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Health-Related Quality of Life in Rare Forms of Childhood-Onset Hereditary Spastic Paraplegia

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ABSTRACT

We assessed health-related quality of life (HRQoL) in 80 children with rare hereditary spastic paraplegias using the Caregiver Priorities and Child Health Index of Life with Disabilities and clinician-reported outcomes. HRQoL was consistently reduced, particularly in relation to motor, autonomic, and bulbar symptoms. Children with complex HSP phenotypes had lower scores than those with pure forms. Scores correlated with established clinical scales but declined with age only in HSP-*SPG11* and HSP-*ZFYVE26*. These findings identify key determinants of reduced quality of life and highlight clinical targets for supportive interventions in childhood-onset hereditary spastic paraplegia.

Trial Registration: Registry and Natural History Study for Early Onset Hereditary Spastic Paraplegia: NCT04712812

1 | Introduction

The hereditary spastic paraplegias (HSPs) are a diverse group of neurogenetic disorders characterized by progressive lower limb spasticity and weakness [1, 2]. Genotype-specific studies have begun to examine outcomes in more common forms such as *SPAST*-associated HSP (SPG4) [3, 4], but the broader impact of rare childhood-onset subtypes on health-related quality of life (HRQoL) remains poorly defined. These forms often present with complex phenotypes, including developmental delay, intellectual disability, movement disorders, dysphagia, or incontinence, which substantially affect daily functioning and caregiver burden [5].

The Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) [6] is a validated instrument for assessing HRQoL in children with severe motor impairments. While its use has been demonstrated in AP-4-associated HSP [7], applicability across diverse childhood-onset subtypes has not been systematically evaluated.

Henri Schmidt and Nicole Battaglia contributed equally to this study.

Here, we assess HRQoL in a well-characterized cohort of children with rare HSPs, examine clinical correlates of reduced quality of life, and explore the influence of age and genotype on disease burden.

2 | Methods

The study was approved by the Boston Children's Hospital Institutional Review Board (IRB-P00033016), and written informed consent was obtained from legal guardians. Children with genetically confirmed HSP were enrolled in a single-center natural history study [8] (Registry and Natural History Study for Early Onset Hereditary Spastic Paraplegia; NCT04712812). Patients with SPG4 or AP-4–related HSP (SPG47, SPG50, SPG51, SPG52) were excluded because of prior publications [7] and ongoing dedicated studies. Caregivers completed the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) questionnaire [6]. Clinical assessments, including the Spastic Paraplegia Rating Scale

TABLE 1 | Demographic and molecular data of this cohort.

Cohort	*N* = 72
Male	35/72 (49%)
Age (y)	Mean: 13.12 (standard deviation: 9.01) [range: 1.17–31.43]
CPCHILD score	Mean: 68.09 (standard deviation: 17.20) [range: 34.58–100.00]
Zygosity	
Compound heterozygous	64/72 (89%)
Homozygous	8/72 (11%)
Genes	
ATL1	15/72 (21%)
ZFYVE26	14/72 (19.4%)
SPG11	12/72 (16.7%)
TECPR2	4/72 (5.6%)
RAB3GAP1	3/72 (4.2%)
CPT1C, CYP7B1, GPT2, PI4KA	Each: 2/72 (2.8%)
AFG3L2, ALDH18A1, ALS2, C19orf12, CCDC82, DDHD2, ERLIN2, FARS2, GBA2, HPDL, KIDINS220, KIF1A, KIF5A, REEP1, REEP2, RINT1	Each: 1/72 (1.4%)
REEP1	1/72 (1.4%)
Complex HSP	47/72 (65%)
SPATAX	
1	1/69 (1.4%)
2	16/69 (23%)
3	12/69 (17%)
4	1/69 (1.4%)
5	15/69 (22%)
6	24/69 (35%)
7	0/69 (0%)
SPRS score	Mean: 22.29 (standard deviation: 10.90) [range: 0.00–44.00]
SPRS spasticity subscore	Mean: 5.24 (standard deviation: 2.59) [range: 0.00–13.00]
Intellectual disability	
None	15/50 (30%)
Mild	26/50 (52%)
Moderate	8/50 (16%)
Severe	1/50 (2.0%)

