Higher Levels of Extroverted Hostility Detected in Gene Carriers at Risk for Huntington's Disease

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Background: Numerous retrospective studies have reported the presence of psychiatric disorders at the prodromal or early stages of Huntington's disease (HD). However, most of the studies comparing gene carriers with non-carriers before the clinical manifestation of the illness have failed to reveal differences in the psychiatric manifestation. The objective of the present study was to detect behavioral and psychological features that differentiate gene carriers from non-carriers.

Methods: Eighty-one Greek patients at 50% risk for HD were recruited prospectively and examined by means of a semi-structured interview and four self-rated questionnaires. The study focused predominantly on hostility/irritability and obsessional behavior.

Results: Gene carriers had significantly higher extroverted hostility than non-carriers ($p = .005$). The elevated level of hostility was unaffected by the proximity to the estimated age of onset. The remainder of the scales did not reveal significant differences.

Conclusions: Extroverted hostility, in particular criticism of others and delusional hostility, is increased in gene carriers well before the onset of clinical HD. Hostility is regarded as a personality dimension rather than as a behavioral pattern.

Key Words: CAG repeats, genetics, hostility, Huntington disease, psychiatric disorders, SCID

Huntington's disease (HD) is an autosomal, dominant, neurodegenerative disease characterized by motor impairment, cognitive decline, and psychiatric manifestations, leading to a functional decline. Clinical observation and classical literature agree that changes of personality and psychiatric disturbances often precede the onset of neurological symptoms or intellectual impairment (Cummings 1995; Heathfield 1967; Lishman 1998).

It has been reported that persons at risk for developing the disease have higher prevalence of psychiatric disturbances than the general population (Watt and Seller 1993). A question that has been raised is whether psychiatric disorders in persons at risk represent an early manifestation of HD or the response to family stress and disorganization (Folstein *et al.* 1983).

Numerous retrospective studies have reported the presence of psychiatric disorders at the prodromal or early stages of the disease (Bolt 1970; Dewhurst *et al.* 1969; Mattsson 1974; Pflanz *et al.* 1991), frequently leading to misdiagnoses (Oliver 1970). The early studies have approached the psychiatric symptomatology through qualitative descriptions, presented either as symptoms lists or as more elaborated coherent syndromes (Folstein *et al.* 1979). The development of clinical instruments has subsequently allowed quantitative approaches to the determination of psychiatric disorders. However, it has been difficult to determine accurately the prodromal phase, because in many cases there was no information on this stage or symptoms were elicited retrospectively (Dewhurst *et al.* 1969).

After the discovery of genetic markers in 1983 (Gusella *et al.* 1983) and the identification of the responsible gene in 1993 (The Huntington's Disease Collaborative Research Group 1993), numerous studies evaluated the psychological and neuropsychiatric characteristics of persons at risk of HD. However, the majority measured the psychological impact of the test result over time (Almqvist *et al.* 2003; Brandt *et al.* 1989; Decruyenaere *et al.* 1996, 2003; Tibben *et al.* 1994). Only a few studies focused predominantly on the comparison between the psychiatric presentation of gene carriers and non-carriers (Baxter *et al.* 1992; Berrios *et al.* 2002; Kirkwood *et al.* 2002; Shiwach and Norbury 1994).

Most of the studies have failed to reveal any difference in psychiatric manifestation between gene carriers and non-carriers before disclosure of the test results. To our knowledge only two studies have shown significant differences in subjects at risk for HD. Baxter *et al.* (1992), in their original study evaluating psychiatric morbidity in persons at risk for HD, reported that subjective "anger/hostility" was significantly higher in those likely compared with those less likely to develop HD. Likewise, Berrios *et al.* (2002) observed that gene carriers scored higher in measures of irritability than non-carriers. Both results are in accordance with previous evidence that irritability is an important element of HD since its early stages (Bolt 1970; Burns *et al.* 1990; Folstein and Folstein 1983).

Obsessive and compulsive (OC) symptoms are common among patients with HD and other illnesses affecting the basal ganglia like Farh's disease, Syndenham's chorea, and Tourette's syndrome. Frontostriatal pathology has been implicated in primary obsessive compulsive disorder (OCD) by neuropsychological and imaging studies (Anderson *et al.* 2001). As neuropathological changes and in particular basal ganglia volume reduction has been observed in asymptomatic HD gene carriers (Aylward *et al.* 1994), the question of whether subtle OC symptoms appear before the manifestation of HD has been raised. De Marchi *et al.* (1998) reported on a pedigree with HD in which three cases of OCD were identified, occurring only in carriers of the CAG expansion. In all cases the onset of OCD occurred well before the onset of HD.

The aim of the present study was to discriminate behavioral and psychiatric features that differentiate gene carriers from non-carriers. The study focused particularly on irritability/hostility, because it has frequently been reported to precede the onset

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Received August 16, 2006; revised November 30, 2006; accepted December 18, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.12.016

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of the clinical symptoms of HD, and on obsessive or compulsive manifestations.

