Specific Psychiatric Manifestations Among Preclinical Huntington Disease Mutation Carriers

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Background: Despite the need for significant clinical intervention owing to the psychiatric manifestations of Huntington disease (HD), there has been a paucity of studies specifically designed to evaluate these symptoms prior to disease diagnosis.

Objectives: To investigate whether the Symptom Check-list 90–Revised (SCL-90-R) and the Center for Epidemiological Studies Depression Scale can be used to detect psychiatric manifestations among preclinical mutation carriers with absent or minimal motor signs of HD.

Design, Setting, and Participants: Individuals at risk for or recently diagnosed with HD were recruited and then evaluated at Indiana University School of Medicine, Indianapolis. All of the subjects completed a uniform clinical evaluation that included the Unified Huntington's Disease Rating Scale–99, molecular testing to determine HD mutation status, the SCL-90-R, and the Center for Epidemiological Studies Depression Scale. The sample was divided into 4 study groups: 171 individuals in the non-mutation carrier group; 29 with minimal, if any, motor signs of HD in the preclinical mutation carrier group 1; 20 with motor abnormalities suggestive of HD in the preclinical mutation carrier group 2; and 34 in the manifest HD group.

Main Outcome Measures: Scores on the SCL-90-R and Center for Epidemiological Studies Depression Scale were compared.

Results: Five SCL-90-R symptom dimensions (obsessive-compulsive, interpersonal sensitivity, anxiety, paranoid ideation, and psychoticism) demonstrated a significant group effect (P<.04). The preclinical mutation carrier group 2 and the manifest HD group scored significantly higher on all 5 dimensions as compared with the non-mutation carrier group. The preclinical mutation carrier group 2 scored significantly higher than the non-mutation carrier group for 3 of the SCL-90-R symptom dimensions (anxiety, paranoid ideation, and psychoticism). A significant group effect was found on the Center for Epidemiological Studies Depression Scale (P=.04). The frequency of depressive symptoms was significantly higher in the manifest HD group and the preclinical mutation carrier group 2 as compared with the non-mutation carrier group.

Conclusion: This study identified specific psychiatric symptom dimensions that differentiate nonmutation carriers from individuals in the early preclinical stages of HD who are either symptom free or have minor nonspecific motor abnormalities.

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HUNTINGTON DISEASE (HD) is an autosomal dominant, neurodegenerative condition caused by an expanded number of CAG repeats in the huntingtin gene on chromosome 4. Early in the progression of HD, motor changes include mild chorea, abnormal muscle stretch reflexes, and diminished rapid alternating movements.1-4 Cognitive manifestations early in disease progression have been described, and they primarily consist of abnormalities in information processing, cognitive flexibility, and memory retrieval.5,5,8 Individuals in early stages of HD are often reported to present with a variety of psychiatric manifestations including depression, anxiety, irritability, and apathy.5,14 It has been reported that 24% to 79% of patients with HD present with psychiatric symptoms as the first manifestation of disease.15

Although HD is characterized by this triad of symptoms, in clinical practice, patients are typically only diagnosed with HD once chorea is present and motor signs are prominent. Several studies1,6-18 of preclinical individuals suggest that subtle motor and/or cognitive signs can be detected in some individuals prior to clinical diagnosis; however, results have not been
uniform.\textsuperscript{19-23} Despite the need for significant clinical intervention owing to the psychiatric manifestations of HD, there has been a paucity of studies specifically designed to evaluate psychiatric manifestations prior to disease diagnosis. In a study with a limited sample of only 19 non-mutation carriers and 14 mutation carriers, Rosenberg et al\textsuperscript{24} used the Symptom Checklist 90–Revised (SCL-90-R) and found no differences between asymptomatic mutation carriers and nonmutation carriers on any of the 9 symptom dimensions. Other previous studies of early psychiatric manifestations in individuals at risk for HD were also limited by the small sample of preclinical gene carriers and, in some cases, by the lack of molecular testing to definitively determine the HD gene status.\textsuperscript{14,24-26}

This article investigates whether psychiatric manifestations are present prior to the onset of classical HD symptoms. For the purpose of the current study, the term psychiatric manifestations refers to emotional, behavioral, psychological, and psychiatric symptoms. Using the SCL-90-R and the Center for Epidemiological Studies Depression Scale (CES-D) instruments, we evaluated a sample of individuals at risk for HD. It was our hypothesis that specific dimensions from these instruments would allow us to identify psychiatric manifestations in preclinical mutation carriers.

