Dystonia-Predominant Adult-Onset Huntington Disease

Association Between Motor Phenotype and Age of Onset in Adults

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Background: In juvenile Huntington disease (HD), dystonia as well as parkinsonism and eye movement abnormalities may be the predominant motor signs rather than chorea. Several patients have come to our attention with adult-onset HD in whom there is prominent dystonia and minimal chorea (ie, an adult-onset form of HD that resembles juvenile HD).

Objectives: To estimate the prevalence of these cases of dystonia-predominant HD in a clinic and to study the relationship between the motor phenotype and age of onset in HD.

Methods: The Unified Huntington’s Disease Rating Scale (UHDRS) was administered to 127 subjects during their initial visit to the Huntington’s Disease Center at the New York State Psychiatric Institute, where dystonia, chorea, bradykinesia, rigidity, and eye movements were rated. The dystonia score was the mean UHDRS rating of dystonia in 5 body regions; the chorea score, the mean rating of chorea in 7 regions; the bradykinesia score, the mean rating of axial and limb bradykinesia; the rigidity score, the mean rating of rigidity in both arms; and the eye movement score, the mean rating of ocular pursuit, saccade initiation, and velocity. Dystonia-predominant HD was defined by the severity of dystonia relative to the severity of chorea.

Results: Fifteen (11.8%) of 127 subjects had dystonia-predominant HD. Age of onset correlated negatively ($r = -0.22, P = .02$) with the dystonia score divided by the chorea score and negatively ($r = -0.28, P = .002$) with the severity of dystonia, bradykinesia, and eye movement abnormalities relative to chorea (ie, $[(\text{dystonia score} + \text{bradykinesia score} + \text{eye movement score})/3] - \text{chorea score}$), suggesting that subjects with younger ages of onset had more severe dystonia, bradykinesia, and eye movement abnormalities relative to chorea.

Conclusions: Cases of adult-onset HD with prominent dystonia and a paucity of chorea may represent 1 in 8 cases in specialty clinics. Age of onset was clearly associated with the motor phenotype. A younger age of onset was associated with more severe dystonia, bradykinesia, and eye movement abnormalities relative to chorea, supporting the notion that in adult-onset HD, the motor phenotype forms a continuum with respect to age of onset.

Arch Neurol. 2000;57:1326-1330

ORIGINAL CONTRIBUTION

From the Gertrude H. Sergievsky Center (Drs Louis, Anderson, and Marder and Ms Thorne) and the Department of Neurology (Drs Louis and Marder and Ms Moskowitz), College of Physicians and Surgeons, Columbia University, New York, NY.
SUBJECTS AND METHODS

SUBJECTS AND SETTING

Subjects consisted of all of the patients with HD who were attending the Huntington’s Disease Center at the New York State Psychiatric Institute in New York City, NY. Subjects were initially evaluated between January 1994 and April 1999.

The diagnosis of HD was made by either of 2 neurologists (E.D.L. and K.M.) based on their evaluations of the following clinical features: presence of chorea, motor impersistence, abnormal eye movements, psychiatric symptoms and signs, cognitive impairment, family history, and medical history (with the exclusion, when appropriate, of other causes, such as hyperthyroidism, neuroacanthocytosis, and systemic lupus). All subjects were aware of their diagnoses. CAG repeat lengths were not obtained routinely.

As part of their initial clinic appointment, all subjects underwent assessment with the Unified Huntington’s Disease Rating Scale (UHDRS). The reliability of the UHDRS has been demonstrated. The UHDRS included a medical history form (which asked for the subjects’ demographic data, initial symptoms, and duration of the disease); a motor skills assessment form (which rated the subjects’ vertical and horizontal eye movements, as well as the severity of chorea, dystonia, rigidity, and bradykinesia); a record of medications form (in which the subjects were asked the names and dosages of their medications); and a total functional capacity score (range, 0 [completely dependent] to 13 [normal]).

DEFINITIONS

For each subject, a mean score was calculated for each item in the UHDRS motor assessment form by summing the score on n items and then dividing by n. The mean score always ranged from 0 to 4. For example, the dystonia score (range, 0-4) was calculated by summing the 5 UHDRS ratings and dividing by 5. Each of the 5 summed ratings was a 0-to-4 rating of dystonia in one region of the body (trunk, right arm, left arm, right leg, and left leg). The chorea score (range, 0-4) was the sum of the 7 UHDRS ratings of chorea (face, oral, trunk, and each limb) divided by 7. The bradykinesia score (range, 0-4) was the sum of 5 UHDRS bradykinesia ratings (axial bradykinesia and limb bradykinesia during finger taps and pronation-supination in each arm) divided by 5. The rigidity score (range, 0-4) was the sum of 2 UHDRS ratings (tone in each arm) divided by 2. The eye movement score (range, 0-4) was the sum of 6 UHDRS ratings (vertical and horizontal ocular pursuit, saccade initiation, and saccade velocity) divided by 6.

