Severity of Cognitive Impairment in Juvenile and Late-Onset Huntington Disease

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Objectives: To compare the severity of cognitive impairment among groups of patients with different age ranges at the onset of Huntington disease (HD) and to evaluate the variable influence of motor and cognitive deficits on functional disability across different ages at the onset of HD.

Design: Cross-sectional multidisciplinary evaluation of patients referred to our institution for care related to a possible diagnosis of HD.

Setting: The Huntington disease program in the Departments of Neurology and Genetics at the Fundación Jiménez Díaz, Madrid, Spain.

Participants: Seventy-one patients with Huntington disease were classified into 3 groups depending on age at onset of motor symptoms: juvenile onset, 25 years of age or younger (group 1, n=15); adult onset, from 26 to 50 years (group 2, n=43); and late onset, 51 years or older (group 3, n=13). Age- and education-matched controls (n=50) were included to compare cognitive performance with patients in groups 1 and 3.

Measures: Cognitive evaluation encompassed a wide neuropsychological battery to assess global cognitive functioning and visuospatial, prefrontal, and memory functions. Clinical data included motor and functional variables measured by using the Unified Huntington’s Disease Rating Scale. Genetic analysis determined the number of CAG trinucleotide repeats.

Results: Patients in group 1 scored 2.9 points and patients in group 3 scored 4.2 points below their respective controls on the Mini-Mental State Examination. Patients in groups 1 and 3 were similarly impaired in verbal memory. Visual function was much more impaired in patients in group 3, and prefrontal functions were slightly worse in patients in group 1. Cognitive scores were correlated only with time of evolution for patients in group 2. Functional scores were not significantly different among the 3 groups, but 11 (85%) of the patients in group 3 were in stage I or II vs 10 (67%) of the patients in group 1. Total functional capacity correlated better with the Mini-Mental State Examination score for patients in group 3 and with motor deficits (akinesia) and prefrontal dysfunction for patients in group 1. The mean±SD CAG repeat length decreased from 59.9±12.6 for patients in group 1 to 46.2±3.5 for patients in group 2 and 41.7±2.6 for patients in group 3. Longer CAG repeats in the HD study population correlated with akinetic features but not with cognitive performance.

Conclusions: Despite the much greater genetic defect, cognitive status is slightly better preserved in patients with juvenile-onset HD. Cognitive impairment in patients with juvenile- and late-onset HD differs in the severity of visual and prefrontal deficits. Functional disability in patients with late-onset HD depends more on global cognitive status, while in patients with juvenile-onset HD, it is conditioned more by motor deficits and prefrontal dysfunction.

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HUNTINGTON disease (HD) is an inherited neurodegenerative disorder characterized by the presence of movement disorders, cognitive decline, and behavioral disturbances.1-3 The age at onset is usually between the third and fifth decades, but symptoms may develop from the first to the ninth decades. Much of the variation in age at onset seems to be accounted for by the number of trinucleotide repeats within the HD gene, with longer CAG repeats implying earlier onset of the disease.6-10 Yet, the amount of genetic defect does not seem to influence other clinical features, such as the nature of symptoms at onset,7,8,10 and there are contradictory reports about the influence of the genetic defect on the rate of progression of the disease.11,12

Patients with onset of HD at juvenile ages have the longest CAG repeats and frequently have a rigid akinetic syndrome rather than the typical choreic movements.13-15 The severity of neuropathological involvement and the degree of functional disability are classically re-
PARTICIPANTS AND METHODS

PARTICIPANTS

We studied 71 patients with a clinical diagnosis of HD who received care in our institution from June 1, 1992, to December 31, 1996. Ten other patients were not included because they did not complete the study, occasionally because of lack of consent, but mainly because of advanced disease with severe disability. The 71 patients included belonged to 47 kindreds. They were subdivided into groups according to age at onset of motor symptoms: group 1, juvenile onset, 25 years of age or younger (n=15); group 2, adult onset, 26 to 50 years (n=43); and group 3, late onset, 51 years or older (n=13). We extended the classic limit of 20 years for juvenile-onset HD because in our study population, 6 of 8 patients with disease onset between 20 and 25 years of age, had a rigid akinetic syndrome, which more closely resembled the juvenile phenotype than the adult, or classic, phenotype of HD. The limit for late-onset HD was defined according to Myers et al. All patients excluded from the study had adult-onset HD. The age at onset was stated according to the relatives’ report, after a careful anamnesis searching for the first motor symptoms or signs of the disease in the lives of the patients. The time of evolution was counted in years from the time of the first evidence of motor symptoms.

