Progression of Symptoms in the Early and Middle Stages of Huntington Disease

Sandra Close Kirkwood, PhD; Jessica L. Su, MS; P. Michael Conneally, PhD; Tatiana Foroud, PhD

Objective: To delineate the progression of symptoms in the early and middle stages of Huntington disease (HD).

Design: A survey of individuals with symptomatic HD completed by a first-degree relative.

Setting: The National Huntington Disease Research Roster for Patients and Families, Indianapolis, Ind.

Participants: The survey included 1238 individuals with a minimum of a 6-year history of symptomatic HD.

Measures: Participating families completed a series of surveys, including the Affected Individual Questionnaire, which consists of 19 physical, emotional, and cognitive signs commonly thought to occur during disease progression. The respondent indicates if each of the symptoms occurred and, if so, at what time during the course of the disease: (1) within 1 year, (2) within 2 to 5 years, (3) within 6 to 10 years, (4) after more than 10 years, (5) has not occurred, or (6) “don’t know.”

Results: The symptoms are categorized into 6 onset periods. Involuntary movements are grouped alone as the earliest reported symptom. The second group is composed entirely of mental and emotional symptoms, including sadness, depression, and difficult to get along with. The third group includes clumsiness, sexual problems, lack of motivation, and suspiciousness/paranoia. As the disease progresses, a variety of motor, emotional/behavioral, and cognitive symptoms are experienced, including unsteadiness, trouble holding onto things, trouble walking, changes in sleeping patterns, delusions and hallucinations, intellectual decline, and memory loss. With the approach of late-stage HD, affected individuals begin to experience speech difficulty and weight loss. In the late stage, patients lose bowel and bladder control.

Conclusions: Even though the symptoms of HD are fairly well characterized, their progression, especially in the early and middle stages, remains uncertain. Clarification of the disease progression is vital to improved understanding of the pathogenesis of HD and to the evaluation of therapeutic agents that are designed to slow the progression of disease. The results of this study assist in clarifying HD progression from early involuntary movements and emotional changes to more overt motor symptoms and difficulty with activities of daily living.

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Huntington disease (HD), an autosomal dominant neurodegenerative disorder, is caused by an increased number of trinucleotide repeats in the coding region of the gene for Huntington disease. A negative correlation has been observed between the number of repeats and the age at onset of disease. Individuals with the largest number of repeats (>50) usually develop the disease in childhood and have a different presentation from those with the more common adult onset, resulting in the categorization of HD into 2 phenotypes: juvenile and adult onset. Approximately 7% of individuals with HD become symptomatic before 20 years of age and are classified as having juvenile HD. The most common presenting symptoms of juvenile HD are an awkward gait and slowed speech due to abnormalities of voluntary movement, including bradykinesia and rigidity. In the initial stages of disease progression, performance on simple cognitive tests is good unless the task is timed. Later in the progression of juvenile HD, seizures may develop and the voluntary movement abnormalities and cognitive decline worsen.

Adult-onset HD is characterized by a triad of progressive motor, cognitive, and emotional symptoms. Although the course of disease is variable, the sequence...
PARTICIPANTS AND METHODS

The sample was obtained through the National Research Roster for Huntington Disease Patients and Families at Indiana University (HD Roster), Indianapolis. The HD Roster has been collecting data for more than 20 years and is the largest available database of detailed information on families affected by HD. Although DNA analysis has not been completed on the HD Roster families, detailed family and clinical information is available. Participating HD Roster families are asked to complete a series of surveys, including the Affected Individual Questionnaire (AQ). The AQ is typically completed by a close relative of the affected individual, such as a spouse or child, and provides information on the demographics, age at onset, initial symptoms, disease progression, treatment, living situation, and clinical, social, and psychiatric histories. One portion of the AQ includes 2 tables listing a total of 19 physical and mental signs commonly thought to occur during disease progression (Table 1). The respondent indicates if each of the symptoms occurred and, if so, how long after the onset of disease the symptoms appeared: (1) within 1 year, (2) within 2 to 5 years, (3) within 6 to 10 years, (4) after more than 10 years, (5) has not occurred, or (6) “don’t know.”

