PAPER

Psychiatric disorders in preclinical Huntington's disease

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Background: Psychiatric symptoms are a common feature of Huntington's disease (HD) and often precede the onset of motor and cognitive impairments. However, it remains unclear whether psychiatric changes in the preclinical period result from structural change, are a reaction to being at risk or simply a coincidental occurrence. Few studies have investigated the temporal course of psychiatric disorder across the preclinical period.

Objectives: To compare lifetime and current prevalence of psychiatric disorder in presymptomatic gene carriers and non-carriers and to examine the relationship of psychiatric prevalence in gene carriers to temporal proximity of clinical onset.

Methods: Lifetime and current psychiatric histories of 204 at risk individuals (89 gene carriers and 115 non-carriers) were obtained using a structured clinical interview, the Composite International Diagnostic Interview. Psychiatric disorders were classified using both standardised diagnostic criteria and a more subtle symptom based approach. Follow-up of gene carriers (n = 51) enabled analysis of the role of temporal proximity to clinical onset.

Results: Gene carriers and non-carriers did not differ in terms of the lifetime frequency of clinical psychiatric disorders or subclinical symptoms. However, gene carriers reported a significantly higher rate of current depressive symptoms. Moreover, the rate of depression increased as a function of proximity to clinical onset.

Conclusions: Affective disorder is an important feature of the prodromal stages of HD. The findings indicate that depression cannot be accounted for by natural concerns of being at risk. There is evidence of a window of several years in which preclinical symptoms are apparent.

Huntington's disease (HD) is an inherited neurodegenerative disorder, characterised by motor dysfunction, cognitive impairment and psychiatric disturbance. HD is associated with a wide range of psychiatric disturbances, including affective disorders,[1–3] irritability,[4–6] apathy[1 3 6] and psychosis.[4 7 8] Both major depression[1 2 4 9] and more subtle mood disturbances[10] have been reported to predate clinical onset, conventionally defined by onset of motor symptoms. However, the basis for psychiatric symptoms remains unclear. Depression has been observed to occur up to 20 years before the onset of motor symptoms,[9 11] raising the possibility that psychiatric symptoms are an early indicator of HD and result from incipient neurodegenerative changes. However, the finding that psychiatric symptoms tend to cluster in certain HD families might indicate that psychiatric changes have a genetic basis and reflect a ''switching on'' of the HD gene early in life.[2 8] High rates of psychiatric disturbance have also been observed in HD family members who do not carry the genetic mutation,[9 10] raising the alternative possibility that affective changes arise in response to emotional stressors, such as being at risk, or the burden of growing up in a family with affected members. A more thorough understanding of the underlying basis of psychiatric changes in preclinical gene carriers is crucial, as future therapeutic strategies are most likely to target such individuals.

Previous psychiatric studies of at risk individuals have yielded inconsistent results. Earlier studies reported high lifetime rates of psychiatric disorder in preclinical gene carriers (eg, 18% major affective disorder),[2] whereas more recent studies indicate little difference between rates for gene carrier and non-carrier groups.[10 12–14] A number of factors may account for these discrepancies. The majority of earlier reports were limited to retrospective observation of affected individuals and therefore lacked appropriate controls.[4 5] The advent of predictive testing has enabled direct comparison of at risk individuals who have the HD mutation and those who do not, thereby controlling for social and environmental factors.[10 12–14] Whereas the majority of earlier studies lacked standardised assessment criteria,[4 7] more recent studies have utilised operational diagnostic criteria, although these have in turn been criticised for failing to detect the more subtle psychiatric disturbances that can occur in HD.[3 15]

Few studies have taken account of the temporal distance to onset of motor symptoms. It is now well established that the clinical onset of HD is typically preceded by a prodromal period of several months or years during which non-specific mild neurological signs arise intermittently.[16] The difficulty in establishing exact dates of onset for retrospective cases may have led to the inclusion in earlier studies of individuals who were already in the early stages of HD. Studies of presymptomatic individuals have typically recruited participants without motor signs, who may have been further from clinical onset.

The present study is a double blind comparison of lifetime and current prevalence of psychiatric disorders in preclinical gene carriers and non-carriers, using a combination of standardised psychiatric diagnostic criteria and a more subtle symptom based approach. Follow-up of gene carriers has enabled analysis of the role of temporal proximity to clinical onset.