The 3 indices of the relative involvement of motor signs included the dystonia score divided by the chorea score; the dystonia score minus the chorea score; and [(dystonia score + bradykinesia score + eye movement score)/3] – chorea score. The latter index was derived in order to simultaneously assess motor signs that are reportedly more prominent (dystonia, bradykinesia, and eye movement abnormalities) and those that are less prominent (chorea) in juvenile HD. The value of ½ was used to apply a proportional weight to the combination of the 3 signs that are reportedly more prominent in juvenile HD relative to the 1 sign (chorea) that is less prominent.

Subjects with dystonia-predominant HD had to fulfill all 4 of the following inclusion criteria: (1) The subject’s dystonia score divided by the subject’s chorea score was greater than 1. (2) The subject’s dystonia score minus the subject’s chorea score was greater than 0. (3) The subject’s dystonia score was greater than the group’s mean dystonia score. (4) The subject’s chorea score was less than the group’s mean chorea score.

The goal of the criteria was to select subjects who, at their initial evaluation, had a motor phenotype in which dystonia rather than chorea predominated. The rationale for criterion 1 was to select those subjects whose dystonia was at least as severe as their chorea. Criterion 2 was important for subjects who had no chorea (chorea score, 0) because for these subjects, a ratio of the dystonia score to the chorea score (criterion 1) could not be calculated. Criterion 3 was important because some subjects fulfilled criterion 1 and 2 because they had more dystonia than chorea but had low scores for both (eg, dystonia score, 0.3; chorea score, 0.2). Criterion 4 was important because some subjects fulfilled criteria 1 and 2 because they had more dystonia than chorea, but had high scores for both (eg, dystonia score, 2.5; chorea score, 2.4).

STATISTICAL ANALYSIS

Only data from the subjects’ initial clinic evaluation were analyzed. Disease duration was based on the raters’ estimate of the duration of symptoms rather than on the diagnosis of HD, which often occurs several years after the onset of symptoms.

Correlations between continuous variables (eg, age of onset and chorea score) were assessed using Pearson correlation coefficients. In order to control for the effects of disease duration when examining the associations between age of onset and motor signs in HD, multiple linear regression models were used (in which the outcome variable was [(dystonia score + bradykinesia score + eye movement score)/3] – chorea score) with independent variables, including age of onset, duration of disease, sex, ethnicity, whether the subject was taking either a dopamine-depleting agent (reserpine or tetrabenazine) or dopamine receptor-blocking agent, whether the subject was taking another medication that reduces the severity of chorea (eg, benzodiazepine), whether or not the subject’s parent was affected (mother vs father) with the disease, and the total functional capacity score.

predominant HD, 24 (18.9%) fulfilled 3 or more criteria, and 33 (26.0%) fulfilled 2 or more criteria. The 3 subjects with onset before age 20 years fulfilled only 1, 2, and 3 of the criteria. The 15 subjects who fulfilled all 4 criteria had a mean age of 44.2 years (range, 33-65 years), a mean age of onset of 37.3 years (range, 26.8-58.8 years), and a mean duration of 7.2 years (range, 0.03-14.7 years). Thirteen (87%) were female.

Of the 15 subjects, 5 were currently taking a dopamine-depleting agent, a dopamine receptor–blocking agent, or both.
tency to 100 mg of chlorpromazine). Among those sub-
equivalents (eg, 5 mg of haloperidol has equivalent po-
stant medications were converted into chlorpromazine
(medications per subject was the same for subjects with
gest that those with dystonia-predominant HD were not
predominant HD (32.1% [36/112] who were taking these
reduced the severity of their chorea; however, this was
predominant HD were taking medications that could have
agent, or another agent that reduces the severity of cho-
reya. The 15 subjects had a mean dystonia score of 1.67
(range, 1.0-2.6, compared with a mean dystonia score of
increased in severity: chorea, dystonia, bradykinesia,
as disease duration increased, each of these signs
increased in severity: chorea, dystonia, bradykinesia,
and eye movement abnormalities (Table 2). However,
there were no correlations between disease duration and
any of the 3 indices of the relative involvement of
motor signs, because for each of these indices, both the
numerator and the denominator increased with disease
duration.