PARTICIPANTS

The HD Roster includes AQ data from 2545 individuals. However, many of these individuals were diagnosed as having HD very recently and thus have not experienced the majority of the symptoms that we sought to delineate. Consequently, to describe the typical HD prodrome, our sample included only those individuals (1) who had disease onset at least 6 years before questionnaire completion; (2) who had the typical adult-onset choreic form of HD; and (3) whose AQ was completed by a first-degree relative or spouse of a first-degree relative to ensure that the respondent was sufficiently familiar with the patient’s symptoms to accurately delineate disease progression. As the clinical presentation for juvenile- and adult-onset HD is quite distinct, those individuals whose disease onset with HD symptoms occurred at younger than 20 years or whose diagnosis of rigid or juvenile-onset HD was confirmed by medical record (n=75) were excluded before analysis. Owing to the known cognitive decline with manifest HD, particularly among individuals who are at least 6 years beyond their reported age at onset, participants who completed their own questionnaires (n=90) were excluded before analysis. A total of 1238 individuals were included in the final analysis of the AQ data. These data include 600 individuals whose disease onset occurred more than 10 years before completion of the AQ.

STATISTICAL ANALYSIS

To delineate the progression of the 19 physical and mental signs of HD, the proportional odds model, a regression model for ordinal data, was used to analyze the AQ data. For each of the individual 19 signs, the 3 responses were (1) within 1 year, (2) within 2 to 5 years, and (3) within 6 to 10 years. The goal of these analyses was to delineate the progression of symptoms in the early and middle stages of HD, as the progression of symptoms in these stages remains ambiguous, while the disease progression in the later stages of HD is fairly well characterized. Also, requiring the participants to have manifest HD for more than 10 years dramatically reduces the sample size; therefore, the responses for the category of after more than 10 years were not used in the analysis. For each symptom, the model uses the number of responses in each of the 3 periods to calculate a cumulative probability of the symptom occurring. A logarithmic function of these cumulative probabilities is used to calculate slope estimates for each individual symptom, which can then be compared directly with one another, allowing the ordering of the symptoms. Larger slope estimates imply an earlier onset, while the symptoms with smaller slope estimates occur later in disease progression.

Although the results of the analysis order each of the 19 symptoms, these symptoms may actually occur simultaneously or at about the same time. Also, variability in symptom onset was observed between individuals. A modified Bonferroni multiple comparisons test was used to determine which of the 19 slope estimates were significantly different from each other, thereby grouping symptoms that develop at approximately the same time in disease progression.

In addition to motor abnormalities, cognitive decline and personality changes are part of the HD phenotype, although their sequence in the typical HD prodrome is uncertain. Although the cumulative evidence suggests that subtle cognitive changes occur before the onset of motor abnormalities, the literature contains many conflicting reports regarding the presence of cognitive deficits preceding the onset of motor deficits. Early in the disease process, the cognitive deficits are focal, with relatively intact language function and deficits in executive system functioning, short-term memory, and visuospatial functioning. Later in the disease process, the cognitive deficits progress to more widespread global subcortical dementia. A change in personality is recognized as one of the cardinal features of HD, the behavioral abnormalities are heterogeneous and without clear progression. Depression, apathy, irritability, impulsiveness, and...
antisocial and suicidal behavior are inconsistently demonstrated by individuals with HD. Depression and apathy may occur several years before the motor abnormalities begin, indicating that they may be an integral part of the disease process rather than a response to the debilitation that occurs during disease progression. Research regarding the relationship between central nervous system deterioration and the personality changes and the timing of their onset is ambiguous.

While the symptom presentation in the early and middle stages of disease progression is variable and not well characterized, HD in the late stages is fairly well delineated. Individuals with late-stage HD are functionally incapacitated, with global dementia and severe limitations in voluntary movement. The later stages are characterized by bradykinesia, spasticity, dysarthria, dysphagia, incontinence, and dependence in the activities of daily living.

Further characterization of disease progression in the early and middle stages of HD is vital to improved understanding of the underlying pathogenesis of disease and may provide important insight regarding mechanistic pathways through which novel therapeutics might be targeted. Also, delineation of the typical disease progression may assist in the evaluations of therapeutic agents during clinical trials. The following analysis was designed to delineate the progression of the motor, cognitive, and emotional symptoms in the early and middle stages of the typical HD prodrome using the largest reported sample of individuals affected with HD to date.