Demographic data for the patients are summarized in Table 1. Education was recorded according to a 5-point scale indicating the level of schooling completed: 1, primary school; 2, secondary school (until 14 years of age); 3, high school (until 18 years of age); 4, college diploma; and 5, university degree. Patients in groups 1 and 3 belonged to 12 kindreds each, allowing enough variability to avoid characteristics based only on intrafamilial features.

Two control groups matched for age and educational level were included to compare cognitive performance with groups 1 and 3. Juvenile controls (group 4) included 22 subjects, mean±SD age, 22.9±4.6 years (range, 17-32 years); 18 (81%) had completed secondary or high school. Group 5, the control group for group 3, comprised 28 subjects, mean±SD age, 63.1±5.5 years (range, 52-72 years); 20 (71.5%) had completed secondary or high school.

CLINICAL EVALUATION

Motor impairment was assessed by using the Unified Huntington’s Disease Rating Scale, in which 0 indicates no impairment and 4 indicates severe impairment. We considered the following variables: finger taps (manual akinesia), arm rigidity, and axial bradykinesia, dystonia, and chorea. Chorea is rated from 0 to +4 in 7 body regions (ie, face, bucco-oralolingual, trunk, and each extremity), giving a total score of 0 to 28 points, and dystonia is rated in 5 regions (ie, trunk and each extremity), giving a total score of 0 to 20 points. Motor evaluation was conducted by 2 experienced neurologists (R.S.P. and P.J.G.R.) who shared the same criteria in the rating, 0 to 4.

Functional status was rated according to the Total Functional Capacity (TFC) score, which ranges from 0 (severely impaired) to 13 (normal) and assesses a patient’s capacity in relevant functional domains including employability, financial tasks, domestic responsibilities, and self-care skills. The stage of illness, rated from 1 to 6 according to the criteria of Shoulson and Fahn, was based on the following TFC scores: 1, 11 to 13; II, 7 to 10; III, 3 to 6; IV, 1 to 2; and V, 0.

GENETIC ANALYSIS

Molecular analysis was performed on genomic DNA isolated from peripheral lymphocytes. Amplification of CAG repeats was performed by using primers designed by Riess et al; polymerase chain reactions were performed with an end-labeled primer, and the products were separated in a sequencing gel (8%). Alleles were identified by sizing relative to an M13 sequencing ladder. The analysis confirmed the diagnosis in more than 38 CAG repeats in the IT15 gene on chromosome 4 in all patients in groups 1 through 3 in the present study.

NEUROPSYCHOLOGICAL ASSESSMENT

We selected a wide battery of neuropsychological tests emphasizing the functions reported to be most affected in HD, such as prefrontal, visuospatial, and memory tasks. One neuropsychologist (A.B.) evaluated all patients by using the following tests: Mini-Mental State Examination (MMSE); digit span (forward and backward); Symbol Digit Modalities Test; Verbal fluency (1 category and 1 letter); copy the Rey Complex Figure; immediate and delayed recall of the Rey Complex Figure; Hooper Visual Organization Test; Stroop test (age-corrected); Trail Making A and B Tests (time in seconds to complete each task, with a maximum of 10 minutes allowed); California Verbal Learning Test (items learned at the last trial, free [ie, without any help or clue] short- and long-term recall, and percentage of recognition).

To simplify analysis and to define profiles of functional impairment, test scores evaluating related functions were grouped in a single factor by principal-component factor analysis (Table 2). The functions measured in each factor and the tests used are listed in Table 2 along with the correlation coefficients, the percentage of variance, and the eigenvalues. The MMSE score, as a measure of overall cognitive status, was considered independently. A global principal-component factor analysis using an interest correlation matrix resulted in the same 3 functional factors accounting for 76.4% of the overall variance, but individual factor analysis was preferred to minimize the effect of missing values. For each participant, unweighted standardized scores were computed for each factor. For all factors, higher scores indicated better performance.