**METHODS**

**PARTICIPANTS**

Study participants were recruited through the National Research Roster for Huntington Disease Patients and Families, a registry of families with HD who are interested in participating in research studies. The national sample consisted of 254 participants between the ages of 19 and 65 years who traveled to Indiana University, Indianapolis, to complete a study visit. All of the subjects had a parent with HD, and individuals diagnosed with HD within the past 2 years as well as those who were at risk for the disease were included. Participants were asked not to disclose their mutation status, if known, to study staff to ensure that the individuals administering the testing protocol were blind to the mutation status. This study was approved by the local institutional review board (Indiana University–Purdue University Indianapolis institutional review board study number 0109-12), and all of the participants gave their written informed consent.

**CLINICAL EVALUATION**

An experienced movement disorder neurologist (X.B. or J.W.) administered the motor portion of the Unified Huntington’s Disease Rating Scale–99 (UHDRS), a widely used, standardized clinical rating scale.\textsuperscript{27} The neurologist was aware that the participants were at risk for HD but was blinded to the results of all other assessments and was not aware of the results of molecular testing for the huntingtin mutation. Based on the results of the motor examination, the neurologist selected a confidence rating on a scale of 0 to 4 to represent the presence or absence of motor abnormalities and the likelihood that the presence of abnormalities was representative of HD. The ratings were defined as follows: 0, normal (no abnormalities); 1, nonspecific motor abnormalities (<50% confidence); 2, motor abnormalities that may be signs of HD (50%-89% confidence); 3, motor abnormalities that are likely signs of HD (90%-98% confidence); and 4, motor abnormalities that are unequivocal signs of HD (≥99% confidence).

The study visit also included the collection of information regarding medical history, current medications being used, and history of alcohol and recreational drug use. Participants were excluded from analyses if they reported a concurrent neurological illness or major psychiatric diagnosis such as schizophrenia or bipolar disorder. Also excluded were participants with self-reported current alcohol or drug abuse. Twenty-one percent of the study population was being treated with an antidepressant, antianxiety agent, antipsychotic, or mood stabilizer.

**MOLECULAR TESTING AND STUDY GROUP CLASSIFICATION**

The participants’ DNA was extracted from either a blood sample or a buccal swab using standard inorganic methods. A polymerase chain reaction–based test was performed to determine the number of CAG repeats in the huntingtin gene.\textsuperscript{28}

The study sample consisted of 4 groups that were assigned based on the combined results of the molecular testing and the diagnostic confidence level obtained from the UHDRS: (1) non-mutation carriers (NC group) (n=171), defined as individuals with 2 unexpanded HD alleles (<32 CAG repeats); (2) preclinical mutation carrier group 1 (PC1 group) (n=29), defined as individuals with an expanded HD gene (≥38 CAG repeats) who demonstrated no abnormalities or nonspecific motor abnormalities (the diagnostic confidence score was 0 or 1 on the UHDSS); (3) preclinical mutation carrier group 2 (PC2 group) (n=20), defined as individuals with an expanded HD gene (≥38 CAG repeats) who demonstrated motor abnormalities that may be or are likely signs of HD (the diagnostic confidence score was 2 or 3 on the UHDRS); and (4) the group with manifest HD (HD group) (n=34), defined as individuals with an expanded number of CAG repeats (≥38 CAG repeats) who demonstrated motor abnormalities that were unequivocal signs of HD (the diagnostic confidence score was 4 on the UHDRS).

**PSYCHIATRIC INSTRUMENTS AND TESTING PROTOCOL**

The SCL-90-R is a symptom inventory framed in a self-report format of 90 statements, and it requires a sixth-grade reading level. This inventory measures psychological symptom patterns of medical and psychiatric respondents as well as symptom patterns of individuals without psychiatric disturbance. Participants were asked to indicate their answer to the question “How much are you distressed by . . . .” on a 5-point scale for each of 90 statements. The scale ranged from 0, indicating not at all, to 4, indicating extremely. Each statement is assigned to 1 of 9 primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Because our adult, at-risk subjects were from a community-dwelling population, data from the nonpatient reference sample rather than the inpatient psychiatric, outpatient psychiatric, or adolescent nonpatient reference samples were used to produce sex-specific T scores (according to the SCL-90-R manual). These T scores were used in all of the statistical analyses.