Methods and Materials

Subjects

Eighty-one subjects (36 men and 45 women) at 50% risk for developing HD were consecutively recruited at the Unit of Clinical and Molecular Genetics, Department of Neurology, "Eginition" Hospital, University of Athens, between 2002 and 2005. As this is the unique reference center in Greece with facilities for genetic testing, participants were recruited from across the country. All subjects were adults (over the age of 18) and had a first degree relative with manifested and genetically confirmed HD. They were all examined by a psychiatrist (EV) at entry into the study (i.e., before genetic testing was performed). All participants were offered pre-test and post-test counseling, and after complete description of the study, written informed consent was obtained.

Motor symptoms were assessed by a neurologist (MP), with the Unified Huntington's Disease Rating Scale (UHDRS). Subjects who came for the genetic testing as symptom-free relatives at risk were excluded from the study when motor defects indicating the onset of HD were detected. The number of family members with manifested HD was recorded, and the illness severity of the proband in each family was rated according to the criteria of the Total Functional Capacity Scale (TFCS) (Shoulson and Fahn 1979).

Psychiatric Assessment

The psychiatric assessment consisted of a semi-structured interview (Structured Clinical Interview for DSM-IV [SCID]) (First *et al.* 1996), and the cognitive state was examined through the Mini Mental State Examination. "Formal" psychiatric diagnoses as well as "sub-threshold" diagnoses, as described in the manual of SCID, were recorded for all participants. Information from medical records, referring physicians, and interviews with relatives was also used to assist the diagnosis of psychiatric disorders. The level of psychological, social, and occupational functioning was measured with the "General Assessment of Functioning" (GAF) scale.

To approach subtle differences in dimensional aspects, all subjects completed four self-rated questionnaires. These included:

Symptom Checklist 90 (SCL-90-R), which was used as a measure of general psychological complaints, providing an overall index (Global Severity Index [GSI]), and nine dimensions of psychopathology (Derogatis 1977). The GSI was chosen a priori to be the primary psychological outcome measure. The SCL-90-R has been standardized in the Greek population.

Snaith Irritability Scale (SIS), which gives an indication of inward and outward irritability, depression, and anxiety (Snaith *et al.* 1978). The two scales measuring irritability were used.

Hostility and Direction of Hostility Questionnaire (HDHQ), which has been constructed from items derived from the Minnesota Multiphasic Personality Inventory (MMPI) and measured introverted and extroverted hostility (Caine *et al.* 1967).

Maudsley Obsessive Compulsive Inventory (MOCI), which provided an indication of the level of obsessional behavior (Hodgson and Rachman 1977).

All subjects completed the questionnaires in the presence of a psychiatrist who clarified ambiguous questions and assessed their motivation and competency. An official translation in Greek existed for SCID and for two of the questionnaires used (SCL-90-R and HDHQ). The remaining (SIS and MOCI) were translated to Greek according to the World Health Organization guidelines (forward and back translation, followed by expert panel review).

Molecular Analysis

Blood samples were collected and DNA was extracted, with a salt extraction standard method. This method involves salting out of the cellular proteins by dehydration, precipitation with a saturated sodium chloride solution, and digestion with protease K (Miller *et al.* 1988).

The region containing the site with CAG repeats in the IT15 gene was amplified by polymerase chain reaction (PCR), as described by Warner *et al.* (1993). The primers used were: 5'ATG AAG GCC TTC GAG TCC CTC AAG TCC TTC3' (forward) and 5'GGC GGT GGC GGC TGT TGC TGC TGC TGC3' (reverse). On the basis of the test results, subjects were divided into gene carriers and non-carriers.

Statistical Analysis

Statistical analysis was carried out by means of SPSS version 10 (SPSS 1999). The categorical biographic characteristics were analyzed with χ^2 test and numerical variables with t test and Mann–Whitney tests, as appropriate. The psychological differences of carriers and non-carriers were analyzed with Mann–Whitney test, because the distributions were not normal. Bonferroni correction for multiple comparisons was used, and the significance level was set at .009.

Proximity to clinical onset was estimated by computing the difference between the person's chronological age and his expected age of onset. The expected age of onset was calculated according to the formula: ln [age of onset] = 6.18 − .054 × [CAG repeats]. The equation was derived from another study, by the same group, on the age of onset in 72 Greek patients with clinically manifested HD (submitted for publication, data not presented here). The exponential regression model best described the association between the CAG repeats and the age of onset of the disease, in accordance with previous reports (Rubinsztein *et al.* 1997).

Results

A total of 81 first degree relatives of patients with HD presented for genetic testing. Seven were excluded from the study: early motor symptoms were detected with UHDRS in four subjects, indicating the onset of the disease; whereas three subjects did not provide consent to participate. Seventy-four subjects underwent psychiatric examination. As HD is often manifested with psychiatric symptoms that predate the onset of neurological symptoms, all the subjects who were suffering from a major mental illness at the time of the examination, as determined by SCID (seven with depression, one with bipolar disorder, and two with psychosis), and tested positive for the mutated gene were excluded from the analysis.

Of 64 participants who entered our analysis, 29 were tested positive and 35 negative for the mutated gene. Sociodemographic characteristics of the participants are presented in Table 1. No

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