ANALYSIS OF THE DATA

First, the comparison of genetic, motor, and functional variables among groups 1, 2, and 3 was done by 1-way analysis of variance (ANOVA) and post hoc Student-Newman-Keuls comparison tests. Second, cognitive performance of groups 1, 2, and 3, together with groups 4 and 5, also was compared by using 1-way ANOVA and post hoc tests. Differences were considered significant at P<.05. The distribution of participants in each group according to sex, educational level, and stage of the disease (patients only) was evaluated by using the χ2 test. Finally, we considered the influence of motor and cognitive variables on functional impairment by groups by using Pearson correlation coefficients. Data are given as mean±SD unless otherwise indicated.
ported as much greater in patients with juvenile-onset HD. Patients with late-onset HD may have CAG repeats in the lower pathological range, and their clinical picture is similar to that of patients with adult-onset HD, but they have less functional impairment and evolution of the disease is more benign. In addition to the differences related to age at onset, including differences in symptoms, rate of disease progression, functional impairment, and the neuropathological lesion, patients with juvenile-onset HD are believed to have a severe cognitive impairment, while patients with late-onset HD have minimal mental deterioration. Major cognitive disabilities in adult HD include attentional deficits, problems with sequencing and planning, disorders in new learning and retrieval of information, and visuospatial dysfunction. However, to our knowledge, there are no reports of formal cognitive evaluations of patients with HD in whom onset was at extreme age ranges.

As part of a prospective multicenter study of HD, we evaluated a large population by using an extensive cognitive protocol. A preliminary examination of the data suggested that the performance of the youngest group of patients, who had predominant rigid akinetic features, was much better than expected. On the contrary, patients who were the oldest at onset seemed to have very poor scores. Therefore, the first objective of this study was to compare the severity of cognitive impairment among groups of patients with different age ranges at the onset of HD, with a focus on the comparison between patients with juvenile-onset HD and patients with late-onset HD. Because age differences are relevant to cognitive performance, the severity of cognitive deterioration was evaluated by comparing the oldest and youngest groups with age-matched controls.

A review of the literature suggested that the severity of cognitive impairment in patients with juvenile- or late-onset HD had been determined more on the basis of functional capacity scores, report of symptoms, or both, than on formal cognitive assessments. Because functional capability for the activities of daily living depends on motor and cognitive functioning, and the motor profile is strikingly different for patients with juvenile-onset HD, it was possible that the influence of motor and cognitive features on functional scores could be different depending on age. The influence of symptoms on functional capacity also is likely to vary depending on the daily activity requirements, which are probably quite different for a 20-year-old than for a 60-year-old person. We hypothesized that functional disability of patients with juvenile-onset HD could depend more on their motor disturbance than on their cognitive status, if the latter was truly demonstrated as better preserved than expected. The second aim of this study was to evaluate the variable influence of motor and cognitive deficits on functional disability across different ages at the onset of HD.

**RESULTS**

**MOTOR AND FUNCTIONAL ASSESSMENT**

Table 3 summarizes motor and functional scores and genetic data for groups 1, 2, and 3. The mean time of
Table 3. Genetic Data and Motor and Functional Scores*

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 15)</th>
<th>Group 2 (n = 43)</th>
<th>Group 3 (n = 13)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of evolution, y</td>
<td>4.8 ± 2.6</td>
<td>7.0 ± 5.0</td>
<td>5.0 ± 3.9</td>
<td>1.80</td>
</tr>
<tr>
<td>Affected parent (M/P)</td>
<td>1/14</td>
<td>22/21</td>
<td>5/6†</td>
<td></td>
</tr>
<tr>
<td>No. of CAG repeats</td>
<td>59.9 ± 12.6§§</td>
<td>46.2 ± 3.5§</td>
<td>41.7 ± 2.6</td>
<td>31.53</td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Manual akinesia</td>
<td>2.3 ± 0.6§§</td>
<td>1.9 ± 1.0</td>
<td>1.3 ± 0.7</td>
<td>4.31</td>
</tr>
<tr>
<td>Rigidity</td>
<td>1.6 ± 0.7§§</td>
<td>0.8 ± 1.0</td>
<td>0.4 ± 0.5</td>
<td>7.60</td>
</tr>
<tr>
<td>Axial bradykinesia</td>
<td>2.7 ± 1.3§§</td>
<td>0.9 ± 1.1</td>
<td>0.8 ± 1.0</td>
<td>13.77</td>
</tr>
<tr>
<td>Chorea</td>
<td>4.9 ± 3.7§‡</td>
<td>12.0 ± 7.0</td>
<td>13.2 ± 4.0</td>
<td>8.52</td>
</tr>
<tr>
<td>Dystonia</td>
<td>5.2 ± 4.1§</td>
<td>2.7 ± 4.3</td>
<td>1.3 ± 1.9</td>
<td>3.17</td>
</tr>
<tr>
<td>TFC</td>
<td>8.6 ± 3.0</td>
<td>8.2 ± 3.9</td>
<td>9.8 ± 2.6</td>
<td>0.93</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD. M/P indicates maternal/paternal; TFC, Total Functional Capacity scale; and ANOVA, analysis of variance. See the footnote for Table 1 for a description of the groups. Ellipses indicate not applicable.
†Unknown in 2 cases.
‡P <.05 vs group 2, post hoc comparison.
§P <.05 vs group 3, post hoc comparison.

