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Supporting Data

Additional Supporting Information may be found in the online version of this article

Patient-Reported Outcomes in Huntington's Disease: Quality of Life in Neurological Disorders (Neuro-QoL) and Huntington's Disease Health-Related Quality of Life (HDQLIFE) Physical Function Measures

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ABSTRACT

Background: There is a need for patient-reported outcome measures that capture the impact that motor impairments have on health-related quality of life in individuals with Huntington's disease.

Objectives: The objectives of this study were to establish the reliability and validity of new physical functioning patient-reported outcome measures in Huntington's disease.

Methods: A total of 510 individuals with Huntington's disease completed 2 Quality of Life in Neurological Disorders (Lower Extremity Function and Upper Extremity Function) and 3 Huntington's Disease Health-Related Quality of Life (Chorea, Speech Difficulties, and Swallowing Difficulties) measures. Clinician-rated and generic self-report measures were also administered.

Results: Reliabilities for the new patient reported physical functioning measures were excellent (all Cronbach's $\alpha > .92$). Convergent, discriminant validity and known group validity was supported.

Conclusions: The results provide psychometric support for new patient-reported physical functioning measures and the fact that these measures can be used as clinically meaningful endpoints in Huntington's disease research and clinical practice. © 2017 International Parkinson and Movement Disorder Society

Key Words: Neuro-QoL; HDQLIFE; Huntington's disease; physical functioning; chorea; motor symptoms; health-related quality of life; patient-reported outcome (PRO)

Huntington's disease (HD) is a progressive neurodegenerative disorder that causes profound cognitive, behavioral, and motor declines. The motor

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phenomenology in HD is multifaceted and affects all body segments and limbs, with profound impacts on daily living and social participation. The most characteristic and best studied motor symptom in HD is chorea.[1-4] Chorea is associated with falls, gait disturbance, and balance difficulties.[5-10] By mid- to late-stage HD, even if chorea is controlled, a host of less-treatable motor problems steadily worsen (dystonia, bradykinesia, rigidity, and ataxia). Motor symptoms also affect oropharyngeal function resulting in worsening dysarthria[11-13] and dysphagia.[14]

Patient-reported outcome (PRO) measures about motor symptoms and associated activity limitations are rarely used in HD trials, even though such outcomes are increasingly recognized as important measures of efficacy for new treatments.[15] In a devastating disease such as HD, where intensive treatment efforts are directed at the development of treatments designed to improve physical activity engagement,[16-21] there is a particular need for meaningful and sensitive PRO measures that capture these aspects of health-related quality of life (HRQOL).

The Huntington Disease Health-Related Quality of Life (HDQLIFE) measurement system[22-25] was designed to provide reliable and valid assessments of HRQOL among individuals with HD. This system includes several HD-specific measures of HRQOL as well as generic HRQOL measures from the Quality of Life in Neurological Disorders (Neuro-QoL) system.[26,27] The goal of this paper is to provide reliability and validity data for the HDQLIFE PROs that evaluate physical function.

Methods

Participants

Individuals with either prodromal (gene-positive status for the HD CAG expansion and no clinical diagnosis) or manifest HD were invited to participate in this study. Participants were ≥ 18 years of age, able to read and understand English, and had the ability to provide informed consent. Participants were recruited through specialized HD treatment centers, the HD Roster, existing data capture systems,[28] and the Predict-HD research study.[29]

Measures

We examined Neuro-QoL Lower Extremity Function and Neuro-QoL Upper Extremity Function[19,29] computer adaptive tests and fixed 8-item short-forms. We also examined simulated computer adaptive tests and 6-item short-form scores for HDQLIFE Chorea,[30] HDQLIFE Speech Difficulties,[31] and HDQLIFE Swallowing Difficulties.[31] Resulting scores are on a *t*-metric (mean [M] = 50, standard deviation [SD] = 10).

