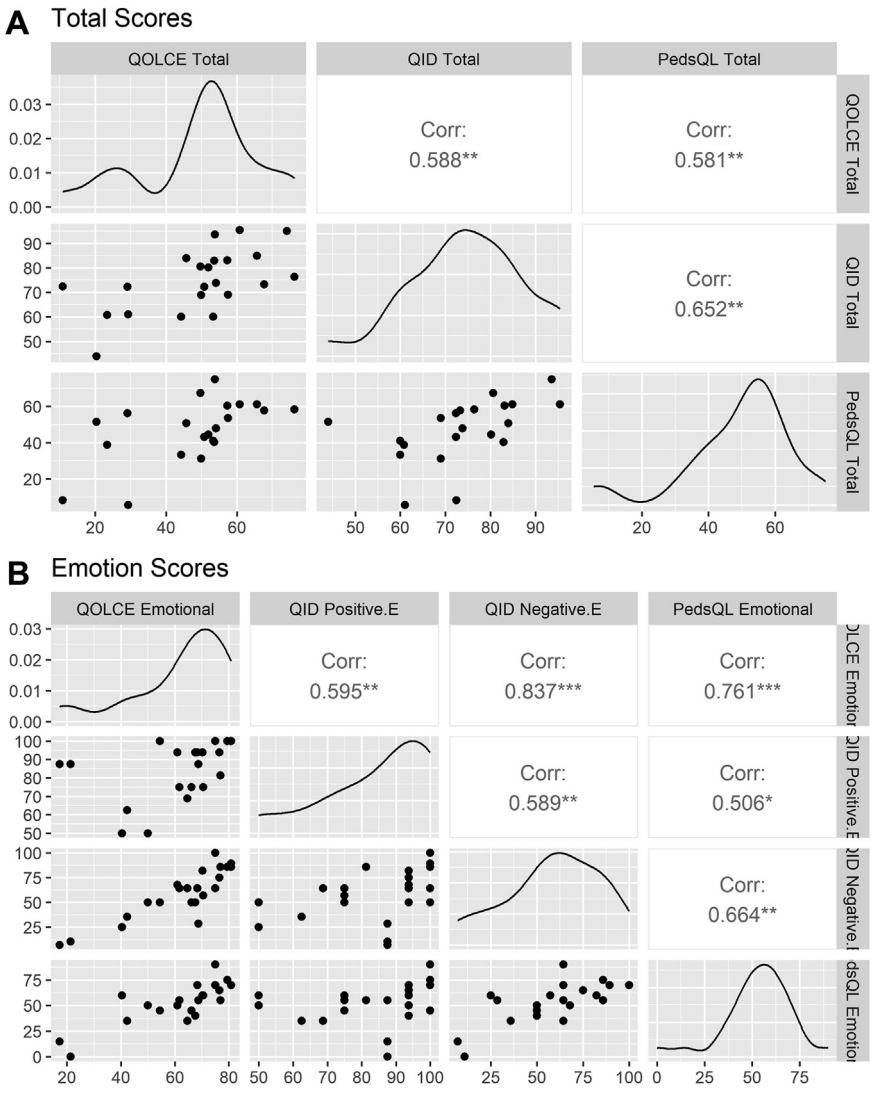

FIGURE 3. Correlation matrix of the (A) total scores and the (B) emotion-related subdomain scores from the QI-Disability (QID), PedsQL-FIM (PedsQL), and QOLCE-55 (QOLCE) QoL measures. The plot shows kernel-density estimations on the diagonal, scatterplots below the diagonal, and Spearman rank-order correlation coefficients above the diagonal. Asterisks next to the correlation coefficient indicate a level of statistical significance corresponding to $P < 0.05$. All total and emotional scores are moderately to strongly correlated with correlation coefficients ranging from $\rho = 0.506$ to $\rho = 0.837$, with the strongest correlation between the QOLCE-55 and QI-Disability's emotional subdomains. QoL, quality of life; QI-Disability, Quality-of-Life Inventory-Disability; PedsQL-FIM, Pediatric Quality of Life Inventory Family Impact Module; QOLCE-55, Quality of Life of Childhood Epilepsy.

exception of a median 10-point reduction in the Family Relationships subdomain on the PedsQL-FIM from time point 1 to time point 2 (range 0 to −25, $P = 0.035$) (see Fig 4).