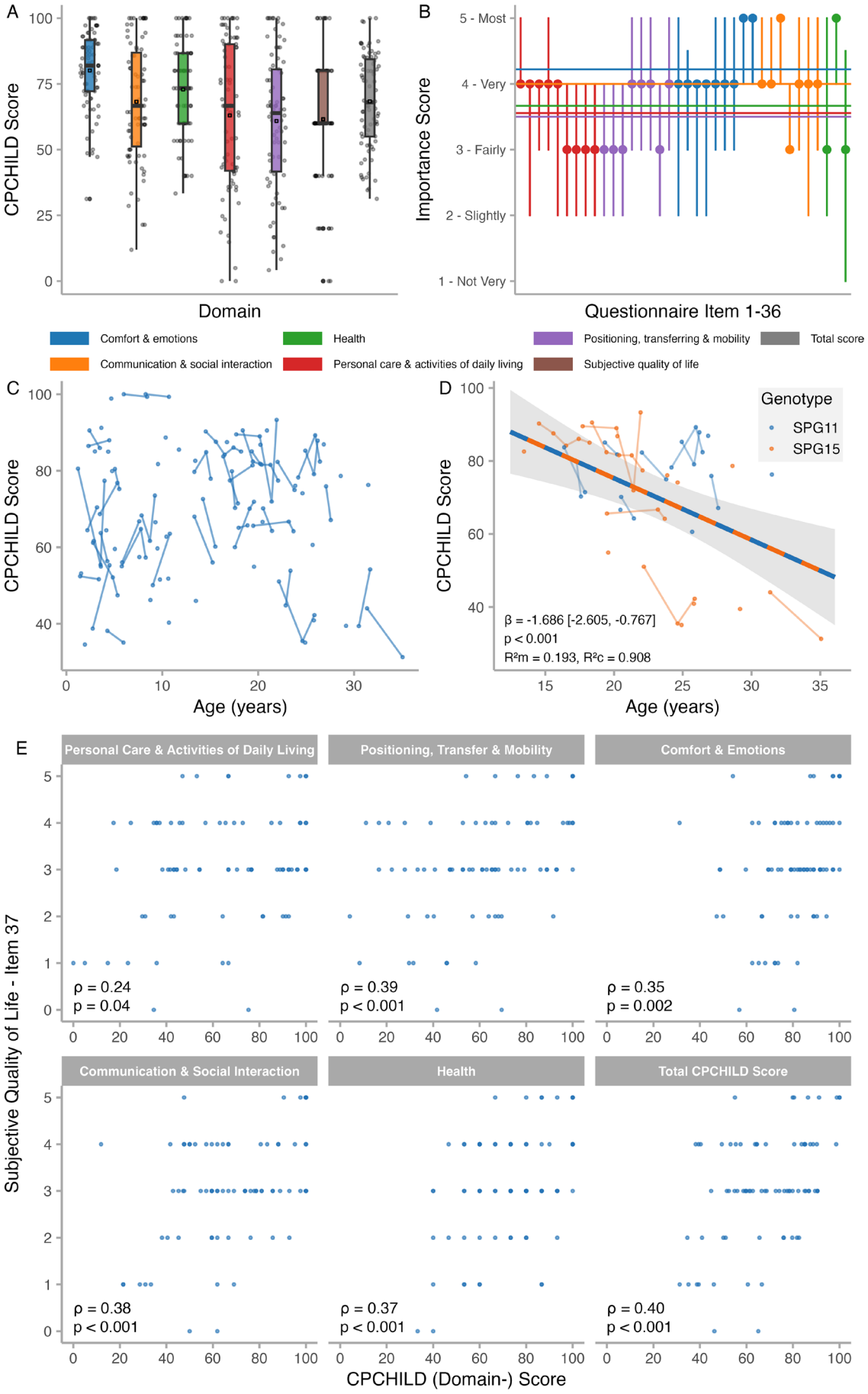


FIGURE 1 | Legend on next page.

FIGURE 1 | CPCHILD domain scores and associations with age. (A) CPCHILD domain-specific scores across the cohort. Boxes show interquartile range (IQR), horizontal lines medians, and black squares group means. Whiskers extend to the most extreme values within 1.5× IQR; outliers are shown as individual points. (B) Perceived importance of each CPCHILD item and domain rated by caregivers. Points indicate medians, error bars IQR, and horizontal lines the average median score across each domain. (C) CPCHILD scores over time for individual patients. Points represent assessments; lines connect repeated measures. (D) Linear mixed-effects model for patients with SPG11 or SPG15, demonstrating a decline of 1.686 CPCHILD points per year. (E) Correlations between subjective quality of life (rated 0 = very poor to 5 = excellent) and CPCHILD (domain) scores. Spearman's rank correlation used due to non-normal distribution. Regression line and 95% confidence intervals shown in (D). Correlation coefficients (ρ), coefficients of determination (R^2), and p-values shown in (E).

