

Cognitive and psychiatric characterization of patients with Huntington's disease and their at-risk relatives

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Abstract We examined cognitive and psychiatric disturbances in patients with Huntington's disease (HD) in comparison to at risk asymptomatic subjects. Cognitive and psychiatric scales and an HD motor scale were administered to 40 HD patients, 17 pre-symptomatic HD gene carriers (AR⁺) and 28 non gene carriers (AR⁻). HD patients did worse than AR⁺ and AR⁻ in all motor, cognitive and psychiatric measures, while AR⁺ and AR⁻ subjects did not differ between each other. HD patients had high scores for negative psychiatric symptoms, but there was no correlation between illness duration and psychiatric or cognitive performance. In HD, disease course and symptomatology are heterogeneous and negative psychiatric symptoms are common.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterised by motor, cognitive and psychiatric disturbances. Motor and cognitive impairment have been fairly extensively investigated, while behavioural and psychiatric aspects have been neglected. However, the latter have a major impact on the lives of patients and their relatives, and render disease management problematic. Psychiatric disturbances are particularly frequent (40% to 70%) at all disease stages [1]. Some studies indicate that psychiatric disturbances are often a prelude to the onset of chorea and cognitive decline [2]. However, this finding was not confirmed on pre-symptomatic gene mutation carriers, who as a group, did not have psychiatric or cognitive impairment [3].

The aim of this study was to examine cognitive and psychiatric disturbances in HD patients in comparison to a group of asymptomatic offspring of HD patients who were therefore at risk (AR) for the disease. We also sought correlations between motor, cognitive and behavioural alterations in patients with HD.

Patients and methods

We studied 85 adults (39 men) from 35 HD families: 40 HD patients (24 men) diagnosed from family history, chorea, or characteristic impairment of voluntary movement on the Quantified

Neurological Scale (QNE) for HD, and confirmed by the genetic test for HD; 17 asymptomatic at risk subjects (7 men) who tested positive for the pathological HD gene (AR⁺); and 28 asymptomatic at risk subjects (8 men) who tested negative (AR⁻).

The neuropsychological tests administered were the Mini Mental State Examination (MMSE) to assess global cognitive function; the Raven Progressive Matrices 1947 (PM47) to investigate deductive reasoning and visuo-perceptive ability; the Short Tale Test to assess long term verbal memory; the Visual Search Test which examines focused attention; the Benton Visual Orientation Line Test to assess orientation and spatial perception; the Verbal Fluency Test (phonemic) to assess strategic word searching and the Nelson simplified form of the Wisconsin Card Sorting Test to assess categorization and set shifting abilities. All except the Nelson Test – for which a correction is not available – were corrected for age and education.

The psychiatric scales were: the Brief Psychiatric Rating Scale (BPRS) a screening test for psychiatric disturbances; the Hamilton Anxiety Scale (HAM-A) which evaluates anxiety, the Hamilton Psychiatric Rating Scale for Depression (HAM-D) whose score is a combination of subjective depressive feelings and the examiner's judgement, the Scale for the Assessment of Positive Symptoms (SAPS) which quantifies positive schizophrenic symptoms (hallucinations, delusions, bizarre behaviour and disturbances of thought), the Scale for the Assessment of Negative Symptoms (SANS) which quantifies negative schizophrenic symptoms (emotional flatness, abulia, apathy, retiring social behaviour, impaired attention, etc).

The genetic test, performed in all subjects, determines the number of CAG repeats (pathological value >36) on the IT 15 gene of chromosome 4. The statistical tests used were one-way ANOVA with post-hoc Scheffé comparison as appropriate, and Pearson's correlation test.

Results

Patients with chorea were significantly older than the AR⁺ and AR⁻ subjects; mean duration of education was higher in the AR⁺ group. CAG expansion length did not differ between patients and AR⁺ subjects (Table 1).

As expected, patients did significantly worse than AR⁺ and AR⁻ in all cognitive tests ($p < 0.0001$). There was no significant difference in cognitive test scores between AR⁺ and AR⁻ subjects, although AR⁺ subjects' scores were consistently lower than those of AR⁻ subjects. Thirteen HD patients had a MMSE score below 24, indicating dementia, while none of the AR⁺ or AR⁻ subjects was demented.