The CES-D is a 20-item instrument commonly used in epidemiologic studies to measure clinical symptoms of depression.\textsuperscript{30} Scores range from 0 to 60, with a higher score indicating more depressive symptoms. Individuals in the general population have an average score of 9, and studies consistently cite scores of 16 or greater as demonstrating more depressive symptoms.\textsuperscript{30,31} The CES-D is appropriate for self-administration with items in easy-to-read language.\textsuperscript{30}
Comparisons were performed by analysis of variance. The hypothesis tested in this study was that the SCL-90-R and CES-D scores differ between the 4 subject groups. This hypothesis was examined using analysis of covariance that tested for a significant (P < .05) group effect. For those portions of the SCL-90-R and CES-D with significant study group effects, post hoc analyses were performed. Our primary analysis examined whether the HD and PC2 groups reported higher levels of psychiatric manifestations than the NC group. Our secondary analysis tested whether the PC1 group reported higher levels of psychiatric manifestations than the NC group. All of the post hoc analyses of the SCL-90-R symptom dimensions used 1-sided t tests to test whether the mutation carrier group had higher levels of psychiatric manifestations than the NC group. For the CES-D, pairwise comparisons of the HD, PC2, and PC1 groups with the NC group were performed using a series of χ² analyses.

Table 1. Sample Demographics*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HD (n = 34)</th>
<th>PC2 (n = 20)</th>
<th>PC1 (n = 29)</th>
<th>NC (n = 171)</th>
<th>P Value</th>
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<tr>
<td>Age, mean ± SD, y</td>
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<td>46 ± 12</td>
<td>46 ± 9</td>
<td>47 ± 10</td>
<td>.47</td>
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<td>Education, mean ± SD, y</td>
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<td>16 ± 2</td>
<td>16 ± 2</td>
<td>15 ± 3</td>
<td>.18</td>
</tr>
<tr>
<td>M/F, No.</td>
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<td>8/12</td>
<td>11/18</td>
<td>41/130</td>
<td>.11</td>
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<tr>
<td>White, %</td>
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<td>100</td>
<td>97</td>
<td>97</td>
<td>&gt; .99</td>
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<td>Non-Hispanic, %</td>
<td>97</td>
<td>100</td>
<td>97</td>
<td>97</td>
<td>&gt; .99</td>
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<tr>
<td>Right-handedness, %</td>
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<td>95</td>
<td>93</td>
<td>99</td>
<td>.89</td>
</tr>
<tr>
<td>UHDRS functional independence subscale score,</td>
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<td>98 (80)</td>
<td>100 (100)</td>
<td>100 (90)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>mean (minimum)</td>
<td></td>
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Abbreviations: HD, group with manifest Huntington disease; NC, nonmutation carrier group; PC1, preclinical mutation carrier group 1; PC2, preclinical mutation carrier group 2; UHDRS, Unified Huntington’s Disease Rating Scale—99.

*The male-female ratio, all percentages, and the UHDRS functional independence subscale score were evaluated by the Fisher exact test. All of the other comparisons were performed by analysis of variance.

Figure 1. Results from the Symptom Checklist 90–Revised. The means and SEs (error bars) for each of the 8 analyzed Symptom Checklist 90–Revised symptom dimensions are presented for the group with manifest Huntington disease (HD), preclinical mutation carrier group 2 (PC2), preclinical mutation carrier group 1 (PC1), and the nonmutation carrier group (NC). The level of significance for the study group classification using analysis of covariance is denoted. *P < .05. †P < .01. ‡P < .001. SOM indicates somatization; OC, obsessive-compulsive; INT, interpersonal sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PAR, paranoid ideation; and PSY, psychotism.

The participants were seated alone in a quiet room to complete the questionnaires. The questionnaires were briefly introduced by a trained study coordinator (J.M. or K.W.) and specific instructions were explained prior to administration. The test administrator was available to answer questions at all times. Both instruments were administered in paper-and-pencil format, and participants were given 30 minutes to complete the questionnaires.

STATISTICAL ANALYSIS

Sex and years of education were used as covariates for the SCL-90-R symptom dimensions. Age at testing was considered for use as a covariate but was not included in the final model because it was significant for only 1 symptom dimension. Initially, each symptom dimension was reviewed after computing regression residuals using sex and years of education in the model. All of the residuals were approximately normal, with the exception of phobic anxiety. Review of the phobic anxiety data indicated that 205 (81%) of the 254 respondents had a score of 0. Given the lack of variation in the distribution of results, the phobic anxiety symptom dimension was not included in further analyses. For the remaining 8 SCL-90-R dimensions, analysis of covariance models with sex and years of education as covariates were used to test for overall group effects.