Composite Scores

Upper and lower extremity composite scores were created by the a priori selection of self-rated and clinician-rated items. The upper extremity self-rated composite was composed of the EuroQoL 5 Dimensions Questionnaire[32] self-care item, 1 Veterans Rand 12-item Health Status Inventory[33] item ("Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?"), 2 World Health Organization Disability Assessment Schedule 2.0[34] items ("In the last 30 days, how much difficulty did you have in: washing your whole body?" and "In the last 30 days, how much difficulty did you have in: getting dressed?"), and items from a self-report version of the UHDRS[35] Total Functional Capacity (TFC; "Are you able to work?" Are you able to manage your own finances?" "Are you able to complete household chores without help?" "Are you able to accomplish daily living tasks, such as bathing, dressing, and meal preparation without help?" "What type of care do you receive?"). Self-reported TFC internal consistency (Cronbach's $\alpha = 0.86$) and convergent validity with the clinician-rated version (intraclass correlation coefficient [ICC] = 0.89; 95% confidence interval .87-.91) were supported. The lower extremity self-rated composite was composed of the EuroQoL 5 Dimensions Questionnaire[32] mobility item, 1 Rand[33] item ("Does your health now limit you in climbing several flights of stairs? If so, how much?"), 2 World Health Organization Disability Assessment Schedule 2.0[34] items ("In the last 30 days, how much difficulty did you have in: standing for long periods such as 30 minutes?" and "In the last 30 days, how much difficulty did you have in: walking a long distance, such as a kilometer [or equivalent]?"), and the self-reported TFC items. The upper extremity clinician-rated composite was composed of the UHDRS[35] Independence Scale, TFC score, and Motor Assessment upper extremity items (finger tapping, pronation, and hand supination; Luria; arm rigidity; upper extremity dystonia; upper extremity chorea). The lower extremity clinician-rated composite was composed of the Independence Scale, TFC score, and Motor Assessment lower extremity items (gait, tandem walking, retropulsion, lower extremity dystonia, lower extremity chorea). All composite scores were coded so that higher scores indicated worse function; scores were transformed to *z* scores, averaged, and transformed to *t* scores (M = 50, SD = 10).

Clinician-rated TFC was used to classify manifest HD participants as either early stage (sum scores of 7-13) or late stage (sum scores of 0-6).[36]

Analyses

Internal Consistency Reliability, Convergent and Discriminant Validity

A multitrait, multimethod correlation matrix where Pearson correlation coefficients are organized such that

each method (PRO and composite measures) is arranged corresponding to different concepts (clinician ratings or self-reported) was used to examine internal consistency reliability (Cronbach's alphas) and determine associations among PROs, self-rated, and clinician-rated composites. Coefficients on the diagonal provide estimated reliabilities. Coefficients between similar methods and concepts (eg, PRO vs PRO composite) should yield the strongest relationships (correlations ≥ 0.6 support convergent validity), and coefficients between different methods and concepts (eg, PRO vs clinician composite) should yield the weakest relationships (0.3 to 0.6 correlations support discriminant validity).[37]

Known-Groups Analyses

Multivariate analyses were conducted to identify group differences (prodromal, early HD, late HD). Prodromal participants should report better functioning than both manifest HD groups; early-HD participants should report better functioning than late-HD participants.

Effect Sizes

Cohen's d were calculated to evaluate the relative influence that symptom severity (determined by a median split using the corresponding clinician-rated scores/item[s] from the UHDRS Motor Assessment) had on self-reported physical functioning. Neuro-QOL scores were compared with the UHDRS Total Motor score, HDQLIFE Chorea was compared with the clinician-rated UHDRS Motor Assessment chorea items, HDQLIFE Speech Difficulties was compared with the clinician-rated UHDRS Motor Assessment speech item, and HDQLIFE Swallowing Difficulties was compared with the clinician-rated UHDRS Motor Assessment swallowing item. Effect sizes for the Neuro-QoL PROs were examined relative to the Neuro-QoL normative sample ($n = 1046$ for Lower Extremity; $n = 1095$ for Upper Extremity; $M = 50$, $SD = 10$); effect sizes for each HDQLIFE PRO was examined relative to this sample. The largest effect sizes should be seen among those with greater clinician-rated severity.

Classification Accuracy (Sensitivity/Specificity)

Logistic regression models were conducted to determine the accuracy with which the PROs could discriminate between different HD groups. Likelihood ratios for clinical decision making should be ≥ 2.[38] Receiver operating characteristic analysis was used to compare diagnostic performance of the PROs (minimal acceptable area under the curve specified as $\geq .70$.[39]

Results

A total of 510 individuals with prodromal ($n = 198$), early- ($n = 195$), or late-stage HD ($n = 117$) participated in this study. Participants ranged from 18 to 81 years of age ($M = 49.10$, $SD = 13.23$), 59.2% of participants were women, and the majority of participants were white (96.1%). Education ranged from 4 to 26 years ($M = 15.06$, $SD = 2.89$). Descriptive data for the PROs are provided in Table 1. An examination of floor effects by group (prodromal, early-, and late-stage HD) confirmed that floor effects were most prevalent in the prodromal group (of those with floor effects, $\geq$65% were prodromal participants).

Internal Consistency Reliability, Convergent and Discriminant Validity

Reliability coefficients for the Neuro-QoL (both = .97) and HDQLIFE measures were excellent (.98 for Chorea and Speech, .97 for Swallowing; Table 1). Validity coefficients were higher between the Neuro-QoL/HDQLIFE measures and the composite self-report measures than they were with the clinician-rated composites, supporting convergent and discriminant validity, respectively.