(SPRS) [9] and SPATAX-EUROSPA disability stage [10], were performed during in-person visits within 12 months of questionnaire completion.

CPCHILD scores, reflecting overall and domain-specific HRQoL, were analyzed cross-sectionally ($n = 80$) and longitudinally ($n = 40$). Associations with clinical features (Table 1), genotype, and age were tested using Pearson or Spearman correlations, linear regression, and linear mixed-effects models (random intercept per patient). Model assumptions were evaluated with Q–Q plots, Shapiro–Wilk tests, and Levene's test. Multiple comparisons were adjusted using the false discovery rate. Analyses were performed in R (v4.4.1) [11], with statistical significance set at $p < 0.05$. Detailed assumption testing is provided in the Supporting Information.

3 | Results

Eighty families with genetically confirmed HSP completed the CPCHILD questionnaire. Demographic and molecular data are summarized in Table 1. The cohort included 25 distinct genetic subtypes. The mean age at first evaluation was 13.43 years [SD: 9.07].

The CPCHILD score evaluates seven domains: (1) Personal Care and Activities of Daily Living, (2) Positioning, (3) Transferring and Mobility, (4) Comfort and Emotions, (5) Communication and Social Interaction, (6) Health, and (7) Overall Quality of Life. Each domain is scored 0–100, with higher scores indicating better function; a weighted composite score reflects total HRQoL.

Across the cohort, highest scores were observed in "Comfort and Emotions," while "Positioning, Transferring, and Mobility" consistently scored lowest (Figure 1A). Caregivers rated "Emotional state or behavior," "Happiness," "Ability to communicate with others," and "Overall health" as the most important items (Figure 1B; Table S4). Perceived domain importance did not correlate with domain-specific CPCHILD scores (Figure S1). However, domain scores showed small to moderate associations with subjective quality of life, with the total CPCHILD score most strongly correlated ($\rho = 0.40$), followed by "Positioning, Transfer and Mobility" ($\rho = 0.39$) and "Communication and Social Interaction" ($\rho = 0.38$) (Figure 1E). Items most strongly associated with subjective quality of life included "Overall health" ($\rho = 0.576$), "Moving about in the home" ($\rho = 0.527$), "Standing for exercise/transfers" ($\rho = 0.474$), and "Moving about outdoors" ($\rho = 0.470$) (Figure S2).

Age was not associated with CPCHILD scores across the entire cohort ($\rho = -0.007$, $p = 0.94$), including after excluding overrepresented genotypes (HSP-*SPG11* (or SPG11), HSP-*ZFYVE26* (or SPG15), and HSP-*ATL1* (or SPG3A)) (Figure 1C). In contrast, patients with HSP-*SPG11* and HSP-*ZFYVE26* showed an age-dependent decline (−1.686 points per year, Figure 1D).

