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Earliest functional declines in Huntington disease

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Abstract

We examined the gold standard for Huntington disease (HD) functional assessment, the Unified Huntington's Disease Rating Scale (UHDRS), in a group of at-risk participants not yet diagnosed but who later phenocconverted to manifest HD. We also sought to determine which skill domains first weaken and the clinical correlates of declines. Using the UHDRS Total Functional Capacity (TFC) and Functional Assessment Scale (FAS), we examined participants from Huntington Study Group clinics who were not diagnosed at their baseline visit but were diagnosed at a later visit (N = 265). Occupational decline was the most common with 65.1% (TFC) and 55.6% (FAS) reporting some loss of ability to engage in their typical work. Inability to manage finances independently (TFC 49.2%, FAS 35.1%) and drive safely (FAS 33.5%) were also found. Functional decline was significantly predicted by motor, cognitive, and depressive symptoms. The UHDRS captured early functional losses in individuals with HD prior to formal diagnosis, however, fruitful areas for expanded assessment of early functional changes are performance at work, ability to manage finances, and driving. These are also important areas for clinical monitoring and treatment planning as up to 65% experienced loss in at least one area prior to diagnosis.

Keywords

Neuropsychological assessment; Depression; Daily functioning; Occupation; ADLs (activities of daily living)

1. Introduction

Huntington Disease (HD) is an autosomal-dominant genetic disease that results in progressive deterioration of motor and cognitive abilities and the emergence of psychiatric symptoms (Huntington Study Group (HSG), 1993, Paulsen et al., 2001a and Shoulson, 1990). The combination of these symptoms eventually contributes to significant declines in functional capacity that affect both activities of daily living (ADLs, e.g., eating, bathing) and instrumental activities of daily living (IADLs, e.g., managing medications and finances). The assessment of functional capacity is a key component of a clinical or research exam

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because it has traditionally been viewed as the closest proxy of “real world” functioning and has immediately discernable practical value (e.g., what tasks is the patient capable of independently completing). The importance of functional level in HD is also apparent in recent drug trials; the FDA has mandated the use of patient-reported outcomes (Bren, 2006). Thus, the sensitive assessment of functional status has significance not only in the clinical monitoring of patients, but also in the advancement of therapies for this disease.

The Total Functional Capacity (TFC) scale (Shoulson and Fahn, 1979), which is a component of the Unified Huntington's Disease Rating Scale (HSG, 1996), is the main assessment tool of functional status in HD clinical care and research. It has been used as the primary outcome measure in several clinical trials in manifest HD. However, the scale was designed to assess progression of HD in patients with manifest disease and accordingly emphasizes self-care, mobility, and independence. Thus the usefulness of the TFC in detecting very early changes in functional capacity is unknown. Clinical experience and research strongly suggest that many gene-expanded individuals experience declines in their functional status and other clinical domains even before formal HD diagnosis (Lawrence et al., 1998 and Paulsen et al., 2008). Recent research in other neurodegenerative disorders has also shown that poor performance in IADLs predicts conversion to dementia 10 years later (Peres et al., 2008).

Clinical trials are currently underway in pre-diagnosed and early-stage HD individuals. It would be helpful for selection of outcomes to know whether the current UHDRS functional assessment scales are capable of detecting early functional changes. Additionally, examination of current brief measures may guide the development of more detailed measures by informing us about which aspects of functioning decline as the early disease-related changes manifest. We examined the functional declines in a sample of at-risk participants who were identified as “phenoconverters” (i.e., those who were not yet diagnosed with HD at their baseline visit but were later rated at a follow-up visit as having “unquestionable” HD based on motor signs) on two measures of functional capacity: the UHDRS TFC scale and the Functional Assessment Scale (FAS). We also determined which aspects of disease (motor score, cognitive performance, depression) were associated with these early declines.