Known-Groups Analyses

Analyses indicated significant group differences among all 3 groups; findings were in the predicted direction (Table 2).

Effect Sizes

As expected, effect sizes were larger for the groups with more clinician-rated severity (Table 2).

Classification Accuracy (Sensitivity/Specificity)

Classification accuracy was generally moderate to high for all PROs when differentiating between prodromal-HD and either manifest HD group (Table 2).

Discussion

The results support the reliability and validity of the Neuro-QoL and HDQLIFE physical functioning PROs in individuals with prodromal and manifest HD. Specifically, the results provided strong support for the internal consistency reliability of the PROs, and although there was some evidence of floor effects (which reflected the fact that the majority of the prodromal group was not exhibiting motor problems), these PROs were free of ceiling effects. Convergent and discriminant validity of the PROs were also supported. Specifically, convergent validity was supported by strong associations between the physical functioning PROs and other measures of self-reported physical functioning, and discriminant validity was supported

TABLE 1. Multitrait, multimethod correlation matrix and descriptive data for Neuro-QoL and HDQLIFE physical function measures

	NQ Lower Extremity Function	NQ Upper Extremity Function	HDQLIFE Chorea	HDQLIFE Speech Difficulties	HDQLIFE Swallowing Difficulties	Lower Extremity Composite - Clinician	Upper Extremity Composite- Clinician	Chorea Composite - Clinician	Speech/ Swallowing Composite - Clinician	Lower Extremity Composite - Self	Upper Extremity Composite - Self
PRO measure											
NQ Lower Extremity Function	*0.97*										
NQ Upper Extremity Function	0.79	*0.97*									
HDQLIFE Chorea	−0.78	−0.77	*0.98*								
HDQLIFE Speech Difficulties	−0.70	−0.68	0.77	*0.98*							
HDQLIFE Swallowing Difficulties	−0.66	−0.66	0.70	0.69	*0.97*						
Composite measure											
Lower Extremity Composite - Clinician	**0.68**	0.72	**−0.66**	−0.55	−0.51	*0.92*					
Upper Extremity Composite- Clinician	0.63	**0.71**	**−0.65**	−0.54	−0.50	0.92	*0.94*				
Chorea Composite - Clinician	0.50	0.53	**−0.60**	−0.47	−0.44	0.73	0.73	*0.95*			
Speech/Swallowing Composite - Clinician	0.53	0.63	−0.54	**−0.47**	**−0.40**	0.79	0.83	0.57	*0.76*		
Lower Extremity Composite - Self	**0.83**	0.77	**−0.77**	−0.65	−0.62	**0.76**	0.73	**0.48**	0.64	*0.91*	
Upper Extremity Composite - Self	0.73	**0.77**	**−0.72**	−0.65	−0.61	0.72	**0.70**	**0.40**	0.64	0.85	*0.84*
Descriptive data											
CAT mean	48.78	44.79	49.12	48.27	49.50	–	–	–	–	–	–
CAT (SD)	(10.61)	(10.70)	(9.30)	(8.89)	(8.73)	–	–	–	–	–	–
SF mean	49.25	44.71	49.62	48.52	49.43	50.06	50.05	50.00	50.03	50.12	50.20
SF (SD)	(9.66)	(10.63)	(8.52)	(8.58)	(8.61)	(7.74)	(7.62)	(8.81)	(8.95)	(8.43)	(7.55)
Cronbach's α (SF only)	0.93	0.94	0.93	0.93	0.92	0.92	0.94	0.95	0.76	0.91	0.84
CAT % with floor effects (high function)	27.2	35.2	27.4	22.4	35.1	–	–	–	–	–	–
CAT % with ceiling effects (low function)	0.2	0.6	0.2	0.6	0.6	–	–	–	–	–	–
SF % with floor effects (high function)	41.5	51.8	50.4	30.1	44.6	5.4	2.6	26.9	52.3	26.6	30.3
SF % with ceiling effects (low function)	0.2	0.2	0.0	0.0	0.0	0.2	0.2	0.4	0.2	0.2	0.6
Administration Time (sec) median (SD)	66 (65)	69 (79)	48 (40)	34 (40)	59 (84)	–	–	–	–	–	–

Correlations are reported for computer adaptive test administrations; Reliability coefficients are provided in italics and validity coefficients are provided in bold; all $P < .01$ level (2-tailed). Neuro-QoL, Quality of Life in Neurological Disorders Measurement System; HDQLIFE, Huntington Disease Health-Related Quality of Life Measurement System; NQ, Neuro-QoL; PRO, patient-reported outcome; CAT, computer adaptive test; SF, Short Form; sec, seconds.