Figure 1. A negative correlation was found between the length of the CAG trinucleotide repeat and the age at onset (r = −0.48; P < .001 for the Huntington disease [HD] study population). The correlation has its highest significance within group 1 and decreases to nonsignificant values for group 3. Group 1 patients (n = 15) had juvenile-onset (25 years old or younger) HD; group 2 (n = 43), adult-onset (26-50 years old) HD; and group 3 (n = 13), late-onset (51 years or older) HD.

**GENETIC ANALYSIS**

The number of CAG repeats in the HD study population was 48.2 ± 8.8 (range, 39.0-90.0). There was a significant gradient in the CAG repeat length (Table 3) from group 1 (mean, 59.9 repeats; range, 46.0-90.0 repeats) to group 2 (mean 46.2 repeats; range, 41.0-56.0 repeats), and group 3 (mean, 41.7 repeats; range, 39.0-47.0 repeats), with overlapping ranges. Longer CAG repeats in the HD study population were correlated with younger age at onset (r = −0.48; P < .001). However, the strongest correlation between age at onset and number of repeats was in group 1, and the correlation decreased steadily in groups 2 and 3 (Figure 1). Longer CAG repeats in the HD study population also correlated with increased akinesia (r = 0.35; P < .05) and bradykinesia (r = 0.57; P < .001). Figure 2 shows the correlation of the number of repeats with motor and functional scores by groups. The sex of the transmitting parent was balanced in groups 1 and 2, but was mainly by the paternal line within group 1 (P < .05).

**COGNITIVE PERFORMANCE**

Results for groups 1 through 5 are summarized in Table 4 and shown in Figure 3. Distribution by sex and educational level was not significantly different among the groups (for sex, χ² = 4.5; P = .34; and for educational level, χ² = 21.0; P = .18). In general, the cognitive scores for the groups showed the following declining profile: group 4, group 5, group 1, group 2, and group 3.

For the groups with HD, group 1 performed significantly better than group 2 on the MMSE and in the verbal memory factor and significantly better than group 3 on the MMSE and in the visual and verbal memory factors. Group 2 performed better than group 3 only in the visual factor. Groups 1 and 3 differed significantly from groups 4 and 5, respectively, in all cognitive variables (ie, MMSE and visual, prefrontal, and verbal memory factors). As shown in Figure 3, the lower verbal memory scores compared with the scores for the respective control groups was similar for group 1 (1.38 points lower;
95% confidence interval [CI], 1.05-1.70) and group 3 (1.36 points lower; 95% CI, 0.82-1.90). The difference for the visual factor was much greater for group 3 (1.67 points lower than group 5; 95% CI, 0.85-2.49) than for group 1 (0.83 points lower than group 4; 95% CI, 0.22-1.43). The difference for the prefrontal factor was slightly greater for group 1 (1.58 points lower than group 4; 95% CI, 1.10-2.07) than for group 3 (1.24 points lower than group 5; 95% CI, 0.65-1.84). For the MMSE, group 1 scores were 2.90 points lower (95% CI, 1.67-4.18) and group 3 scores 4.20 points lower (95% CI, 1.53-6.85) than groups 4 and 5, respectively.

In the HD study population, as well as in group 2, all factor scores were significantly correlated with the MMSE score (P<.005) and the time of evolution (P<.01) but not with the number of repeats. In group 1, the cognitive factors did not correlate with the MMSE score or with the time of evolution. Scores for the prefrontal factor were almost significantly correlated with the number of CAG repeats (r=−0.57, P=.06). For group 3, there were no significant correlations among cognitive factors, time of evolution, or number of repeats.