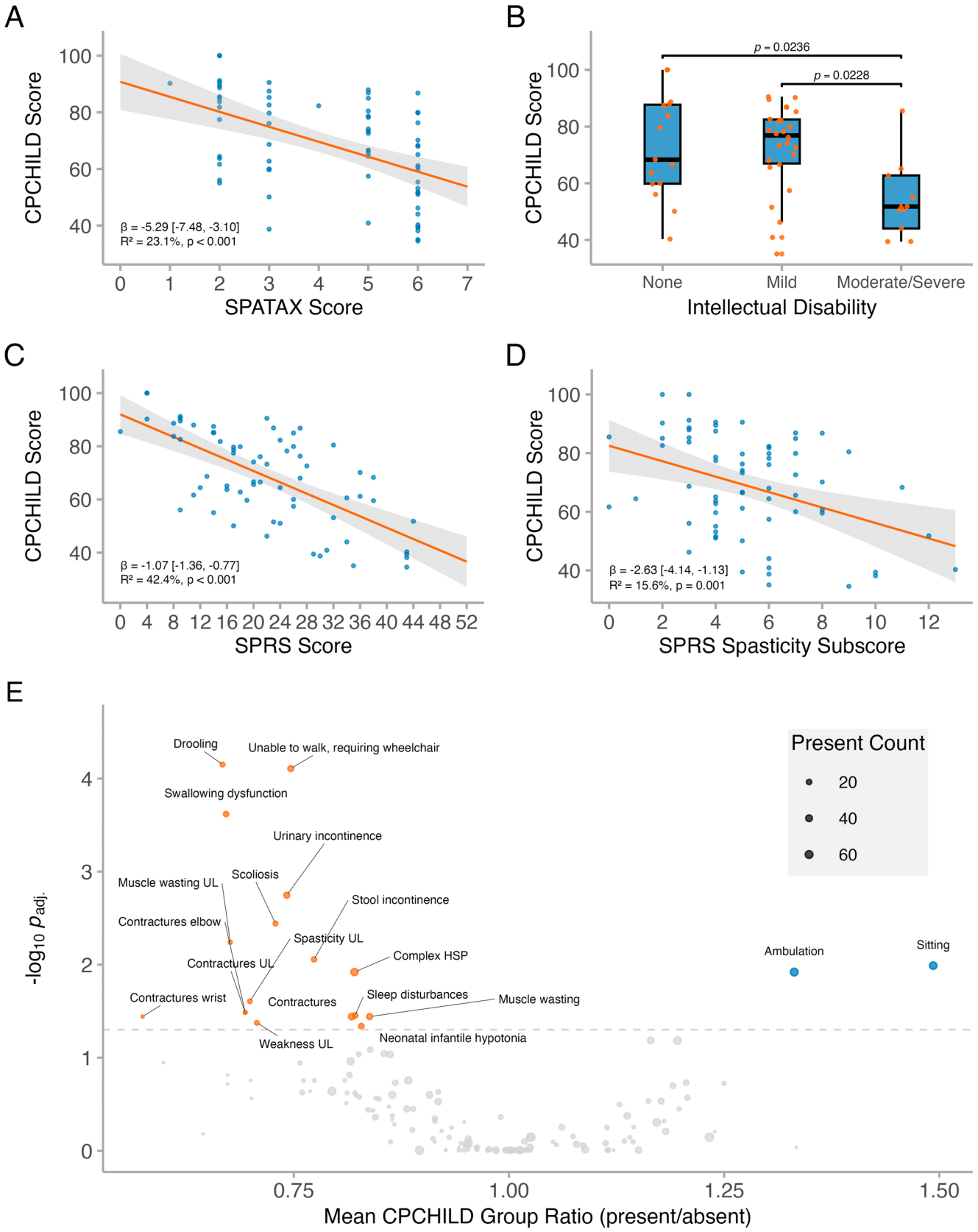
Clinical disability scores were available for a subset (Table 1). Each one-point increase in SPATAX stage corresponded to a 5.29-point decrease in CPCHILD score (Figure 2A), and each one-point increase in SPRS total score reduced CPCHILD by 1.07 points (Figure 2C). At mean age and mean disability levels, predicted CPCHILD scores were 68.4 (SPATAX model) and 68.7 (SPRS model). Within SPRS subscores, each one-point increase in spasticity reduced HRQoL by 2.63 points (Figure 2D). Patients with moderate or severe intellectual disability had significantly lower CPCHILD scores than those with none or mild impairment ($p = 0.02$, Figure 2B). Neither SPRS nor SPATAX scores correlated with age (Figure S3).

Screening of 153 clinical variables identified strong associations between lower HRQoL and motor-, bulbar and autonomic symptoms, including contractures, drooling, dysphagia, muscle wasting, and urinary/fecal incontinence (Figure 2E). Tetraparesis was linked to lower scores than diplegia, and complex HSP phenotypes (with ataxia, dystonia, myoclonus, dysarthria, neuropathy, or seizures) had significantly lower scores than pure forms. Higher scores were observed in patients retaining sitting or ambulatory function. Psychosocial comorbidities (e.g., impulsivity, anxiety, autism) and communication impairments (e.g., anarthria, dysarthria) were not significantly associated. Neither inheritance pattern nor seizures, tremor, or nystagmus influenced HRQoL.

4 | Discussion

HRQoL is an essential endpoint in neurogenetic disorders [12], yet validated tools to assess HRQoL in pediatric HSP remain scarce. Originally developed for children with cerebral palsy [6], the CPCHILD questionnaire has been applied in AP-4–related HSP [7] but not systematically across the broader spectrum of rare HSP subtypes.

