

Disease Severity and Motor Impairment Correlate With Health-Related Quality of Life in AP-4-Associated Hereditary Spastic Paraplegia

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Abstract

Objective

AP-4-associated hereditary spastic paraplegia (AP-4-HSP) is a childhood-onset neurogenetic disease and mimic of cerebral palsy. Data on health-related quality of life (HRQoL) are lacking. To establish a metric for HRQoL and caregiver priorities, we used the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) questionnaire to assess HRQoL in correlation with disease severity in 64 patients with AP-4-HSP.

Methods

A cross-sectional analysis of caregiver-reported HRQoL was performed using the CPOCHILD questionnaire in combination with a detailed clinical characterization.

Results

HRQoL was impaired in all domains in patients with AP-4-HSP (mean score: 59.6 ± 12.6 [SD]), with no significant difference between the 4 subtypes. Age, as a surrogate for disease duration, and Spastic Paraplegia Rating Scale scores, as an indicator for corticospinal tract dysfunction and motor impairment, correlated with lower CPOCHILD scores (Pearson $r = -0.31$, $p = 0.01$ and $r = -0.52$, $p < 0.0001$, respectively). Patients with tetraplegia showed lower CPOCHILD scores compared with individuals with diplegia or no spasticity. Wheelchair dependence reduced HRQoL in all domains. The presence of seizures, including medically refractory epilepsy, was not associated with lower CPOCHILD scores. Standardized assessment of caregiver priorities identified several areas of high importance to HRQoL.

Conclusions

We show that the CPOCHILD questionnaire, developed for use in children with cerebral palsy, can be used to assess HRQoL in patients with childhood-onset complex hereditary spastic paraplegia. HRQoL is reduced in patients with AP-4-HSP and correlates with the degree of motor impairment. These results provide a framework for medical decision making and a baseline for the future development of treatment guidelines and interventional trials.

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Glossary

4FMS = 4-stage functional mobility scale; **AP-4-HSP** = AP-4-associated hereditary spastic paraplegia; **CPCHILD** = Caregiver Priorities and Child Health Index of Life with Disabilities; **HRQoL** = health-related quality of life; **SPRS** = Spastic Paraplegia Rating Scale.

Biallelic mutations in genes encoding the subunits of the AP-4 complex (*AP4B1*, *AP4M1*, *AP4E1*, and *AP4S1*) lead to childhood-onset and complex hereditary spastic paraplegia (SPG47, SPG50, SPG51, and SPG52).^{1,2} Not unlike in cerebral palsy, motor symptoms in AP-4-associated hereditary spastic paraplegia (AP-4-HSP) are accompanied by global developmental delay and intellectual disability, seizures, and secondary musculoskeletal problems.¹⁻³ All patients with AP-4-HSP experience difficulties with their activities of daily living, communication, and mobility and depend on their caregivers for most of their needs. The morbidity that arises from progressive motor symptoms has a significant effect on families. Symptomatic treatment of spasticity, contractures, or seizures is aimed at preventing or relieving discomfort and at enabling optimal development and quality of life.¹ In this setting, it is important to establish a metric for health-related quality of life (HRQoL) and to understand caregiver perspectives. Such a metric can inform shared medical decision-making and the development of treatment guidelines. HRQoL measures are complementary to the assessment of clinical disease severity, and it is important to establish if correlation exists. Such correlation would have implications for the choice of clinical rating scales in longitudinal natural history studies and interventional trials. To approximate HRQoL in AP-4-HSP, we used the revised Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) questionnaire⁴ in 64 individuals with AP-4-HSP and investigated correlations with major symptoms and disease severity.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review board at Boston Children's Hospital (No. IRB-P00033016). Written consent was obtained.

Data Collection and Statistical Analysis

Primary caregivers of 64 patients with genetically confirmed AP-4-HSP were asked to complete the CCHILD questionnaire⁴ (eMethods, links.lww.com/NXG/A440). Spastic Paraplegia Rating Scale (SPRS) total and spasticity subscores^{5,6} and the 4-stage functional mobility scale (4FMS) were assigned as described previously² (eMethods). Statistical analysis was performed with GraphPad Prism v9.0 and IBM SPSS v27. Unpaired *t* test or one-way analysis of variance with multiple comparisons was used to determine the significance of differences between conditions. Linear regression analysis and