Discussion

This is the first study to report on the distribution of QoL scores on commonly used QoL proxy-report measures including the QI-Disability, the QOLCE-55, and the PedsQL-FIM. Higher scores on each of these measures correspond to better QoL. Although all these measures share a common score range from 0 to 100, score distributions varied. Although there was a moderate correlation between total scores across all three measures, the median score of the QI-Disability measure was significantly higher. This finding suggests that individuals could be expected to have a relatively higher score on the QI-Disability when compared with the PedsQL-FIM or QOLCE-55, and conversely, a low score on the QI-Disability may be interpreted as more negative QoL than a comparable score on either the PedsQL-FIM or QOLCE-55. Each measure captures different aspects of the patient's experience, and direct comparison without careful interpretation might lead to misleading conclusions. Further investigations are needed, but higher scores on the QI-Disability measure may be in part due to the broad spectrum of neurodevelopmental disability seen in SLC6A1-NDD. The QI-Disability measure was designed for a population with predominantly moderate to severe neurodevelopmental disability, but some individuals with SLC6A1-NDD have relatively mild neurodevelopmental disability. Future studies should investigate the relationship between QoL measure scores and clinical characteristics.

Although we have generated reference range estimates on these three QoL measures, validation studies are still needed in a larger population of SLC6A1-NDD. Subdomains differed between the measures, but all three QoL measures captured symptoms related to social and emotional functioning and physical abilities. Scores on the emotional subdomains were similar between all three measures, suggesting that each measure captures the impact of these symptoms similarly. However, scores on the physical abilities and

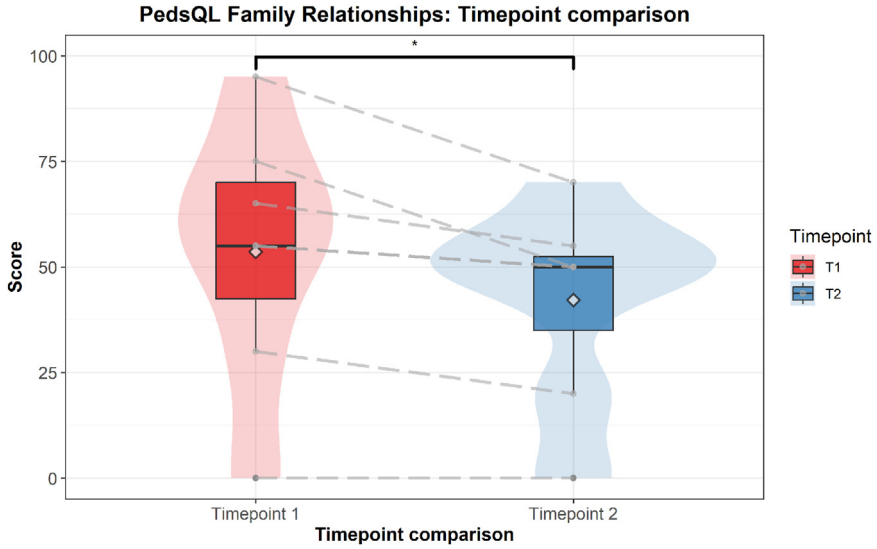

FIGURE 4. Box and violin plot of the Family Relationships subdomain on the PedsQL-FIM. Mean values are provided by the gray diamonds. Changes in participant scores are tracked by the gray dashed lines. Wilcoxon signed-rank test shows a significant difference between the two time points at which the test was administered to n = 7 participants with a median reduction of 10 points from time point 1 to time point 2 (range 0 to −25, $P = 0.035$). PedsQL-FIM, Pediatric Quality of Life Inventory Family Impact Module. The color version of this figure is available in the online edition.