2. Methods

2.1. Participants

Participants were seen for a clinical research evaluation at one of 55 sites affiliated with the Huntington Study Group (HSG) in North America, Europe, or Australia. All HSG sites who had contributed de-identified data during the 1990s were included, regardless of specific ongoing studies individuals may have been participating in at the time of their visit. The total number of participants available for analysis was all HSG participants at visit 1 ($N=4423$). Selection criteria for this analysis required that participants have a family history of HD, but the genetic status of participants was unknown (i.e., “at risk”). The summary score from the standardized neurological exam, the UHDRS (HSG, 1996), was used to determine whether participants were showing manifest motor symptoms of HD meeting research criteria for a diagnosis of HD. Any participants who were rated as having a 0 (no motor signs), a 1 (soft signs only), or a 2 (signs of HD that were insufficient for a definitive diagnosis) on the UHDRS Diagnostic Confidence Level (DCL) item were included. Participants who were already rated as having “unquestionable” HD (i.e., a DCL = 3) at the first available visit were excluded. This criterion has been used in prior analyses attempting to capture the earliest signs of disease in a pre-diagnosed sample (Langbehn and Paulsen, 2007). Because this sample of at-risk individuals could have included people who were, in fact, non-gene expanded, we further limited the sample to those individuals who had at least

one follow-up exam resulting in definite diagnosis according to the UHDRS (i.e., “unquestionable HD,” a DCL = 3). This resulted in a final sample of 265. Although gene status was not available on these individuals, positive status is inferred based on a movement disorder specialist's rating of greater than 99% confidence that they had HD. All data were aggregated and stored in a research database. This version of the database was stripped of all subject, examiner, and site specific identifiers. This de-identification and the subsequent use of this data for research was approved by the IRB at The University of Iowa where this analysis was conducted. For further information about the sample, please see (Langbehn & Paulsen, 2007 and Paulsen et al., 2001b).

2.2. Measures

The UHDRS was administered to evaluate participants at every visit, typically on an annual basis (HSG, 1996). The UHDRS consists of a motor examination, cognitive assessment, and psychiatric assessment, in addition to the functional scales (details noted below).

2.2.1. Functional capacity—The two functional capacity assessments from the UHDRS are determined by patient interview with input from the family, when available. The TFC is a broad measure of functional capacity and consists of five global items that assess occupation, finances, domestic chores, activities of daily living, and care level, with scores on each item ranging from 0 to either 2 or 3 (e.g., “occupation — 0 = unable, 1 = marginal work only, 2 = reduced capacity for usual job, 3 = normal”). TFC total scores range from 0 to 13 with greater scores indicating higher functioning. These total scores have been grouped into 5 categories that correspond to stages of disease, with lower stage indicating more intact functioning (e.g., TFC scores between 13 and 11 = stage 1). The FAS is a more detailed measurement of functional capacity and consists of 25 yes/no questions about specific functional abilities. The FAS examines tasks related to occupation (e.g., accustomed work, volunteer work), finances (e.g., cash transactions, financial management), activities of daily living (e.g., driving, hygiene), domestic chores (e.g., home maintenance, laundry), level of care (e.g., home or supervised care), and physical abilities (e.g., walking, getting out of bed, falls). FAS scores range from 0 to 25. Greater scores indicate greater functionality.

2.2.2. Motor functioning—The sum of individual motor signs (e.g., finger tapping, oculomotor, chorea, rigidity, dysarthria) was the Total Motor Score with higher scores indicating more impaired motor functioning (range 0–124). Based on the results of the individual motor items, the rater selected a confidence rating on a scale of 0–3 to represent the presence or absence of motor abnormalities and their opinion of the likelihood that the signs were indicative of HD. As noted above, the DCL is a scale from 0 (normal) to 3 (unquestionable HD, ≥ 99 confidence) operationally defined as the unequivocal presence of an otherwise unexplained movement disorder in a subject at risk for HD. However, it is a research classification, not a clinical diagnosis. The diagnostic confidence level has previously shown adequate inter-rater reliability in a sample of 75 clinicians (weighted kappa 0.67) (Hogarth et al., 2005).

2.2.3. Depression—The frequency and severity of psychiatric symptoms were rated by clinicians, with input from the patient and family, on scales ranging from 0 to 4 (highest possible = 16). Frequency and severity ratings were multiplied together to get a composite score (Marder et al., 2000). A single item measure of depression was used from the psychiatric assessment component of the UHDRS, with higher scores indicating greater depressed mood.