**CORRELATIONS WITH FUNCTIONAL DISABILITY**

The TFC score for all patients with HD, correlated well with time of evolution of the disease (r=−0.68, P<.001), with global cognitive status as assessed by the MMSE (r=0.49, P<.05), with prefrontal performance (r=0.76, P<.001), and the following motor variables: chorea (r=−0.59, P<.05), manual akinesia (r=−0.72, P=.001),
and axial bradykinesia ($r = -0.64$, $P = .005$). There was no significant correlation between TFC scores and age at onset.

Correlations between the TFC scores and the cognitive and motor variables for groups 1 and 3 are given in Table 5. In group 1, TFC scores, manual akinesia, axial bradykinesia, and prefrontal deficits were highly intercorrelated. However, in group 3, the TFC score was well correlated with the MMSE, but there were no significant correlations with the motor variables. The TFC score in group 2 correlated significantly with all motor and cognitive variables (the highest correlation with the TFC score was obtained with chorea, the MMSE score, and the prefrontal and verbal memory factors; data not shown).

In group 1, the TFC score correlated with number of CAG repeats ($r = -0.68$, $P < .01$) (Figure 2) but not with the time of evolution, while in groups 2 and 3, the TFC scores correlated strongly with the time of evolution ($r = -0.72$ and $r = -0.71$, respectively; $P < .01$ for both) but not with the repeat length.

### COMMENT

Before the availability of genetic analysis, several authors reported differences in motor symptoms and severity of HD depending on age at onset, emphasizing the different rate of clinical progression and the variable neuropsychological involvement. The length of the abnormal CAG repeat sequence has been implicated as the major determinant of age at onset, the degree of atrophy in the striatum, and the rate of clinical progression. The lengthiest repeats and, therefore, the earliest onset seem to be related to a more severe expression of the disease. A distinct motor profile is associated with juvenile-onset HD. However, to our knowledge, no studies have evaluated the severity of cognitive impairment at various age ranges through formal neuropsychological assessments and with appropriate controls. In the present study, we attempted to compare the severity of cognitive impairment among groups of patients with different age ranges at the onset of HD to evaluate the variable influence of motor and cognitive deficits on functional disability across different ages at the onset of HD. This was done in an attempt to determine whether the severity of cognitive deficits in juvenile and late-onset HD is in agreement with other clinical and genetic features.

Our cohort was suited to this study because it included patients in whom the onset of disease occurred at different ages and who belonged to enough kindreds to avoid conclusions based only on infrafamilial characteristics. Six of 8 patients who were between 20 and 25 years old at onset had a predominant rigid akinetic syndrome that more closely resembled the juvenile phenotype than the adult, or classic, HD phenotype, so the limit defining juvenile onset was extended to 25 years. Except for 1 case, all patients in group 1 had their first symptoms of the disease between 14 and 25 years of age. As reported by van Dijk et al., the distinction between juvenile- and adult-onset cases is more clear when the motor phenotype and the age at onset are considered than when only age at onset is considered. The cutoff point of 25 years of age permitted us to conduct a more coherent study relating severity of cognitive impairment to specific motor profiles. In fact, in their review of rigid akinetic forms of HD, Bittnender and Quadfasel reported a mean age at onset of 22.2 years in these forms of HD.

The mean time of evolution of the disease was similar for groups 1, 2, and 3. However, it is possible that these data would be more accurate for group 1 because the patients were likely to be under close scrutiny from parents or tutors, with more margin for error possible for groups 2 and 3. Several authors have reported a similar survival and rate of progression in patients with HD independent of age at onset, so it could be assumed that the 3 groups with HD were in a similar stage of disease evolution. Nevertheless, other studies have found a faster rate of progression in patients with juvenile-onset HD, which could mean that 5 years might be half of the evolution for a patient with juvenile-onset HD but just a third of the evolution for a patient with adult-onset HD. Even in this situation, the better cognitive preservation would be emphasized among patients with juvenile-onset HD, despite a greater genetic defect and a more advanced stage of the disease.