social functioning had weak correlations, which suggests that an individual may have conflicting scores on these symptom domains. When selecting a QoL measure to use in a research study, it will be imperative that investigators consider which symptoms they seek to measure and that items are evaluated for their appropriateness, especially when considering symptoms of social and physical abilities. Scores on the QoL measures were relatively stable over one year in our limited sample with longitudinal data. The only notable difference was a modest reduction in the Family Relationships subdomain scores of the PedsQL-FIM measure. This finding indicates a slight worsening in family relationships over time; however, this finding requires further exploration in a larger sample.

Despite being studied in other genetic neurodevelopmental disorders, the reference ranges in SLC6A1-NDD have not been established. In this study we demonstrated differentiation between low scores in the 10th percentile range, average scores in the 50th percentile range, and high scores in the 90th percentile range using the bootstrap resampling method on all three QoL measures. We had the largest number of data points for the QI-disability measure, generating clearer separation between more percentiles; this suggests that even with as few as approximately 50 data points, reference range estimations can be generated using the bootstrap resampling method. In rare disease studies with limited sample sizes, bootstrap resampling may be a powerful tool to develop clinically meaningful reference range estimations.

Our group previously showed that in addition to seizures, caregivers identified symptoms that drive disease burden in SLC6A1-NDD including hypotonia, movement disorders, and impairments in communication and cognition that limit the patient's ability to function independently in their daily lives.[25] In this study, we demonstrated that the lowest subdomain scores included a potentially similar spectrum of symptoms including Physical Ability and Negative Emotions. Higher scores were seen on domains of Social and Positive Emotions, which coincided with high scores on the Cognitive subdomain on the PedsQL-FIM. It was surprising that scores on physical abilities were relatively lower than cognitive abilities given our draft conceptual model; however, scores on all QoL measures were generally low. Future studies should explore how demographic and clinical characteristics such as age, gender, race/ethnicity, and medical comorbidities like autism, developmental regression, and seizure burden contribute to QoL scores.

This study is limited by a small sample size. The original sample size for the UTSW cohort was fewer than 30, which is suboptimal for invoking the central limit theorem's assumptions. We optimized our sample size by incorporating all available data points from participants and including Simons Searchlight registry data (SFARI). Including longitudinal data in our group-level analysis led to seven known nonindependent data points. We did not match participants between the UTSW and SFARI cohorts, leading to an additional unknown number of duplicate participants and therefore nonindependent data points. We are also limited by the use of proxy-report measures to capture how a disorder impacts an individual with disabilities, a limitation inherent to the study of many neurodevelopmental disorders. Although we have potentially oversampled from a highly motivated group of participants, this study importantly takes an initial step toward establishing reference ranges on commonly used QoL measures in a new population, SLC6A1-NDD.

Conclusions

This is the first study to investigate QoL measures for SLC6A1-NDD. Findings suggest that scores within the 10th percentile's confidence interval could be clinically significant, referring to QI-Disability scores of <61, QOLCE-55 scores of <46, and PedsQL-FIM scores of <42. It is likely these measures, or other like these, may be incorporated into future clinical trials as outcome measures that could assess the impact of a new intervention on the participant. This study uncovered an initial score interpretation system, but future validation studies are needed.

CRediT authorship contribution statement

Hamza Dahshi: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Sanjana Kalvakuntla:** Writing – review & editing, Writing – original draft, Data curation. **MinJae Lee:** Writing –

review & editing, Visualization, Methodology, Formal analysis. **Kimberly Goodspeed:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: For work unrelated to this research, Kimberly Goodspeed reports a relationship with AllStripes, Astellas Gene Therapies, Jaguar Gene Therapies, and Taysha Gene Therapy that includes consulting or advisory. Kimberly Goodspeed reports a relationship with COMBINEDBrain that includes board membership. For work unrelated to this research, Hamza Dahshi reports a relationship with Elpida Therapeutics that includes consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.03.030.

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