2.2.4. Cognitive functioning—Three cognitive tests are included in the UHDRS: Stroop Interference Test (Stroop, 1935), a verbal fluency test (Benton and Hamsher, 1978), and the

Symbol Digit Modalities Test (Smith, 1973). Standard scores were used (mean = 100, SD = 15), with higher scores indicating better cognitive functioning on all tasks.

2.3. Analysis

2.3.1. Early functional decline—Individuals who were at-risk for HD but not yet diagnosed and who had at least one follow-up exam resulting in the research diagnosis (i.e., a DCL = 3 or “unquestionable” HD) were selected ($N = 265$). Univariate and bivariate frequency count tables of the TFC and FAS items were used to determine the ranges of both scales and to investigate the functional deficiencies indicated by particular items. Early functional losses were then identified by examining the most frequently reported declines on both scales.

2.3.2. Clinical correlates of functional decline—Logistic regression analysis was then conducted on FAS items to examine which aspects of disease (UHDRS total motor score, depression score, and the three cognitive variables combined as a composite and individually) were most related to functional decline.

3. Results

3.1. Participant demographics and functional descriptive results

Participants were included if they had a DCL less than 3 at their first visit and converted to a DCL of 3 at a subsequent visit. In our sample, the majority of participants meeting these criteria had a DCL of 2 at the first visit ($n = 185$, 69.8%; DCL 1 $n = 58$, 21.9%; DCL 0 $n = 22$, 8.3%), which indicates that they were nearing diagnosis. The sample had an equal gender distribution (50.4% male), an average age of 44.47 years ($SD = 12.37$), and 13 years of education. Participants had baseline clinical scores consistent with early stage HD: average TFC was stage 2 ($M = 10.0$, $SD = 3.3$), average total motor score was 23.0 ($SD = 17.5$), depression score was 3.6 ($SD = 4.2$), and cognitive standard score means were between 1.4 and 2.3 standard deviations below normative values suggesting mild impairments. We examined the functional scale total scores at the baseline visit. Thirty-nine percent reported no decline on the FAS and 31.8% had a perfect score on the TFC. On the FAS half the sample had scores indicating minimal functional impairment with scores between 23 and 25. Similarly, 55% had TFC scores between 11 and 13, which corresponds to stage 1, also indicating minimal functional impairment (Shoulson and Fahn, 1979).

Descriptive data for the item distributions of the TFC and FAS at the baseline visit are summarized in Table 1. Occupational decline was the most frequently reported functional loss on the TFC, with 65.1% of participants reporting some loss of ability to engage in work. On the FAS, 55.6% were unable to engage in their usual work, 37.8% were unable to engage in any gainful employment, and 23.9% could not engage in volunteer work. Inability to manage finances without help (TFC 49.2%, FAS 35.1%), inability to drive safely (FAS 33.5%), and the inability to supervise children (FAS 28.6%) were other common functional declines. Declines in ADLs were also reported on the TFC (30.9%). Inability to independently shop for groceries, perform housework, do laundry, and prepare meals were all reported by approximately 20% on the FAS.

3.2. Relationships of disease variables to functional loss

Results of the logistic regression analysis for the most frequently endorsed FAS items and disease variables are summarized in Table 2. In a logistic regression model that included depression, motor functioning, and three cognitive subscales, functional loss was most strongly related to motor scores. However, cognitive scores were also associated with most functional losses and depression was related to loss of ability to engage in usual

employment. Higher motor impairment was associated with lower likelihood of being able to perform all three of the work items [odds ratio = 0.936/point; 95% CI, (0.907 to 0.966) for usual employment; OR = 0.929/point; 95% CI, (0.899 to 0.961) any employment; OR = 0.962/point; 95% CI (0.931 to 0.995), for volunteer employment], driving safety [OR = 0.953/point; 95% CI (0.923 to 0.983)], managing finances [OR = 0.943/point; 95% CI (0.913 to 0.974)], and supervising children [OR = 0.936/point; 95% CI (0.905 to 0.969)]. These results indicate that for each point increase on total motor score, the likelihood of being able to complete certain skills (e.g., engage in any work) is reduced by about 10%. The measure of depression predicted only an inability to engage in one's accustomed work [OR = 0.869/point; 95% CI (0.799 to 0.945)] and handle money in a simple cash transaction [OR = 0.861/point; 95% CI (0.761 to 0.974)].