Similarly, psychiatric scores were significantly worse in HD patients than AR⁺ and AR⁻ subjects. We considered a score of ≥ 17 as indicating definite depressive disturbance on the Hamilton depression scale; by this criterion nine HD patients and one AR⁺ subject had depression while none of the AR⁻ subjects was depressed. However, AR⁺ subjects had higher (but not significantly so) depression and anxiety scores than AR⁻ (Table 1).

Correlation analysis of severity of illness parameters (illness duration, QNE), psychiatric scales and cognitive tests in

Table 1 Demographic data and psychiatric scores in HD patients, at-risk carriers (AR⁺) and at-risk non carriers (AR⁻)

	HD (n=40)	AR ⁺ (n=17)	AR ⁻ (n=28)	<i>p</i>
Men, n (%)	24 (60)	7 (14)	8 (29)	–
Age, years	43.0 (11.7)	30.2 (7.2)	31.6 (12.3)	<0.0001*†
Education, years	9.3 (3.7)	12.7 (2.8)	10.7 (3.2)	<0.005‡
Illness duration, months	43.8 (24.2)	NA	–	
QNE score	31.7 (13.7)	0.9 (2.0)	0.5 (1.1)	<0.0001*†
CAG repeats, n	47.8 (5.0)	45.9 (4.6)	20.4 (4.3)	<0.0001*†
Psychiatric scale scores				
BPRS	31.0 (11.0)	24.1 (4.4)	20.6 (5.0)	<0.0001*†
HAM-D	11.4 (8.5)	5.8 (6.0)	1.7 (3.4)	<0.0001
HAM-D	9.6 (1.0)	6.2 (5.9)	3.3 (4.7)	0.0019
SANS	26.4 (25.5)	2.1 (5.6)	0.1 (0.4)	<0.0001
SAPS	3.1 (10.0)	0.3 (1.0)	0 (0)	>0.05

*HD vs. AR⁺; †HD vs. AR⁻; ‡AR⁺ vs. AR⁻

NA, not applicable

Numbers in brackets are standard deviations unless otherwise indicated

the HD group showed that QNE correlated with illness duration (0.58, $p < 0.001$), that psychiatric scale scores correlated among each other, and that the cognitive tests MMSE, Benton Test, Raven Test and Short Tale Test also inter-correlated. Severity of illness did not correlate with psychiatric or cognitive status. Length of CAG expansion did not correlate with cognitive performance, psychiatric scales or illness severity, but correlated inversely with age at disease onset (-0.75 , $p < 0.001$). In general the psychiatric scales did not correlate with cognitive tests except the Visual Search score that correlated significantly with depression score (-0.61 , $p < 0.001$) and negative schizophrenia symptoms score (-0.49 , $p < 0.01$). There were no correlations between negative and positive schizophrenia symptoms.

orbital, dorso-lateral and cingulate cortices – concerned with cognitive, affective and motivational aspects – are impaired [7]. The apathy may be the expression of an underlying affective disorder, or of an initial cognitive impairment starting as an attentional defect. Alternatively the attention deficit may be a consequence of the apathy. It is also possible that the nature of the apathetic disorder may vary with disease stage. Since our HD patients were all at an intermediate disease stage, it is necessary to investigate cognitive, psychiatric and behavioural modifications in HD patients with early and advanced illness in order to provide indications as to source of apathy in HD.

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Discussion

In AR⁺ subjects we found no cognitive or psychiatric alterations suggesting that disease onset might be occurring before the development of motor impairment. The most interesting findings concern HD patients. We found that psychiatric symptoms are prominent in HD, and combine with the usual motor and cognitive compromise to contribute to overall disability. The most frequent psychiatric problems were depression, anxiety and apathy, while positive symptoms such as delusions, hallucinations and mania were less frequent. The lack of correlation between illness severity, as evaluated by illness duration and motor compromise, and cognitive and psychiatric impairments indicates that disease course is not uniform in HD. In addition, and as reported previously [4–5], we found that the severity of the cognitive and behavioural disturbances were not related to GAG length.

It is noteworthy that apathy was frequent in our HD patients, and that negative psychiatric symptoms (including apathy) correlated with depression and lack of attention. These findings suggest that apathy may arise from a combination of cognitive, affective and motivational factors [6]. In HD the circuits joining the striatal structures to the fronto-

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