Table Summary of Demographic Information and Clinical Scores

Patients with AP-4-HSP (n = 64), n (%)	
Female	30 (46.9)
SPG47 (<i>AP4B1</i>)	31 (48.4)
SPG50 (<i>AP4M1</i>)	21 (32.8)
SPG51 (<i>AP4E1</i>)	2 (3.1)
SPG52 (<i>AP4S1</i>)	10 (15.6)
Age, y (n = 64)	
Mean ± SD	12.45 ± 10.53
Range	1.45–49.52
Consanguinity (n = 64), n (%)	
More than 1 affected family member (n = 64), n (%)	24 (37.5)
Severity of intellectual disability (n = 64), n (%)	
Severe	24 (37.5)
Moderate	20 (31.3)
Mild	7 (10.9)
Too young or information not available	13 (20.3)
SPRS (total score) (n = 51)	
Mean ± SD	30.2 ± 10.8
Range	0–52
SPRS (spasticity subscore) (n = 51)	
Mean ± SD	7.2 ± 3.6
Range	0–16
4FMS (n = 62), n (%)	
I	1 (1.6)
II	9 (14.5)
III	26 (41.9)
IV	26 (41.9)
Developmental support (n = 64), n (%)	
Physical therapy	42 (65.6)
Occupational therapy	34 (53.1)
Speech therapy	39 (60.9)

Abbreviations: 4FMS = 4-stage functional mobility scale; AP-4-HSP = AP-4-associated hereditary spastic paraplegia; SPRS = Spastic Paraplegia Rating Scale.

Pearson correlation coefficient were used to determine statistical correlation. The Spearman rank correction coefficient was used to ensure a monotonic relationship.

Data Availability

Data are available from the corresponding author on reasonable request.