A combined cognitive composite variable was associated with nearly all reported FAS declines with the exceptions of ability to perform usual employment, do laundry, and manage medications. When the individual cognitive tests were examined, Stroop interference was associated with functional loss for the ability to manage finances, drive safely, supervise children, volunteer, and grocery shop (see Table 2). The Symbol Digit Modalities Test was associated with inability to grocery shop and use public transportation. Verbal Fluency was not related to loss of function.

4. Discussion

The current analysis is the first attempt to evaluate which aspects of functional capacity show early decline in patients with HD and whether the UHDRS functional scales may be extended downward to participants who do not yet meet diagnostic criteria. On both the TFC and FAS, declines in occupational performance were the most commonly endorsed functional problems by participants. Up to 65% (TFC) and 55% (FAS) of participants reported some loss of ability to engage in work. Inability to manage finances was endorsed as a second area of decline (TFC 49%, FAS 35%). Additional areas of specific decline were identified on the FAS compared to the TFC (inability to drive safely, supervise children, or volunteer). While the results are not necessarily surprising, they provide a target for development of more detailed functional instruments in the areas of work performance and financial management. Additionally, clinicians should be sensitive to changes in these functional areas even before formal diagnosis, as more than half reported not being able to do their accustomed work and a third could not manage finances or drive safely. The results also suggest that a hierarchical approach to the FAS may be appropriate since the majority of functional disability was captured in the first 10 of 25 items. For example, in patients who are in stage 1 or are not yet diagnosed, it may be appropriate to ask only those questions and continue the full assessment only if there are impairments noted. Such a revision would require validation.

UHDRS total motor score was the clinical variable most strongly associated with the FAS items endorsed by this sample, as shown in Table 2. Motor performance was highly predictive of loss of ability to work, manage finances, drive and supervise children. A one point increase in UHDRS total motor score (range 0–124) was associated with a 5–10% loss in the likelihood of being able to perform the above skills. Ability to control movement is clearly an important component of successful completion of the above tasks, so this is not unexpected. Additionally, although none of the participants was diagnosed when these data were collected, nearly 70% were displaying signs sufficient for a diagnostic confidence level rating of “probable” HD indicating that motor abnormalities were present (thus, this is not a true “prodromal” sample). This finding supports the motor exam as a key component of clinical and/or research monitoring as measured by the current UHDRS standardized assessment because it was most strongly associated with functional performance. However,

as more detailed functional assessments become available to capture earlier and more subtle changes in daily function, the role of motor and cognitive performance and psychiatric status will need to be re-evaluated.

Similar to other studies (Hamilton et al., 2003, Marder et al., 2000, Nehl & Paulsen, 2004 and Rothlind et al., 1993), we also found neuropsychological performance and depression to be predictors of functional loss. Certainly cognition is a critical component of all of the above functional skills, particularly work performance, managing finances, and driving. Previous research has shown that, even in pre-diagnosed individuals who are decades before motor diagnosis, cognition is affected (Lawrence et al., 1998 and Paulsen et al., 2008). In this study, we found the combined cognitive variable that included all three UHDRS cognitive scores to be a significant predictor of decline on nearly all FAS items. Specifically, the Stroop (a measure that taps multiple cognitive domains, such as processing speed, working memory, and attention) was as strong a predictor of ability to manage finances, drive safely and volunteer as motor performance. The one cognitive test with a motor component, the SDMT, was also associated with ability to shop for groceries and use public transportation, consistent with previous research from our group (Langbehn and Paulsen, 2007). Interestingly, verbal fluency was not independently associated with functional skills. Verbal fluency captures multiple aspects of cognition, but is typically thought to be a measure of executive functions and language. However, the specific skills required for verbal fluency (e.g., initiation and generation of items from a category) may be less critical for the performance of the functional tasks assessed by the UHDRS, like driving and managing finances, which are probably better captured by tests of working memory, attention, and processing speed. Verbal fluency might better capture more subtle changes in flexibility in verbal processing and problem solving that are not currently assessed on the FAS.