TABLE 2. Known-groups validity, effect sizes, and classification accuracy of the new patient-reported outcome computer adaptive tests

	Prodromal HD (n = 197)		Early HD (n = 188)		Late HD (n = 106)				Clinician-Rated Severity on UHDRS Motor Exam item(s)	
Known-groups validity	Mean	SD	Mean	SD	Mean	SD	*F*	Partial η^2	Low	High
Lower Extremity Function/Mobility[a,b,c]	56.07	7.33	46.92	8.91	0.401	8.59	163.021	0.401	−0.71	0.52
Upper Extremity Function - Fine Motor ADL[a,b,c]	52.49	6.60	43.24	8.85	0.467	7.98	214.214	0.467	−1.15	0.12

	Prodromal HD (n = 194)		Early HD (n = 191)		Late HD (n = 106)				Clinician-Rated Severity on UHDRS Motor Exam item(s)	
Known-group validity	Mean	SD	Mean	SD	Mean	Low	*F*	Partial η^2	Low	High
HDQLIFE Chorea[a,b,c]	43.43	3.80	51.64	7.83	0.391	8.27	156.978	0.391	1.40	−0.09
HDQLIFE Speech Difficulties[a,b,c]	42.87	6.16	50.29	7.56	0.309	7.62	109.143	0.309	2.20	−0.19
HDQLIFE Swallowing Difficulties[a,b,c]	44.17	5.70	51.03	8.19	0.296	7.97	102.354	0.296	0.44	−0.06

	Prodromal vs Early			Prodromal vs Late			Early vs Late		
Classification accuracy	Sensitivity, specificity	Area under the curve	Likelihood ratio	Sensitivity, specificity	Area under the curve	Likelihood ratio	Sensitivity, specificity	Area under the curve	Likelihood ratio
Lower Extremity Function/Mobility	70.2, 72.1	0.78	2.36	86.8, 92.9	0.95	6.58	55.7, 82.4	0.80	1.26
Upper Extremity Function - Fine Motor ADL	72.3, 70.6	0.78	2.61	77.6, 88.8	0.93	3.46	52.3, 85.1	0.75	1.10
HDQLIFE Chorea	82.2, 79.6	0.86	4.62	77.2, 91.6	0.92	3.39	22.8, 91.4	0.67	0.30
HDQLIFE Speech Difficulties	70.7, 69.9	0.78	2.41	70.0, 87.0	0.87	2.33	24.5, 92.7	0.66	0.32
HDQLIFE Swallowing Difficulties	68.1, 71.6	0.74	2.13	60.7, 84.5	0.84	1.54	17.9, 92.7	0.62	0.22

All $P < .0001$. There were significant differences among all 3 groups for all Neuro-QoL and HDQLIFE measures. Neuro-QoL, Quality of Life in Neurological Disorders Measurement System; HDQLIFE, Huntington Disease Health-Related Quality of Life Measurement System; HD, Huntington's disease; CAT, computer adaptive test; ADL, activities of daily living.
[a]Significant differences between prodromal and early HD.
[b]Significant differences between prodromal and late HD.
[c]Significant differences between early HD and late HD.

by slightly smaller associations between the PROs and the clinician-rated composites.

As expected, we also found that individuals with prodromal HD had less physical dysfunction than either manifest HD group and that individuals with late HD had more severe motor functional impairments than early HD. Furthermore, effect sizes for the PROs were higher for participants with lower clinician-rated functioning than those with better functioning. Together, these findings support the construct validity of these new measures in HD.

Finally, moderate to high sensitivity and specificity were found for almost all the new PROs. In particular, scores on all PROs suggested that they could be used to discriminate between individuals with prodromal and early HD, and between prodromal and late HD (except HDQLIFE Swallowing Difficulties), suggesting that these measures may be especially sensitive to tracking disease progression over time.

Although this study provides important psychometric support for these new PROs, there are limitations to this study. First, participants were recruited through other research studies and through established HD clinics; this convenience sample may not represent the HD population at large. Furthermore, multitrait, multimethod analyses relied on composite scores that were generated using individual items from existing scales and self-report versions of clinician-administered measures. This departure from their intended use and/or standardized administration may either over- or underestimate the participants' "true" abilities, which could potentially weaken the interpretation of this validity data. Finally, symptom progression in HD includes cognitive impairments[40-45] and anosognosia (lack of self-awareness)[46] that may preclude the ability to examine HRQOL using PROs. Regardless, such self-report measures should be used in conjunction with other information (eg, performance-based and clinician-rated assessments) when making clinical decisions, especially among individuals who are later in the disease process.

The Neuro-QoL and HDQLIFE PROs provide brief, reliable, and valid assessments of physical functioning.

Furthermore, these PROs are able to differentiate between individuals with prodromal versus early- or late-stage HD. As such, these measures fill a significant gap in HD clinical interventions where sensitive PROs are needed to detect improvements in motor impairment and physical activity engagement. ■

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