### RESULTS

The demographics for the 1238 participants are presented in Table 2. The participants were primarily white (98.1%), with similar numbers of male (n=607) and female (n=631) participants. The mean ± SD age at onset reported by the participants (41.4 ± 10.2 years) is similar to the average age at onset reported in the literature for adult-onset HD.

The individual responses for each category of the AQ are presented in Table 3. As described in the “Participants and Methods” section, the results are based on the cumulative probabilities for 3 response groups according to when the symptoms occurred during the course of the disease: (1) within 1 year, (2) within 2 to 5 years, and (3) within 6 to 10 years. The data were found to be consistent with the use of a proportional odds model and were therefore entered into a proportional odds model. Estimates were calculated, and based on these estimates, the symptoms were ordered. After the use of the proportional odds model, the modified Bonferroni multiple comparisons test was used to categorize the symptoms into 6 onset periods termed initial, early, early-middle, middle, middle-late, and late (Figure).

Voluntary movements were grouped alone as the earliest reported symptom. The second group of symptoms, which occur early in disease progression, after involuntary movements, consists of a group of clinical findings that are composed entirely of mental and emotional symptoms, including sadness, depression, and difficult to get along with. The majority of individuals in the sample reported these symptoms as occurring less than 5 years into disease progression, equally represented between the within-1-year category and the 2-to-5-year category. The early-middle symptoms include clumsiness, lack of motivation, sexual problems, and suspiciousness/paranoia. A larger percentage of individuals reported these symptoms as occurring 2 to 5 years after HD onset. As the disease progresses, a variety of motor, emotional/behavioral, and cognitive symptoms are experienced. These middle-disease symptoms include motor difficulties that interfere with functional activities, such as unsteadiness, trouble holding onto things, and trouble walking. In addition to the motor symptoms, affected individuals experience changes in sleeping patterns and delusions or hallucinations. Cognition also begins to deteriorate, leading to intellectual decline and memory loss. The symptoms in this middle-disease range were reported to develop in the 2- to 5-year and 6- to 10-year range in approximately equal percentages. In the middle- to late-disease stage, affected individuals begin to experience speech difficulty and weight loss. These symptoms typically occurred 6 to 10 years after disease onset, but in many individuals were delayed until more than 10 years after onset. Late in the disease, individuals lose bowel and bladder control (Table 3).

**Table 1. Signs of Huntington Disease (HD) as Indicated on Affected Individual Questionnaire**

<table>
<thead>
<tr>
<th>Physical Signs of HD</th>
<th>Mental and Emotional Signs of HD</th>
</tr>
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<tbody>
<tr>
<td>Involuntary movements</td>
<td>Sadness</td>
</tr>
<tr>
<td>Trouble walking</td>
<td>Depression</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>Lack of motivation</td>
</tr>
<tr>
<td>Unsteadiness, imbalance</td>
<td>Difficulty to get along with</td>
</tr>
<tr>
<td>Trouble holding objects</td>
<td>Sexual problems</td>
</tr>
<tr>
<td>Speech difficulty</td>
<td>Memory loss</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Intellectual decline</td>
</tr>
<tr>
<td>Difficulty with bladder control</td>
<td>Delusions or hallucinations</td>
</tr>
<tr>
<td>Difficulty with bowel control</td>
<td>Suspiciousness, paranoia</td>
</tr>
<tr>
<td>Changes in sleeping patterns</td>
<td></td>
</tr>
</tbody>
</table>

*See “Participants and Methods” section for further explanation of the questionnaire.

**Table 2. Demographics for the 1238 Participants With HD**

<table>
<thead>
<tr>
<th>Relationship of AQ</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondent to Participant</td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>449 (36.3)</td>
</tr>
<tr>
<td>Daughter</td>
<td>421 (34.0)</td>
</tr>
<tr>
<td>Son</td>
<td>131 (10.6)</td>
</tr>
<tr>
<td>Sister</td>
<td>79 (6.4)</td>
</tr>
<tr>
<td>Mother</td>
<td>44 (3.6)</td>
</tr>
<tr>
<td>Brother</td>
<td>37 (3.0)</td>
</tr>
<tr>
<td>Daughter-in-law</td>
<td>27 (2.2)</td>
</tr>
<tr>
<td>Ex-spouse</td>
<td>24 (1.9)</td>
</tr>
<tr>
<td>Sister-in-law</td>
<td>19 (1.5)</td>
</tr>
<tr>
<td>Father</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Brother-in-law</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