Table 2. Correlations Between Disease Duration,
Age of Onset, and Motor Signs in Subjects
With Huntington Disease*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Disease Duration</th>
<th>Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rP</td>
<td>rP</td>
</tr>
<tr>
<td>Chorea score</td>
<td>0.36 &lt;.001</td>
<td>0.18 .06</td>
</tr>
<tr>
<td>Dystonia score</td>
<td>0.37 &lt;.001</td>
<td>0.17 .08</td>
</tr>
<tr>
<td>Bradykinesia score</td>
<td>0.39 &lt;.001</td>
<td>0.11 .26</td>
</tr>
<tr>
<td>Rigidity score</td>
<td>0.41 &lt;.001</td>
<td>0.08 .39</td>
</tr>
<tr>
<td>Eye movement score</td>
<td>0.33 &lt;.001</td>
<td>0.19 .04</td>
</tr>
<tr>
<td>Dystonia score/chorea score</td>
<td>0.03 .73</td>
<td>0.22 .02</td>
</tr>
<tr>
<td>Dystonia score – chorea score</td>
<td>0.03 .70</td>
<td>0.19 .05</td>
</tr>
</tbody>
</table>
| [(Dystonia score + bradykinesia
  score + eye movement
  score)/3] – chorea score       | 0.05 .57         | 0.28 .002    |

* Bold indicates significant at P < .05.
† The sample size of 124 excludes 3 subjects with age of onset before 20 years.
‡ Pearson correlation coefficients.

As disease duration increased, each of these signs
increased in severity: chorea, dystonia, bradykinesia,
and eye movement abnormalities (Table 2). However,
there were no correlations between disease duration and
any of the 3 indices of the relative involvement of
motor signs, because for each of these indices, both the
numerator and the denominator increased with disease
duration.

There was a correlation between the severity of cho-
reya and the age of onset of HD (ie, the younger the age
of onset, the less severe the chorea, with borderline
significance [P = .06]) (Table 2). There was a negative
association between the age of onset and the severity of
dystonia, bradykinesia, and eye movement abnormali-
ties (ie, the younger the age of onset, the more severe
the dystonia, bradykinesia, and eye movement abnormali-
ties, although the correlation was significant only for eye
movement abnormalities [P = .04]). In addition, there were
correlations between the age of onset and all 3 of the
indices of the relative involvement of motor signs, suggest-
ing that the younger the age of onset, the more severe
the dystonia, bradykinesia, and eye movement abnormali-
ties relative to the severity of chorea (Table 2 and
Figure).

In linear regression models, the following variables
were associated with the outcome variable (which was
more highly treated than those without dystonia-
predominant HD.

ASSOCIATION BETWEEN
DISEASE DURATION, AGE OF ONSET,
AND MOTOR SIGNS IN HD

Five (33%) of the subjects with dystonia-
predominant HD were taking medications that could have
reduced the severity of their chorea; however, this was
similar to the percentage of subjects without dystonia-
predominant HD (32.1% [36/112]) who were taking these
medications (χ² = 0.01, P = .93). The mean number of such
medications per subject was the same for subjects with
(0.33) vs without (0.47) dystonia-predominant HD
(t = 0.61, P = .54). Doses of dopamine receptor antago-
nist medications were converted into chlorpromazine
equivalents (eg, 5 mg of haloperidol has equivalent po-
tency to 100 mg of chlorpromazine). Among those sub-
jects taking dopamine receptor antagonist medications,
there was no difference between those with (mean
chlorpromazine-equivalent units, 93.3 mg) vs without
(mean chlorpromazine-equivalent units, 140.5 mg) dystonia-
predominant HD (F₁,23 = 0.68; P = .42). These data sug-

Table 1. Baseline Demographic and Clinical Characteristics
of 127 Subjects With Huntington Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Subjects†</th>
<th>Disease Duration</th>
<th>Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rP</td>
<td>rP</td>
<td></td>
</tr>
<tr>
<td>Age, mean/median/range, y</td>
<td>48.4/48/22-78</td>
<td>-0.62 .00</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (58.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>53 (41.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>105 (82.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.8)</td>
<td></td>
<td></td>
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<tr>
<td>Parent affected, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>53 (41.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>49 (38.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (19.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, y*</td>
<td>7.19 (0.33-20.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset, y*</td>
<td>41.82 (14.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently taking a dopamine-depleting agent</td>
<td>41 (32.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(reserpine, tetrabenazine), dopamine receptor–blocking agent, or another agent that reduces the severity of chorea (eg, benzodiazepine), No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total functional capacity score*</td>
<td>8.24 (0-14.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia score*</td>
<td>0.97 (0-3.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea score*</td>
<td>1.58 (0-4.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinesia score*</td>
<td>1.48 (0-4.00)</td>
<td></td>
<td></td>
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<tr>
<td>Rigidity score*</td>
<td>0.46 (0-3.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye movement score*</td>
<td>1.40 (0-4.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia score/chorea score*</td>
<td>0.76 (0-9.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia score – chorea score*</td>
<td>−0.62 (−3.60 to 2.49)</td>
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</tr>
</tbody>
</table>