As previously described, the motor profile in juvenile-onset HD was characterized by a predominant rigid bradykinetic syndrome, with less chorea and more dystonia than adult-onset HD. In an opposite profile, as reported by Myers et al., late-onset HD more closely resembled adult-onset HD, as manifested by prominent choreic movements, with a slight trend in our data toward less rigid akinetic features. This distinction shown by the Unified Huntington’s Disease Rating Scale emphasizes the value of this simple scale from 0 to 4 when rating motor signs. It is unlikely that motor symptoms would have been substantially influenced by treatment in groups 1 and 3 because none of the patients had received neuroleptic drugs. At the time of the study, most patients were receiving only calcium antagonists, and only
a few in group 2 were receiving tetrabenazine to ameliorate chorea. It is also unlikely that treatment with calcium antagonists (eg, nicardipine hydrochloride) had substantially influenced the outcome of the cognitive evaluation.

Cognitive performance was globally deteriorated in patients with HD, in agreement with the findings of many previous studies.20-27 There was a steady decline in all neuropsychological scores from younger to older ages. That is, group 1 performed more successfully than groups 2 and 3 in most of the neuropsychological tasks. Group 2 had better scores than group 3, but only the visual factor was significantly worse for group 3. This age-related gradient resembled, but for some factors exceeded, the mild deterioration noted with aging among the healthy controls. A higher educational level could be expected for groups 2 and 3 than for group 1, because the onset of the disease interfered with education of patients in group 1. These differences in educational level may confound the comparison of cognitive performance among the groups with HD. However, the patients in group 3 who were oldest at disease onset did not finish high school or college because of socioeconomic limitations, while many patients in group 1, with onset of the disease at the end of the second decade of life, were able to complete high school.

More important than the comparison between juvenile- and late-onset HD was the magnitude of the differences between groups 1 and 3 and groups 4 and 5, their respective controls. Global cognitive status as measured by the MMSE was slightly more impaired for group 3 (ie, scores were 4.2 points below those for group 5) than for group 1 (scores were 2.9 points below those for group 4). Scores for the verbal memory factor were similar between groups 1 and 3 in relation to groups 4 and 5, respectively. Scores for the prefrontal factor, however, were slightly more impaired for patients in group 1, while scores for the visual factor were much worse for patients in group 3.

In general, cognitive performance was better preserved in group 1, except for functions in the prefrontal factor. This was the only cognitive measure in which patients in group 1 had a relatively greater deficit compared with group 4. Two of the tests included in this factor (Symbol Digit and Trail Making tests) involved motor performance, and the scores were probably adversely affected by the prominent rigid bradykinetic syndrome evident in patients in group 1. Many other variables in this factor did not require motor function (eg, verbal fluency, Stroop test, and digit span) but some were subjected to time constraints. We observed that patients in group 1 were relatively successful in the cognitive tasks but performed them slowly, regardless of the presence of motor involvement. It is possible that this relative prefrontal deficit reflects a global bradyphrenia in patients with juvenile-onset HD as the cognitive correlate of the motor bradykinetic syndrome. This is supported by the high correlation between both manual akinesia and axial bradykinesia and scores for the prefrontal factor.

Table 5. Correlation Coefficients Between Functional Disability and Motor and Cognitive Variables

<table>
<thead>
<tr>
<th>TFC</th>
<th>Chorea</th>
<th>Akinesia</th>
<th>Rigidity</th>
<th>Bradykinesia</th>
<th>Dystonia</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFC</td>
<td></td>
<td>.798†</td>
<td></td>
<td>−.781†</td>
<td></td>
<td>.713</td>
</tr>
<tr>
<td>Chorea</td>
<td>.584</td>
<td></td>
<td></td>
<td></td>
<td>.582</td>
<td></td>
</tr>
<tr>
<td>Akinesia</td>
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<td>.777†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td>.632</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td></td>
<td></td>
<td>.777†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.754</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>.642</td>
<td></td>
<td></td>
<td>−.601</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The upper right of the table corresponds to correlations within group 1, while the lower left refers to group 3. Only correlations with significance greater than \( P < .05 \) are shown. Akinesia refers to the extremities and bradykinesia refers to the trunk. TFC indicates Total Functional Capacity scale; MMSE, Mini-Mental State Examination; and ellipses, data not shown because \( P > .05 \). For a description of the groups, see the footnote for Table 1; for a description of the factors, see Table 2.

†\( P < .001 \).
ever, analysis of the neuropsychological data as global factors did not allow for further qualitative analysis of cognitive performance, for which an independent analysis of the tests would have been more appropriate. The relative cognitive preservation in younger patients suggests that they might benefit from special and continuous educational support.