In this mixed cross-sectional and longitudinal study, we show that CPCHILD is applicable across diverse forms of childhood-onset HSP. CPCHILD scores correlated with established disease severity measures, including the SPRS and SPATAX stage, underscoring their validity as indicators of patient-centered



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outcomes. HRQoL was consistently reduced across subtypes, with the lowest scores observed in complex phenotypes compared to pure HSP.

Motor-, bulbar- and autonomic dysfunction—indicated by symptoms such as contractures, incontinence, and dysphagia—emerged as primary drivers of reduced HRQoL. By contrast,

FIGURE 2 | Clinical correlates of caregiver-reported quality of life. (A) Association between CPCHILD score and SPATAX disability stage (0 = no functional handicap, 7 = confined to bed). Each one-point increase corresponded to a 5.29-point decrease in CPCHILD. (B) CPCHILD scores by intellectual disability severity. Patients with moderate or severe impairment had significantly lower scores; the single severely affected individual is indicated by a larger triangle. Kruskal–Wallis test with Dunn's post hoc test and Benjamini–Hochberg correction used. (C) Association between CPCHILD and total Spastic Paraplegia Rating Scale (SPRS) score. Each one-point increase in SPRS corresponded to a 1.07-point decrease in CPCHILD. (D) Association between CPCHILD and SPRS spasticity subscore. Each one-point increase corresponded to a 2.63-point decrease in CPCHILD. (E) Volcano plot of associations between clinical features and CPCHILD scores. *X*-axis: Ratio of mean CPCHILD scores in patients with vs. without a feature. *Y*-axis: $-\log_{10}$ adjusted *p*-value (Benjamini–Hochberg). Statistical tests included Student's *t*-test, Welch's *t*-test, or Mann–Whitney *U* test, depending on assumptions. Point size reflects sample size. Significant associations color-coded (orange = reduced HRQoL; blue = increased HRQoL); non-significant associations gray. Dashed line indicates adjusted $p < 0.05$ threshold.

psychosocial comorbidities, seizure history, and communication impairments had less measurable impact in this cohort. Consistent with prior genotype-specific studies, CPCHILD scores declined with age in HSP-*SPG11* and HSP-*ZFYVE26* but not across the cohort overall. Importantly, caregiver ratings of domain importance did not align with actual contributions to HRQoL, suggesting that perceived burden may diverge from measurable functional impact.

This study has limitations. The heterogeneity of more than 40 rare subtypes constrained power for genotype-specific analyses. CPCHILD, while validated, reflects caregiver rather than patient perspectives, limiting its scope in children capable of self-report. Most analyses were cross-sectional, restricting conclusions about progression and responsiveness to clinical change. The absence of normative data also limits the interpretation of the degree of impairment observed. Our study also extended the application of the CPCHILD beyond its validated age range to include individuals younger than 5 and older than 18 years, which should be considered when interpreting the findings. Finally, the sensitivity of CPCHILD to detect treatment effects in interventional trials remains untested, and validation against other HRQoL instruments is warranted and larger multicenter studies are needed for definitive genotype-based comparisons.

Despite these limitations, our findings support CPCHILD as a feasible tool for assessing HRQoL across a wide range of childhood-onset HSP subtypes. Its correlation with clinician-reported measures reinforces its value as a patient-centered outcome for natural history studies and potential therapeutic trials. These insights may guide clinicians in prioritizing interventions and inform strategies to improve the quality of life for children with HSP.

Author Contributions

Conceptualization: D.E.F. Data Curation: All authors. Formal Analysis: H.J.D.S., N.B., J.E.A, D.E.F. Investigation: J.R., A.T., S.C., V.Q., K.Y., Z.Z., L.S., K.B. Writing - Original Draft: H.J.D.S., N.B., J.E.A, D.E.F. Writing - Review & Editing: All authors

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Ethics Statement

The study was performed in accordance with the Declaration of Helsinki. This study was approved by the Boston Children's Hospital Institutional Review Board (IRB, P00033016).

Conflicts of Interest

D.E.-F. has served as a consultant to Guidepoint LLC, received speaker honoraria from the Movement Disorder Society, publishing royalties from Cambridge University Press and reports research funding through a joint research agreement with Astellas Pharmaceuticals Inc. The other authors declare no potential conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** acn370244-sup-0001-Supinfo.pdf.