Depression was less strongly predictive of functional impairment than motor and cognitive performance. A caveat in the interpretation of these results is that the assessment of depression was obtained only from the UHDRS psychiatric assessment, which should be considered a screening measure. More work is needed to determine which aspects of depression (and other psychiatric symptoms) are specifically related to functional loss. For example, is self-reported depression reflective of the classically defined syndrome of Major Depressive Disorder, or is there a component of depression unique to HD that may contribute to functional decline (e.g., physical symptoms such as fatigue vs. cognitive symptoms such as decreased concentration vs. affective symptoms such as apathy)?

Although the current study utilized a large, collaborative database which allowed us to examine this important research question, some limitations should be noted. First, the gene status of the participants was unknown. However, each participant was rated as having HD with greater than 99% confidence by a movement disorders specialist using the motor exam from the UHDRS. It is unlikely that our sample contains more than a negligible number of individuals without HD. The motor exam has been shown to have excellent inter-rater reliability (0.94 for total score) and to be sensitive for tracking longitudinal change (HSG, 1996). Further, it is not standard in routine clinical practice to obtain confirmatory genetic testing in individuals with signs of HD in the context of a positive family history. However, because diagnosis was based on the presence of motor signs, patients with atypical phenotypes would not be represented in this sample. Second, we have little information about the reasons participants were seen in these clinics, so the clinical characterization of the sample is lacking. Functional losses may be due to factors other than HD, such as depression or other medical conditions. Third, there may be some bias with regard to patients who returned for follow-up which may limit the generalizability of these findings (e.g., only patients with less severe pathology may have been able to return to the clinic).

Finally, our assessment of functional status was limited to the measures on the UHDRS. Future studies should examine patients with well characterized clinical information (including CAG repeat length) and target the areas identified in this analysis (work functioning and financial skills) with more detailed functional assessments. In conclusion, functional deficits are common, even in individuals who are not yet diagnosed, and should be carefully monitored. This finding also has implications for the diagnosis of dementia in patients with early HD as functional impairment is a criterion for a dementia diagnosis, which may be more common at early stages than is currently recognized.

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Table 1

Frequently reported early functional losses by phenoconverters prior to HD diagnosis on the TFC and FAS.

Functional decline items	n	Percent reporting loss of function
Total Functional Capacity (TFC)		
Occupation	170	65.13
Financial management	128	49.23
Activities of daily living	81	30.92
Domestic Chores	80	30.89
Care Level	23	8.81
Functional Assessment Scale (FAS) ^a		
Unable to engage in usual work	144	55.6
Unable to engage in any work	98	37.84
Unable to manage finances	91	35.14
Unable to drive safely	86	33.46
Unable to supervise children	74	28.57
Unable to volunteer	62	23.94
Unable to shop for groceries	52	20.08
Unable to do housework	50	19.31
Unable to prepare meals	48	18.53
Unable to do laundry	46	17.69

^aOnly functional losses endorsed by more than 15% of participants are reported.

Table 2

Odds ratios per point change for predictors of frequently reported early functional declines on the FAS.

FAS functional decline items	Motor	Depressive	Cognitive functioning ^a		
	Functioning	Symptoms	Verbal fluency	SDMT	Stroop
Unable to engage in usual work	0.936 ***	0.869 **	1.012	1.006	1.011
Unable to engage in any work ^b	0.929 ***	0.948	0.998	1.028	1.012
Unable to manage finances ^b	0.943 **	0.931	0.991	1.012	1.064 **
Unable to drive safely ^b	0.953 **	0.931	1.008	1.004	1.052 **
Unable to supervise children ^b	0.936 **	0.919	0.998	1.015	1.040 *
Unable to volunteer ^b	0.962 *	0.948	1.002	1.025	1.045 *

FAS = Functional Assessment Scale, SDMT = Symbol Digit Modalities Test, Stroop = Stroop Interference Task.

^aOdds ratios are per point lower standardized score.

^bOdds ratio for a combined score of the cognitive tests were also significant at $p < 0.05$ for these items.

 $p < 0.0001$.

**
 $p < 0.01$.

*
 $p < 0.05$.