*HD indicates Huntington disease; AQ, Affected Individual Questionnaire.*
Even though the symptoms that occur with HD are fairly well characterized, the progression of symptoms, especially in the early and middle stages, remains uncertain. Clarification of the sequence of symptom presentation is useful in determining the efficacy of therapeutic agents that are designed to delay the progression of symptoms.
and helpful when counseling families and mildly affected individuals. The literature contains conflicting reports indicating that, in some instances, emotional and cognitive symptoms precede the onset of motor symptoms, while others report chorea as the presenting symptom.\(^5\) The current sample, the largest reported sample of individuals affected with HD, helps to clarify the typical progression of symptoms. According to our analyses, involuntary movements and behavioral symptoms such as sadness, depression, and irritability characterize the first year after disease onset in some individuals, while others begin experiencing these symptoms 2 to 5 years after onset. Following these initial personality changes, approximately 2 to 5 years after the onset of HD, the affected individuals experience additional emotional symptoms, such as suspicion, lack of motivation, changes in sleeping patterns, and sexual problems, along with worsening motor control, leading to clumsiness. The cognitive decline in this sample is reported to occur after these personality changes and concomitant with further motor decline in the middle stage of disease progression. The symptoms that occur later in disease progression are, as expected, speech difficulty, weight loss, and incontinence.

Previous studies have suggested that HD presentation may not be homogeneous and that although the majority of cases may begin with motor disturbance, a subset of individuals may have a period of cognitive or emotional difficulties before the onset of motor abnormalities. To determine if our sample was heterogeneous, the data reported by individuals who stated that they had experienced cognitive or emotional symptoms in the first year were examined. In addition to the examination of frequency data, the proportional odds model was rerun. Similar patterns in symptom presentation were observed for all subgroups, and there was no evidence supporting heterogeneous disease progression early in HD.

In our previous analyses of presymptomatic gene carriers, subtle cognitive deficits were found before the onset of obvious motor abnormalities on clinical examination.\(^1,2,14\) This finding of involuntary movements as the initial symptom is not necessarily contradictory to these previous findings.\(^1,2,14\) The cognitive deficits we observed were subtle using sensitive neuropsychological tests and thus may not be obvious to affected individuals or family members. Thus, cognitive deficits might be reported only in the later stages of disease as global dementia worsens and the deficits interfere with daily activities.

The response rate was good for all symptoms except the more personal ones: sexual problems, change in sleeping patterns, and delusions and hallucinations (Table 3). The response rate for these more personal symptoms would be expected to be lower, as relatives rather than the participants completed the surveys. Also, since the participants were required to be a minimum of 6 years from disease onset, some symptoms that are expected to begin very late in the disease, such as weight loss, speech difficulty, and bowel and bladder problems, have not yet been observed by many participants. Therefore, the data collected on these late-onset symptoms show a large percentage of responses indicating that the affected individual does not have the symptom, when the symptom simply may not have developed yet. These factors could lead to a misleading representation of disease progression through our questionnaire method. However, by collecting these data from a variety of relatives, most with intimate association with the patient’s disease, we hope to have reduced the impact of nonresponsiveness and lack of awareness of particular symptoms.

In addition, greater variability in the response data was introduced through the collection method, since the sequence of symptom appearance was obtained through family report and not through direct clinical examination. Data collected through repeated examinations presymptomatically and throughout disease progression would result in more accurate data. However, longitudinal data on such a large sample of individuals with HD are not currently available, and our sample has provided important clinical information. The size of the sample allows us to make generalizations regarding the typical HD prodrome. The progression of HD reported herein provides the clinician with the general disease progression as observed by individuals affected with HD and their family members. This information can be used when counseling individuals and families regarding the expected progression of HD. Also, this sample confirms the importance of careful assessment by the clinician to fully evaluate disease symptom and progression. To evaluate the efficacy of therapeutic agents that are designed to delay or prevent HD progression, measures that are sensitive to motor and cognitive function and behavior abnormalities that are specific to HD must be used in the clinical setting.

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Corresponding author and reprints: Sandra Close Kirkwood, PhD, Department of Medical and Molecular Genetics, Indiana University School of Medicine, 975 W Walnut St IB 130, Indianapolis, IN 46202 (e-mail: sclosch@iupui.edu).

REFERENCES