* Values are mean (range).
† The sample size of 124 excludes 3 subjects with age of onset before 20 years.
While prominent dystonia, parkinsonism (rigidity and bradykinesia), and eye movement abnormalities commonly accompany the juvenile form of HD, these features may be present in a proportion of adult-onset HD cases as well, and some authors have suggested that the phenotypic distinction between the juvenile and adult-onset forms of HD is somewhat arbitrary. We report that approximately 12% of subjects with adult-onset HD had a phenotype that is characterized by prominent dystonia with a relative paucity of chorea. These individuals also had prominent bradykinesia and eye movement abnormalities, but none had seizures, which are sometimes a feature of juvenile-onset HD.

Much of the literature documents the presence of “rigidity” in both juvenile HD cases and adult cases with the Westphal variant. When a subject has dystonia as well as paratonia, both conditions that increase limb tone, it may be difficult to be certain of the presence of a third cause of hypertonia, namely extrapyramidal rigidity. While the tendency has been to combine all of these different movements under the rubric rigidity, the precise representation of each of these different movements is not clear. A strength of the UHDRS is that it asks the rater to try to separate these different motor phenomena and to rate them separately.

One of our most striking findings is that the age of onset in these predominantly adult-onset cases of HD was clearly associated with the motor phenotype, with a younger age of onset associated with more severe dystonia, bradykinesia, and eye movement abnormalities relative to chorea, supporting the notion that in adult-onset HD, the motor phenotype forms a continuum with respect to age of onset. Previous investigators have suggested an association between the age of onset and motor manifestations in juvenile cases. Whether the association between age of onset and motor phenotype in HD is a function of CAG repeat length is not clear and needs to be further investigated. Siesling et al., based on a retrospective review of practitioners’ clinical records of 53 juvenile HD cases, and van Dijk et al., based on a review of 195 cases of juvenile HD in the literature, divided cases into rigid vs choreatic types, and noted that the mean age of onset among those with rigidity was significantly lower than among those with chorea. Farrer and Conneally, examining data from a questionnaire administered to 28 patients with juvenile HD, noted that those who reported rigidity had a significantly earlier age of onset than did those who reported chorea. One of the strengths of the present study is that the motor manifestations were assessed using a reliable instrument (the UHDRS). Using this instrument, dystonia, rigidity, and other motor phenomena were rated separately, and each was rated in multiple body areas using a graded scale (0-4) rather than just “present” or “absent.”

We found that being female was associated with a predominance of dystonia, bradykinesia, and eye movement abnormalities relative to chorea. Age of onset did not differ between males and females (41.2 years for males and 42.6 years for females; \( t = 0.58, P = .56 \)). We are not aware of a previous report of this finding, and the explanation is not clear. Our sample was clinic based, and these findings should be reassessed in larger samples, such as the Venezuela Collaborative Huntington’s Disease Project or the Huntington Study Group.

This study had limitations. First, subjects were not evaluated at the time of disease onset, but rather at the time of their initial visit. The average subject had had HD for 7.19 years at the initial evaluation. It is possible that the association between dystonia, chorea, and age of onset may have been an artifact of disease duration. However, we did not find an association between disease duration and any of the indices of the relative involvement of motor signs (Table 2). To further examine this issue, we adjusted for any effects of disease duration in our linear regression models. Second, we realize that our definition of dystonia-predominant HD was somewhat arbitrary, as dystonia and chorea form a continuum. We chose 4 rather than only 1 or 2 inclusion criteria so that our prevalence estimate would be conservative. Third, CAG repeat lengths were not obtained routinely; our findings should be extended in a study in which CAG repeat lengths are obtained routinely. This would provide definitive confirmation of clinical diagnoses and would allow one to determine whether the association between age of onset and motor manifestations is a function of CAG repeat length. Another issue is that age of onset was
estimated retrospectively, and a prospective study design would have allowed us to make a more valid determination of age of onset. Finally, our sample was clinic based; our findings should be confirmed using large samples.

Accepted for publication October 13, 1999.

This study was supported by grants NS01863 (Dr Louis), NS36519 (Dr Marder), NS36630 (Dr Marder), RR00645 (Dr Marder), and AG10963 (Dr Marder) from the National Institutes of Health, Bethesda, Md; by a Paul Beeson Physician Faculty Scholars in Aging Research Award, Alliance for Aging Research, Washington, DC (Dr Louis); by the Huntington's Disease Society of America, New York, NY (Dr Marder); and by the Parkinson's Disease Foundation, New York (Dr Marder).

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REFERENCES