In accord with its designed use, the CES-D scores were categorized into 2 groups: scores of 0 to 15 were considered normal, and scores of 16 or greater were considered to exhibit depressive symptoms. A categorical test of significance, the Cochran-Mantel-Haenszel test, controlling for sex and years of education was used to test for an association between the CES-D category and the subject’s group assignment.

A total of 254 subjects completed the SCL-90-R questionnaire and 247 completed all of the questions on the CES-D. Table 1 summarizes the demographic measures for the 4 study groups. There were no significant differences between groups on any of the demographic variables. As expected, there was a significant mean difference between groups on the UHDRS functional scale (P = .006).

Analysis of covariance revealed significant group effects for 5 of the 8 SCL-90-R symptom dimensions (obsessive-compulsive, P = .008; interpersonal sensitivity, P = .03; anxiety, P = .03; paranoid ideation, P = .04; and psychoticism, P < .001) (Figure 1). For these 5 dimensions, we then compared the HD and PC2 groups with the NC group (Table 2). For all 5 dimensions, the HD and PC2 groups reported significantly higher levels of symptoms than the NC group.
We sought to determine whether psychiatric manifestations were present prior to a diagnosis of HD. Using the SCL-90-R and the CES-D, we identified a set of specific psychiatric manifestations that were more prominent in the 2 preclinical HD groups (the PC2 and PC1 groups) compared with the NC group. These results suggest that some individuals in the preclinical stage of HD already have psychiatric manifestations.

All of the preclinical mutation carriers were examined by 1 of 2 trained movement disorder experts (X.B. or J.W.) who, based on their neurological evaluation, felt that the subjects did not have sufficient motor findings to warrant a diagnosis of HD. By separating the preclinical subjects into 2 groups based on their UHDRS diagnostic classification, we were able to identify psychiatric manifestations that may be associated with very early changes in the disease progression. Specifically, we found that the group with motor signs that are consistent with HD but not sufficient for diagnosis differed from controls in several psychiatric dimensions. Importantly, the scores of the PC1 group, those exhibiting no abnormalities or nonspecific motor abnormalities, differed from the NC group on only 3 SCL-90-R symptom dimensions, anxiety, paranoid ideation, and psychoticism. These results support our hypothesis that specific psychiatric manifestations are present very early in the progression of HD and that additional symptoms are manifested later in the progression.

Results from the limited number of previous studies that have examined psychiatric manifestations in preclinical gene carriers have been mixed. The current study has several strengths in testing whether psychiatric manifestations occur very early in disease progression. Unlike prior studies, we evaluated a large sample of individuals (n=254), used molecular testing to determine mutation status, and reduced the variation in the neurological evaluation by assessing study subjects using only 2 movement disorder specialists. A further strength of this study is the use of subjects who are all at risk for HD; thus, both the mutation carrier and nonmutation carrier groups come from families with HD and have similar environmental effects owing to the presence of family members with HD.

Despite these strengths, there are also several potential limitations to this study. First, 21% of the study population was being treated with an antidepressant, antianxiety agent, antipsychotic, or mood stabilizer. It is possible that the use of these agents may have markedly improved the psychiatric manifestations of individuals receiving these medications. Despite this potential loss of power, we still found higher rates of psychiatric manifestations in the preclinical groups. Second, each of the instruments included in this study uses self-reported responses to evaluate psychiatric manifestations. As a result, the responses may not be an accurate representation of psychiatric manifestations; rather, individuals at risk for HD may underreport or overreport the severity of their symptoms. Additionally, our analyses have shown that many symptoms were reported less frequently in those (all P < .05). A second series of post hoc comparisons compared the PC1 group with the NC group for the same 5 dimensions. Significant differences (all P < .03) were found for 3 of the comparisons, anxiety, paranoid ideation, and psychoticism. The PC2 group, which had significantly more specific motor abnormalities than the PC1 group, had higher scores than the PC1 group on all 8 symptom dimensions.

For the CES-D, subjects were classified as either normal (score < 16) or exhibiting a clinical elevation in depressive symptoms (score ≥ 16). Figure 2 depicts the proportion of individuals in each study group classified as exhibiting depressive symptoms. The proportion of individuals who scored higher than the clinical cutoff differed between the study groups (P = .04). Pairwise χ² comparisons indicated a higher proportion of individuals who scored higher than the clinical cutoff in the HD and PC2 groups as compared with the NC group (P = .01 and .03, respectively). The proportion of individuals with depressive symptoms in the PC1 group did not differ significantly from that in the NC group (P = .18).