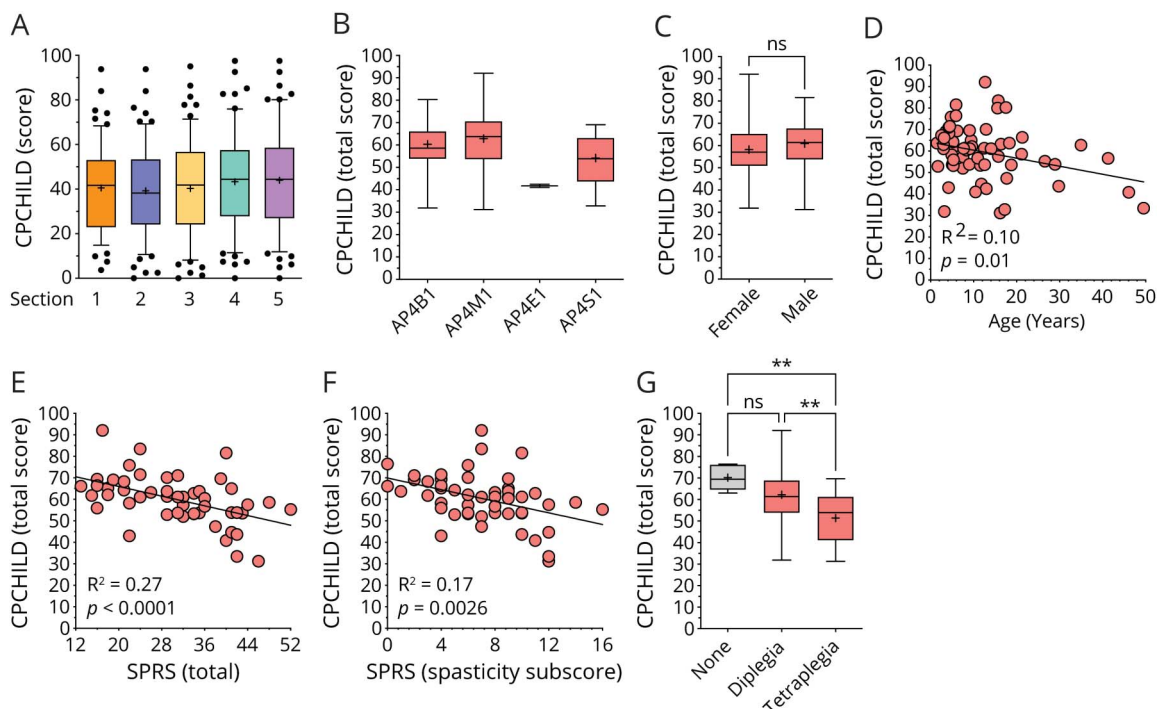
Results

Demographic and clinical characteristics of the study cohort are summarized in Table. The most common subtype of AP-4-HSP was *AP4B1*-associated SPG47, comparable with the general prevalence of this subtype.^{1,2} The mean age was 12.5 ± 10.5 (SD) years (range 1.5–49.5 years). Most families resided in Europe, North America, and the Middle East. Approximately 38% of participating families had more than 1 affected child. The mean SPRS score was 30.2 ± 10.8 (SD) consistent with a moderate degree of corticospinal tract dysfunction. The distribution of the 4FMS indicated that the majority of patients requires assistance with ambulation (4FMS = 3) or are wheelchair-dependent (4FMS = 4) (Table). The standardized CPCHILD score showed an even distribution between subsections (Figure 1A). The mean total score was $59.6 \pm$

12.6 (SD) with no significant difference between the 4 AP-4-HSP subtypes (Figure 1B) or between male and female patients (Figure 1C). All patients had access to special education programs, and supportive therapy was provided to the majority of patients at the time of evaluation (Table).

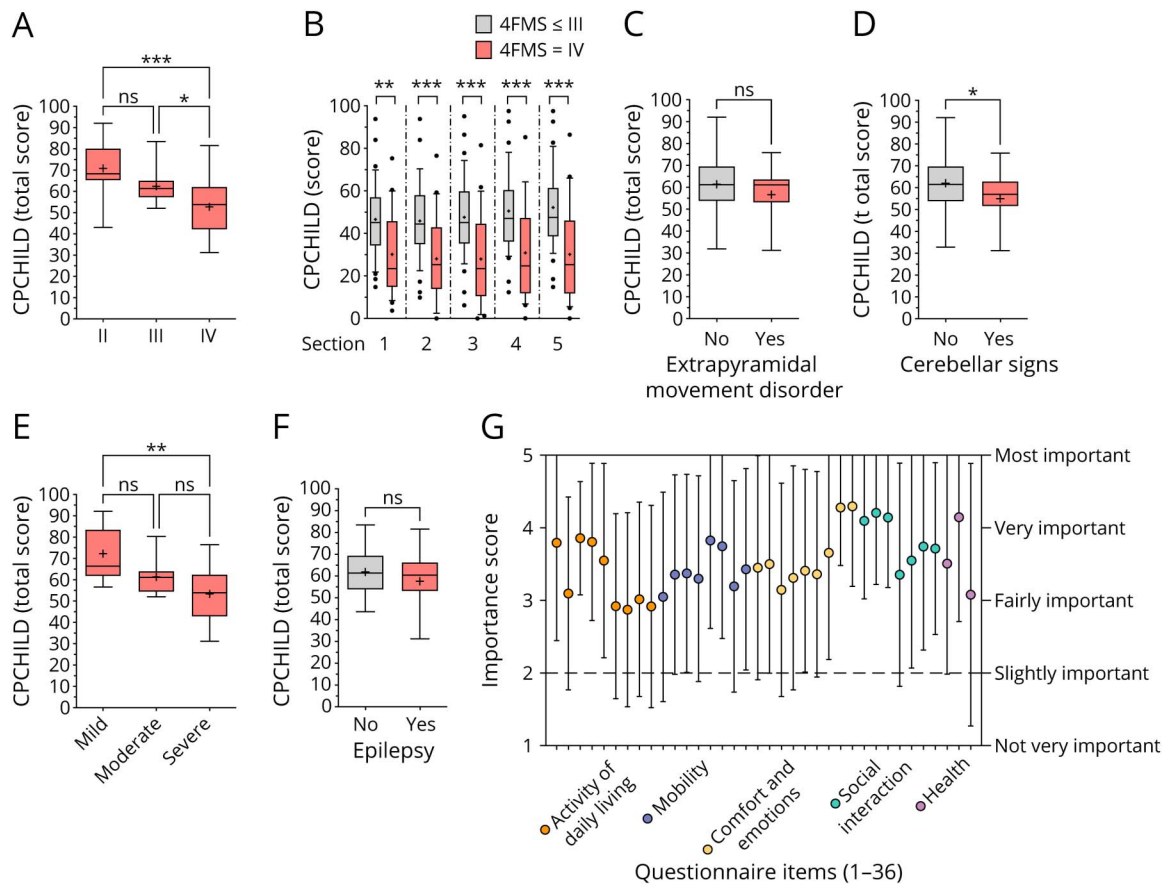
Based on evidence derived from studies in children with cerebral palsy,^{4,7,8} we hypothesized that patients with severe AP-4-HSP disease would have lower HRQoL. We found that age, as a surrogate for disease duration, and SPRS scores correlated with lower CPCHILD scores (Figure 1, D and E). The spasticity subscore of the SPRS showed a moderate correlation as well, indicating that severity of motor symptoms and resulting disability contribute to HRQoL (Figure 1F). This was further corroborated by significantly lower CPCHILD scores in patients with tetraplegia compared with individuals with diplegia or no spasticity (Figure 1G). Based on this finding, we hypothesized that HRQoL for nonambulatory patients would be worse than for ambulatory patients. Indeed, a significantly lower mean CPCHILD score was found in wheelchair-dependent patients (Figure 2A). To assess whether this was the result of impaired QoL related to positioning, transferring, and mobility (section 2), we compared

