Psychiatric Symptoms in Huntington's Disease before Diagnosis: The Predict-HD Study

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Background: Psychiatric disturbances are relatively common in manifest Huntington's disease (HD), but less is known about these symptoms in the earliest phase of the illness.

Methods: This study examined self-reported psychiatric symptoms in a large sample (N = 681) of prediagnosed individuals who show the gene expansion for HD ("expansion-positive") compared with a sample of individuals who do not show the gene expansion but are at risk for HD ("expansion-negative").

Results: Using baseline Symptom Checklist 90—Revised (SCL-90-R) data from the Predict-HD study, expansion-positive individuals reported significantly more psychiatric symptoms (e.g., depression, anxiety, obsessive–compulsiveness) than expansion-negative individuals. Within the expansion-positive group, individuals with more motor signs had higher levels of psychiatric symptoms. The SCL-90-R scores had stronger relationships with reported abilities to perform activities of daily living than other markers of HD. Finally, when companions of the expansion-positive individuals also completed the SCL-90-R on the participants, there was considerable consistency in the ratings of psychiatric symptoms.

Conclusions: Subtle, subclinical psychiatric symptoms are present in this prediagnosed HD sample, even though most are estimated to be more than 10 years from HD diagnosis. As suggested by other research, these subtle symptoms might be the earliest markers of the disease; however, longitudinal data are needed.

Key Words: Huntington's disease, pre-diagnosis, psychiatric symptoms

Huntington's disease (HD) is an autosomal dominant, progressive neurologic disorder characterized by motor disturbance, cognitive dysfunction, and psychiatric symptomatology (Paulsen 1999). The disease typically does not manifest until the fourth or fifth decade of life; however, recent research has demonstrated that subtle abnormalities may be present much earlier. Although more emphasis has been placed on detecting the early cognitive and neuroimaging markers of HD (Aylward *et al.* 1996, 1997, 2004; Kirkwood *et al.* 1999; Lawrence *et al.* 1998; Nehl *et al.* 2001; Paulsen *et al.* 2001, 2004, 2006), emotional dysfunction might also predate the clinical HD diagnosis. The identification of early psychiatric symptoms may be particularly important in HD because of its possible deleterious effects on everyday functioning and quality of life (Marder *et al.* 2000).

Investigations into the psychiatric functioning in prediagnosed HD have yielded equivocal results. Some have found that individuals with the gene expansion for HD have higher levels of psychological distress, irritability, and hostility (Berrios *et al.* 2002; Brandt *et al.* 1989; Kirkwood *et al.* 2002a). Others, however, have found no differences in individual symptoms (e.g., depression, anxiety) or prevalence of psychiatric disorders between gene expanded and nongene expanded individuals (Kirkwood *et al.* 2002b; Shiwach and Norbury 1994; Soliveri *et al.* 2002).

The lack of consistency in findings could be due to methodologic and conceptual differences in these studies. For example, with the exception of one study (Kirkwood *et al.* 2002b), the sample sizes of the at-risk, expansion-positive group was less than 20. Other methodologic weaknesses in these studies included poor sensitivity of assessment instruments to detect subtle psychiatric changes, measuring psychological functioning in close temporal proximity to genetic testing, unavailable or inadequate information about estimated time to diagnosis of HD, absence of collateral information, and the presence of concomitant motor, and/or cognitive symptoms in the participants, or a combination of these. Finally, and perhaps most importantly for these prediagnosed individuals, some of the studies used a categorical approach (i.e., the presence or absence of symptoms) to assessment. Berrios *et al.* (2001) has noted that a dimensional approach (i.e., the severity of symptoms) might be more sensitive to identify subtle psychiatric symptoms in expansion-positive, prediagnosed HD individuals.

In this study, we sought to improve on some of these methodologic and conceptual differences to assess the psychiatric status in prediagnosed HD. Using a large cohort from the Neurobiological Predictors of Huntington's Disease Onset Study (Predict−HD; Paulsen *et al.* 2006), it was hypothesized that prediagnosed, expansion-positive individuals would display heightened levels of psychiatric symptomatology compared to normative data and expansion-negative individuals. Using cross-sectional data, it was hypothesized that other markers of disease progression (e.g., subtle motor signs and decreasing striatal volume on imaging) would be related to increasing psychiatric symptomatology. An inverse relationship was expected between the psychiatric symptoms and functional status (i.e., activities of daily living). Lastly, it was hypothesized that participant and companion ratings of psychiatric symptoms for participants would be closely related.

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Methods and Materials

Participants

Participants included 681 individuals enrolled in the Predict-HD study. Additional details about the recruitment and characterization of the sample can be found in Paulsen *et al.* (2006). Briefly, this multicenter, longitudinal project recruited individuals who carried the expanded CAG HD gene but were not diagnosed for HD. All individuals in the study knew they were at risk for HD because of their family histories, and all had undergone genetic testing before and independent of participation in Predict-HD. The "expansion-positive" participants (n = 589) were predominantly female (64%) and Caucasian (97%). Some of these "expansion-positive" individuals were displaying equivocal or very mild motor, cognitive, or psychiatric symptoms, but study examiners (i.e., primarily neurologists or other movement-disorder specialists) did not diagnose them as having HD at the time of enrollment in the study. Predict-HD has also recruited a smaller sample (n = 92) of "expansion-negative" (i.e., at risk by having a parent with HD but who did not carry the expanded HD gene) individuals, which serves as a control group. These "expansion-negative" participants were also recruited from HD support and advocacy groups and are predominantly blood relatives of the expansion-positive participants. Demographic and disease-related information is presented in Table 1.