The visual factor encompassed a visuoconstructive task, immediate and delayed visual memory, and visuospatial perception. Although the motor component is required to copy and, later on, reproduce by memory a complex figure, the tasks were not timed, and the imprecision of the drawing due to choreic movements was not penalized. The severe visual impairment in patients in group 3 was not likely due to primary visual problems, according to data from the anamnesis (the patients did not undergo a standardized ophthalmologic examination at the time of the study). Other causes, such as oculomotor impairment; high visual-association deficits; excessive, and, perhaps neglected, visual loss related to aging; or a combination of these factors, could contribute to the failure on tasks that were part of the visual factor.

Despite these distinct motor and cognitive features in patients in groups 1 and 3, no significant differences in functional capacity scores were found across the 3 groups with HD. There was an advantage for group 3 in the distribution according to the Shoulson and Fahn stages of the disease, with 11 (85%) of the patients in stages I or II vs 10 (67%) of the patients in group 1 in those stages. This distribution supports the classical idea of greater functional disability associated with juvenile HD. One important point is the difficulty of scoring the abilities of young patients by using the available functional scales and staging systems. Items such as occupation and management of finances could be difficult to apply to young adults who may have never achieved an independent life before the onset of their disease. Sometimes the score was determined by guessing rather than by a clear demonstration of the capacity. Our group of patients with juvenile-onset HD was studied at a mean of 23.7 years of age, and only 1 patient demonstrated full capacity for occupation and management of finances. However, several patients were considered able to perform low-skill jobs or manage finances with some assistance.

The correlation of the clinical deficits with functional scores was different across the groups. For group 2, all motor and cognitive variables were correlated significantly. For group 1, the TFC score was highly correlated with manual and axial bradykinesia and with the prefrontal factor, while for group 3, the TFC score correlated only with the MMSE score. It is surprising that in the light of the very low cognitive performance of group 3, the TFC score was slightly better than that for group 1. Two explanations can account for this. First, bradykinetic features are a major reason for disability among patients with HD (as seen in patients with juvenile-onset HD), which is not the case for patients with late-onset HD. Motor disability, produced by chorea, in patients in their sixties did not seem to handicap daily functioning to a great extent. Second, cognitive requirements for patients in group 3 were probably quite restricted. A routine and the simplification of daily living activities at these ages may mask a severe cognitive dysfunction and appear, instead, as an acceptable functional capacity. The contrary occurs at juvenile ages, when the requirements during a period of maximum intellectual and physical development are much higher for motor and cognitive capabilities. A determination of the deficits that most strongly condition functional disability at different ages may be useful for the selection of the most beneficial therapeutic strategies. Functional scores correlated with the time of evolution for patients with adult- and late-onset HD, but not for patients with juvenile-onset HD.

Finally, genetic definition of groups 1, 2, and 3 agreed with several previous reports that found a larger number of CAG repeats with earlier-onset HD. The number of repeats for group 1, 59.9±12.6, was almost 14 repeats more than for group 2, 46.2±3.5. Group 3 had a shorter range of repeats (41.7±2.6). James et al also found very short CAG repeats in patients who were older than 60 years at the onset of the disease. Repeat length ranges in groups 1, 2, and 3 greatly overlapped, with no clear cutoff points that would allow for a definite prediction of the age at onset of the disease. However, the data suggest that when the number of repeats is more than 55, a young onset of HD is likely, while for patients with 39 to 41 repeats, HD might not manifest until late in life. The greatest correlation with age at onset was within group 1, and the correlations were nonsignificant for group 3. For group 1, the disease was mainly inherited through the paternal line, as reported by multiple studies. For group 3, the sex of the transmitting parent was balanced, but unknown in 2 patients. However, we found no predominance for maternal inheritance as has been described in these cases.

In summary, patients in group 1 had the longest CAG repeat lengths and a motor disturbance characterized by rigid akinetic features. However, cognitive impairment was less significant than at other ages at onset, except for prefrontal dysfunction. Motor and prefrontal dysfunction strongly conditioned the TFC scores in this group. On the other hand, the inheritance of CAG repeats in the very low range was common in group 3. This late-onset HD more closely resembled adult-onset chorea in motor features and manifested with significant cognitive impairment, in particular severe visuospatial dysfunction. Functional capability in group 3 was more dependent on cognitive functioning than on motor performance.

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REFERENCES


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