Figure 1 Disease Severity and Motor Impairment Correlate With Health-Related Quality of Life in 64 Patients With AP-4-HSP



(A) No significant difference between mean scores in each of the CPCHILD sections (1 = activities of daily living and personal care; 2 = positioning, transferring, and mobility; 3 = comfort and emotions; 4 = communication and social interaction; and 5 = health). (B and C) No significant differences are found in the mean CPCHILD score between subtypes of AP-4-HSP (AP4B1 = SPG47, AP4M1 = SPG50, AP4E1 = SPG51, and AP4S1 = SPG52) or female and male patients. (D–F) Lower CPCHILD scores correlate with age (Pearson correlation coefficient: $r = -0.31$, $p = 0.01$; Spearman correlation coefficient: $r = -0.25$, $p = 0.05$), higher total SPRS scores (Pearson correlation coefficient: $r = -0.52$, $p < 0.0001$; Spearman correlation coefficient: $r = -0.55$, $p < 0.0001$), and spasticity subscores (Pearson correlation coefficient: $r = -0.41$, $p = 0.0026$; Spearman correlation coefficient: $r = -0.46$, $p = 0.0008$). (E) One data point is outside the axis limits. (G) Patients with spastic tetraplegia ($n = 19$) have lower CPCHILD scores compared with patients with spastic diplegia ($n = 40$) or no spasticity ($n = 5$). Box and whisker plots in (A); Whiskers indicate 10–90 percentile. Box and whisker plots in (B, C, G); Whiskers indicate the full range (min-max). “+” denotes the mean. Significance: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. AP-4-HSP = AP-4-associated hereditary spastic paraplegia; CPCHILD = Caregiver Priorities and Child Health Index of Life with Disabilities; ns = not significant; SPRS = Spastic Paraplegia Rating Scale.

Figure 2 Correlation of Health-Related Quality of Life With Additional Symptoms and Caregiver Priorities in AP-4-Associated Hereditary Spastic Paraplegia



(A) Patients with an 4FMS score of IV, indicating dependence on a wheelchair ($n = 26$), have lower CPCHILD scores compared with those ambulating with assistance (4FMS = III, $n = 26$) or independently (4FMS = II, $n = 9$). (B) Assessment of mean scores for each section of the CPCHILD shows that wheelchair-dependent patients have lower scores in all domain compared with patients who do not require a wheelchair. (C and D) The presence of an extrapyramidal movement disorder (dystonia, chorea, athetosis, myoclonus, tremor, rigidity, or postural instability, $n = 24$) did not lead to significantly lower CPCHILD scores, whereas the presence of cerebellar signs (cerebellar ataxia, dysmetria, nystagmus, or intention tremor, $n = 22$) did. (E) The mean CPCHILD score was reduced in patients with severe intellectual disability ($n = 24$) compared with patients with mild intellectual impairment ($n = 7$). No difference was found between patients with severe and moderate intellectual disability ($n = 20$). (F) Surprisingly, the presence of epilepsy did not influence CPCHILD scores. (G) Rating of importance for each item on the CPCHILD questionnaire. No items were rated below the threshold level of importance (2.0 = slightly important). Items relating to communication and social interaction, comfort and emotions, and health were, on average, considered more important contributors to quality of life than items relating to positioning, transferring, and mobility, and personal care and activities of daily living. Box and whisker plots in (A-G): Whiskers indicate the full range (min-max). “+” denotes the mean. Significance: $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$. 4FMS = 4-stage functional mobility scale; CPCHILD = Caregiver Priorities and Child Health Index of Life with Disabilities; ns = not significant; SPSP = Spastic Paraplegia Rating Scale.