Procedures

Following informed consent, all participants were evaluated with the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group 1996), neuropsychological testing, psychiatric assessments, and magnetic resonance imaging. Included in the psychiatric assessments was the Symptom Checklist 90 Revised (SCL-90-R; Derogatis 1975), which was completed by participants and their companions. Each companion was instructed to complete the SCL-90-R based on his or her view of the participant's functioning at that time. Thirty-six expansion-positive participants did not have companion-provided collateral ratings.

Measures

The SCL-90-R is a 90-item self-report symptom inventory designed to reflect patterns of current psychological symptoms. Each item is rated on a 5-point scale, from 1 = *not at all* to 5 = *extremely.* The measure yields three global indices of distress (Global Severity Index [GSI], Positive Symptom Total [PST], Positive Symptom Distress Index [PSDI]) and nine primary symptom dimensions (Somatization [SOM], Obsessive–Compulsive [O-C], Interpersonal Sensitivity [I-S], Depression [DEP], Anxiety [ANX], Hostility [HOS], Phobic Anxiety [PHOB], Paranoid Ideation [PAR], and Psychoticism [PSY]). Normative data are available for gender and patient status (inpatient, outpatient, nonpatient) that results in T scores, which have a mean of 50 (SD = 10).

The UHDRS is a standardized clinical rating scale that assesses four components of HD: motor function, cognition, behavior, and functional abilities. A neurologist examined the participant's individual motor signs (e.g., bradykinesia, chorea, dysarthria) and then determined an overall confidence level that the participant had HD. This diagnostic confidence level ranges from 0 (*normal*) to 4 (*motor abnormalities that are unequivocal signs of HD*), with intermediate values representing nonspecific motor abnormalities (1), motor abnormalities that may be signs of HD (2), or motor abnormalities that are likely signs of HD (3). Other measures used in the Predict-HD study are reviewed in Paulsen *et al.* (2006). For the purposes of our study, only the Total Motor and the Total Functional Capacity scores of the UHDRS were used. Briefly, the Total Motor score is the sum of the ratings across 31 motor items (e.g., ocular pursuit, finger taps, chorea), and ranges from 0 to 124, with higher scores indicating more impaired motor functioning. The Total Functional Capacity score (Shoulson *et al.* 1989) quantifies a participant's ability to perform both basic and instrumental activities of daily living, which is derived from reports of the participant and his/her companion, and ranges from 0 to 13, with higher scores indicating more intact functioning. Several other markers of disease progression were assessed: total volumes of the striatum, calculated from magnetic resonance imaging data; CAG repeat length; and Digit Symbol scores. One final marker of disease progression is predicted years to onset of HD (Langbehn *et al.* 2004), which uses CAG repeat length and current age to estimate the number of years to diagnosis of HD. Although actual diagnosis of HD by a physician is complicated by a variety of factors, including the physician's own threshold for making this clinical decision, this formula was developed using thousands of actual cases of HD diagnosis, which presumably considers some of these complexities. Addi-

Table 1. Demographic Information

	Expansion-Negative	Expansion-Positive Dx Confid = 0	Expansion-Positive Dx Confid = 1	Expansion-Positive Dx Confid = 2	Expansion-Positive Dx Confid = 3
n	92	212	260	84	33
Age (years)	43.7 (10.0)	39.8 (9.6)[a]	41.2 (9.4)	43.8 (10.0)	44.58 (10.6)
Gender (F/M)	64/28	134/78	169/91	50/34	22/11
Education (years)	14.7 (2.4)	14.6 (2.3)	14.4 (2.5)	14.4 (2.6)	14.2 (3.1)
CAG Length	20.0 (3.4)[a]	42.3 (.2)[a]	42.6 (2.5)[a]	42.4 (2.6)[a]	43.9 (4.3)
Predicted Years to Onset	n/a	15.7 (7.2)[a]	13.9 (6.9)[a]	13.2 (6.5)[a]	9.0 (3.4)
Total Motor	2.3 (2.6)[a]	1.2 (1.7)[a]	5.7 (3.4)[a]	10.3 (5.1)[a]	16.6 (7.5)
Total Functional Capacity	13.0 (.1)[a]	12.9 (.4)[a]	12.7 (1.1)	12.6 (.9)	12.5 (1.1)
Total Striatal Volume (cc)	15.4 (2.8)[a]	14.4 (2.3)[a]	14.4 (2.6)[a]	13.3 (2.6)	11.9 (2.3)
Digit Symbol (number correct)	53.9 (8.4)[a]	54.8 (10.3)[a]	49.2 (11.0)[a]	46.8 (10.3)[a]	41.6 (11.9)
SCL-90-R GSI	47.5 (9.1)	50.5 (9.6)	54.1 (11.8)	52.2 (12.2)	55.3 (10.9)
SCL-90-R PST	48.1 (9.8)	50.8 (10.1)	53.9 (11.7)	51.9 (11.7)	54.3 (11.0)
SCL-90-R PSDI	45.9 (.8)	48.8 (7.5)	51.8 (9.4)	51.5 (9.7)	55.3 (7.9)

Means (and SD) are presented unless otherwise noted. Dx Confid, diagnostic confidence level from Unified Huntington's Disease Rating Scale item 17; F, female; GSI, Global Severity Index; M, male; PSDI, Positive Symptom Distress Index; PST, Positive Symptom Total; SCL-90-R, Symptom Checklist 90—Revised.

[a] $p < .05$ in comparisons to Expansion-Positive Dx Confid = 3 group.