METHODS

Participants

The study population consisted of 227 consecutive referrals for predictive testing to two regional genetic centres in Manchester

Abbreviations: CIDI, Composite International Diagnostic Interview; DSM-III, Diagnostic and Statistical Manual of Mental Disorders 3rd edition; HD, Huntington's disease; QNE, quantitated neurological examination

Table 1 Participant demographic information

	Carrier	Non-carrier
n	89	115
Sex (M, F)	33, 56	48, 67
Age (y)	37 (9)	39 (10)
QNE	6 (8)	2 (3)

QNE, quantitated neurological examination.
Values are mean (SD) or number.

and Leeds between 1987 and 2000. All participants had a family history of HD and were blind to their gene status at the time of assessment. Participants' neurological status was assessed using the Quantitated Neurological Examination (QNE).[17] Participants were excluded from the study if they exhibited neurological signs indicative of definite HD, such as significant chorea, oculomotor dysfunction, dysarthria and dystonia. Participants gave written informed consent for the study, which was approved by the Central Manchester Research Ethics Committee. Twenty-three participants were excluded from the study: 10 decided not to proceed to testing, two were rated by the examiner as showing definite motor signs of HD, two suffered from another neurological disease and nine received an uninformative linkage test. Cases for whom only linkage analysis results were available were only retained in the study if risk estimates were produced with a maximum confidence margin of 7%. Of the remaining 204 participants, 154 individuals were given the mutation test directly and 50 were tested for HD by linkage analysis; 13 of these later received confirmation of their genetic status through mutation testing. A total of 89 (44%) individuals received unfavourable predictions (33 males, 56 females) whereas 115 received a favourable test result (48 males, 67 females).

Demographic information for all participants is summarised in table 1. At risk gene carrier and non-carrier groups did not differ significantly in terms of sex distribution ($\chi^2 = 0.46$, $p = 0.5$) or age ($t = 1.15$, $p = 0.25$). However, gene carriers scored significantly higher on the QNE ($t = -4.42$, $p = 0.000$) because of the inclusion of a few individuals with mild motor abnormalities rated by the examiner as evidence of possible HD but not considered sufficient to justify a definitive diagnosis.

Neuropsychiatric assessment

Psychiatric assessment was performed using the Composite International Diagnostic Interview (CIDI),[18] a fully structured interview designed to facilitate formal classification of psychiatric symptoms according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders 3rd edition (DSM-III).[19] The interview probes lifetime history of a variety of psychiatric disorders (see table 4 for a list of disorders). For each major psychiatric disorder, probe questions determine the presence of a core symptom (eg, for major depression, 2 weeks of persistently low mood). Each symptom is validated against a set of severity criteria and is only scored as present if it is sufficiently severe to interfere with daily life or requires medical attention, and if it is not caused by a physical illness or psychoactive substance abuse. A positive response to a probe question leads to further investigation of associated psychiatric symptoms (eg, feelings of worthlessness, suicidal ideation). Associated symptoms are also validated using the same set of severity criteria. An algorithm is then applied to determine whether symptoms meeting these severity criteria are sufficient in number to meet a formal DSM-III diagnosis. Information regarding the onset and most recent occurrence of each symptom is also elicited, enabling accurate measurement of lifetime and current (12 months preceding interview) psychiatric diagnoses.

Most of the psychiatric assessments were administered by two trained interviewers (DC and GT) prior to completion of genetic testing; consequently, the interviewers were blind to the participants' gene status. Interviews were performed in a single session, lasting approximately 1 h. Responses were recorded using a paper and pencil version, leading to establishment of lifetime and current diagnoses according to the criteria set by DSM-III. The final 18 participants in the series completed a computer administered version of the CIDI (the CIDI-Auto version 1.1),[20] instead of the interview administered version. Responses were directly recorded and scored by the computer, generating lifetime and current diagnoses according to the criteria of the revised DSM-III.[21] Because the diagnoses generated by the paper and computerised versions of the CIDI were based on different DSM criteria, a separate computer algorithm was used to analyse responses from the computerised version and establish full psychiatric diagnoses according to DSM-III criteria.

A further analysis was carried out to identify individuals who did not meet formal DSM-III diagnostic criteria, but reported a number of relevant symptoms which did meet the CIDI severity criteria (ie, interfered with daily life or required medical attention, not due to physical illness, etc). For each set of questions associated with a formal diagnostic entity (eg, major depression, generalised anxiety), ratings were produced on a scale of 0 to 3, where (0) indicates a negative response to the core symptom question, (1) denotes individuals who met severity criteria for the core symptom but did not report any associated symptoms, (2) refers to individuals who met severity criteria for the core symptom and at least one associated symptom and (3) specifies individuals who achieved a formal psychiatric diagnosis according to DSM-III criteria (see table 2 for examples).