mean scores for each section and discovered that wheelchair-dependent patients had significantly lower scores in all domains (Figure 2B). The presence of contractures was not associated with lower CPCHILD scores ($p = 0.25$) as was the presence of extrapyramidal movement disorders (Figure 2C). Cerebellar signs, most commonly ataxia, were associated with lower HRQoL (Figure 2D), possibly due to the fact that this is often a manifestation of advanced disease stages.²

Of interest, we found that CPCHILD scores did not discriminate between patients with moderate and severe intellectual disability, although scores were significantly lower in the group with severe intellectual impairment compared with those in the mild range (Figure 2E). Surprisingly, the presence of epilepsy did not correlate with HRQoL (Figure 2F). To investigate whether this was due to the fact that seizures were

well controlled on <2 antiepileptic drugs in the majority of patients, we explored the subgroup with medically refractory epilepsy. We did not detect a significant difference in CPCHILD scores between patients with uncontrolled epilepsy, controlled epilepsy, or no seizures at all ($p = 0.87$ and $p = 0.52$, respectively).

Finally, we assessed whether having 2 or more affected children would affect HRQoL, given the increased resources needed to care for multiple family members. Of interest, we did not detect any difference between CPCHILD scores in individuals from families with 1 vs multiple affected family members ($p = 0.26$).

Section 7 of the CPCHILD incorporates the caregivers’ perspective on the importance of each item in the questionnaire.

The mean importance rating for all CPCHILD items was 3.5 ± 0.4 (SD) indicating that all items were deemed fairly important to very important (Figure 2G). Items relating to (1) communication and social interaction, (2) comfort and emotions, and (3) health were considered the most important contributors to quality of life.

Discussion

Although quality of life has been assessed in adults with HSP,^{9,10} including as an end point in interventional trials, standardized assessments of HRQoL in children with complex hereditary spastic paraplegia are lacking. Here, we show that (1) the CPCHILD questionnaire, developed for use in children with cerebral palsy,⁴ can be used to assess HRQoL in patients with childhood-onset complex HSP and (2) HRQoL is impaired across the age spectrum of patients with AP-4-HSP and correlates with disease duration and motor impairment. Similar to findings in children with severe cerebral palsy (Gross Motor Function Classification System IV),^{4,8} we found that tetraplegia and wheelchair dependence were associated with lower CPCHILD scores. Of interest, we did not observe a correlation of HRQoL with epilepsy or a significant difference between patients with moderate or severe intellectual disability, indicating that these are less impactful contributors to HRQoL in AP-4-HSP. We speculate that the progressive nature of motor impairment in AP-4-HSP² with associated gradual decline in the ability to participate in daily activities may explain the greater effect on HRQoL compared with the relatively static findings of intellectual impairment and epilepsy. This is being further investigated as part of a longitudinal natural history (ClinicalTrials.gov identifier: NCT04712812).

There are limitations to our study: (1) Our cohort is enriched in patients residing in countries with access to specialized health care and developmental support compared with larger cohorts.² Future studies will need to assess whether correlations prevail in different health care settings. (2) The cross-sectional nature of our study precludes a longitudinal assessment of HRQoL at the level of an individual. Prospective natural history studies will need to assess whether changes in HRQoL over time correlate with the rate of disease progression. (3) It will be important to compare results obtained with the CPCHILD questionnaire with other metrics of HRQoL designed for cerebral palsy or children and adults with other neurodisabilities.

Despite these limitations, our results establish the CPCHILD questionnaire as a metric to assess HRQoL in complex HSP. Integrating an assessment of HRQoL in the routine care of patients with AP-4-HSP may guide clinicians toward a better understanding of caregiver priorities, may inform decision-making about interventions, and may provide a means to assess outcomes.

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Appendix Authors

Name	Location	Contribution
Catherine Jordan, BA	Boston Children's Hospital, MA	Acquisition of data, analyzed the data, and revised the article
Gregory Geisel, BS	Boston Children's Hospital, MA	Acquisition of data and revised the article
Julian E. Alecu, cand. med.	Boston Children's Hospital, MA	Acquisition of data and revised the article
Bo Zhang, PhD	Boston Children's Hospital, MA	Analyzed the data and revised the article
Mustafa Sahin, MD, PhD	Boston Children's Hospital, MA	Design and conceptualized study and revised the article
Darius Ebrahimi-Fakhari, MD, PhD	Boston Children's Hospital, MA	Design and conceptualized study, analyzed the data, and drafted and revised the article

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