COMMENT

We sought to determine whether psychiatric manifestations were present prior to a diagnosis of HD. Using the SCL-90-R and the CES-D, we identified a set of specific psychiatric manifestations that were more prominent in the 2 preclinical HD groups (the PC2 and PC1 groups) compared with the NC group. These results suggest that some individuals in the preclinical stage of HD already have psychiatric manifestations.

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diagnosed with HD. Therefore, a trend to underreport the severity of symptoms may increase in later stages of the disease manifestation. In spite of this possible limitation, we have still identified a number of different scales on which preclinical mutation carriers differ from the non-mutation carriers. Third, to avoid any potential source of bias, participants were specifically instructed not to inform the study coordinators if they had undergone presymptomatic mutation testing. Therefore, although we are aware that some participants have undergone such testing, we cannot estimate the frequency of presymptomatic testing in our sample. Similarly, we cannot estimate the possible effects of this knowledge on our study results for either the individuals found to carry the CAG expansion or those found not to be mutation carriers.

Fourth, our sample was an adult at-risk population. Given the age-at-onset distribution of HD and the age range of our study participants, it was to be expected that our sample would consist of a majority of nonmutation carriers. In fact, two thirds of our sample were nonmutation carriers. Therefore, the sample sizes in our 4 diagnostic groups are unequal, with the largest group of subjects being nonmutation carriers. This group inequality would only reduce the power to detect preclinical effects. Fifth, by dividing the 49 preclinical mutation carriers into 2 smaller groups (29 individuals in the PC1 group and 20 individuals in the PC2 group) to more efficiently test for differences at various stages in early disease progression, we have also limited our power to test for significant differences between the 2 preclinical groups.

Individuals may present with psychotic manifestations prior to a diagnosis of HD. Depression, anxiety, irritability, and apathy have all been described in the early progression of HD. Frontal-striatal brain circuits, affected early in HD, are known to be involved in emotional and psychiatric functioning. Furthermore, neuropsychiatric manifestations are common in other degenerative disorders and have been shown to be present in the prodromal phase of specific neurodegenerative disorders. There is also a great deal of interest in the role of neuropsychiatric manifestations and functional capacity. Some investigators suggest that behavioral disturbances, such as personality change, irritability, disinhibition, and obsessive-compulsive disorder, are the result of brain changes associated with HD and manifest prior to the onset of motor abnormalities. Longitudinal studies such as ours that examine the progression of psychiatric manifestations beginning in the preclinical period and continuing into symptomatic HD may offer important insights about associations between specific brain changes and psychiatric symptoms.

In summary, this study has identified a specific set of psychiatric symptoms from the SCL-90-R and the CES-D that demonstrate significant change early in the progression of HD, prior to the onset of involuntary movements. Several psychiatric domains were elevated in the PC2 group and fewer were elevated in the PC1 group, suggesting that some types of psychiatric manifestations increase as the disease progresses toward manifest HD. However, it is important to note that even among preclinical individuals with little, if any, abnormality in the UHDRS motor examination results, we were still able to identify significant differences between this group and the NC group on 3 symptom dimensions of the SCL-90-R. These results suggest that specific psychiatric manifestations are an early finding of HD and may be an important target for future therapeutic interventions. Because psychiatric manifestations have the potential to impair the successful functioning of individuals at risk for HD, we suggest that more attention should be focused on characterizing psychiatric manifestations in the preclinical period of HD. Raising physician awareness of this early presentation may help to ensure that more aggressive therapeutic interventions to decrease or ameliorate psychiatric manifestations of HD are implemented.

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Author Contributions: Mss Marshall and White contributed equally to the manuscript. Dr Foroud had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Stout, Gray, and Foroud. Acquisition of data: Marshall, White, Beristain, Wojcieszek, and Foroud. Analysis and interpretation of data: Weaver, Flury Wetherill, Hui, Stout, Johnson, Gray, Wojcieszek, and Foroud. Drafting of the manuscript: Marshall, White, Flury Wetherill, Wojcieszek, and Foroud. Critical revision of the manuscript for important intellectual content: Marshall, White, Weaver, Flury Wetherill, Hui, Stout, Johnson, Beristain, Gray, Wojcieszek, and Foroud. Statistical analysis: Weaver, Flury Wetherill, Hui, Stout, Johnson, and Foroud. Obtained funding: Hui, Gray, and Foroud. Administrative, technical, and material support: Marshall, White, Beristain, Gray, Wojcieszek, and Foroud. Study supervision: Stout, Wojcieszek, and Foroud.

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