Follow-up information

Following their predictive test result, all participants were offered regular clinical follow-up at their Regional Clinical Genetic Service. The medical records of individuals who received an unfavourable test result were reviewed to

Table 2 Examples of scoring criteria for sub-threshold psychiatric classifications

Score	Depression	Mania	Panic disorder
0	No depressive symptoms	No manic symptoms	No panic attacks
1	Depressed mood lasting at least 2 weeks	Irritable or expansive mood lasting at least 1 week	Limited symptom attacks (less than 4 physical symptoms)
2	Depressed mood and/or anhedonia lasting at least 2 weeks plus minimum 1 other associated symptom (eg, feelings of worthlessness, suicidal ideation)	Irritable or expansive mood lasting minimum 1 week plus maximum 2 associated symptoms−3 if irritable mood (eg, flight of ideas, inflated self-esteem)	Full symptom attacks (more than 4 physical symptoms) of limited frequency (less than 4 in 1 month)
3	Major depressive episode (depressed mood and/or anhedonia plus at least 4 other associated symptoms)	Manic episode (irritable or expansive mood plus at least 3 associated symptoms−4 if irritable mood)	Full panic disorder (full symptom attacks occurring more than 4 times in 1 month)

Table 3 Follow-up demographic information

	>10 y	6–10 y	1–5 y	<1 y
n	11	17	14	9
Sex (M, F)	6, 5	6, 11	4, 10	5, 4
Age (y)	31 (6)	36 (10)	44 (8)	40 (10)
QNE	2 (2)	3 (2)	6 (4)	24 (8)

QNE, quantitated neurological examination.

determine whether they had begun to show clinical symptoms of HD and, if so, the date of clinical onset. Clinical onset was defined by the presence of neurological signs indicative of definite HD (see participants section). Of the 89 individuals with an unfavourable genetic test result, we obtained reliable information on 51 individuals. To facilitate analysis of psychiatric symptoms in relation to temporal proximity of disease onset, participants were classified according to the number of years elapsed between administration of the CIDI and clinical onset of HD as follows: definitive diagnosis within 1 year, 1–5 years, 6–10 years or more than 10 years after administration of the CIDI.

Demographic information on the follow-up cohort is shown in table 3. Within the group of gene carriers who were followed-up, participants with a clinical onset of more than 10 years distant were significantly younger than carriers within 5 years of onset ($t = 4.11$, $p<0.01$). Carriers less than 1 year from clinical onset scored significantly higher on the QNE than the other carrier groups (1–5 years: $t = 6.76$, $p<.01$; 6–10 years: $t = 9.15$, $p<0.01$; more than 10 years: $t = 7.75$, $p<0.01$). No other significant demographic differences were observed.

Statistical analysis

Statistical analyses were carried out using SPSS for Windows version 13.0. Non-parametric χ^2 tests were used to compare the total number of full psychiatric diagnoses in gene carrier and non-carrier groups. Fisher's exact test was used for comparisons where the expected cell frequencies fell below a cut-off score of 5. Mann–Whitney U tests were used to compare psychiatric severity scores between groups. Further χ^2 and Kruskal–Wallis tests were carried out to examine the relationship between psychiatric prevalence and temporal proximity to clinical onset. In the latter analysis, we did not correct for multiple comparisons in view of the small sample sizes and exploratory nature of the study. Two tailed tests were adopted. The level of significance was set at $p<0.05$.

RESULTS

Prevalence of psychiatric disorder in HD gene carriers and non-carriers

Lifetime prevalence of psychiatric disorder

Lifetime rates of DSM-III psychiatric disorder are shown in table 4. Gene carriers and non-carriers did not differ significantly in terms of the lifetime prevalence of either major psychiatric disorder or more subtle psychiatric disturbances (as outlined in table 2).

Current prevalence of psychiatric disorder

Table 4 shows prevalence rates for DSM-III disorders occurring at the time of interview. Current prevalence of formal psychiatric disorder did not differ significantly between groups; however, when psychiatric disturbances too subtle to warrant a DSM-III diagnosis (table 2) were included, gene carriers exhibited a significantly greater prevalence of current depressive symptoms (25%) compared with non-carriers (15%) ($z = -2.01$, $p<0.05$). Gene carriers were 1.74 times (95% CI 1 to 3.07) more likely to report a depressive disorder than non-carriers. There were no other significant differences. A numerical trend was noted in the domain of mania, with gene carriers reporting a greater prevalence of ''manic'' symptoms (11%) compared with non-carriers (4%) ($z = -1.86$, $p = 0.06$). In every case, the symptom reported was irritability rather than expansive or elevated mood.

Prevalence of psychiatric disorder and temporal proximity to clinical onset

Figure 1 shows the current prevalence rate of affective disorder reported by gene carriers in relation to closeness of clinical onset. Prevalence rates for non-carriers and published population estimates are also shown for comparison.[22] Individuals who were closer to onset at the time of interview had a significantly higher prevalence of DSM-III affective disorder compared with individuals more distant from onset ($\chi^2 = 14.52$,

Table 4 DSM-III psychiatric disorder

	Carriers (n = 89)		Non-carriers (n = 115)	
	Lifetime No (%)	Current No (%)	Lifetime No (%)	Current No (%)
Anxiety disorder	15 (17)	13 (15)	29 (25)	21 (18)
Generalised anxiety	10 (11)	8 (9)	19 (17)	13 (11)
Panic disorder	7 (8)	5 (6)	6 (5)	3 (3)
Simple phobia	7 (8)	6 (7)	8 (7)	7 (6)
Agoraphobia	8 (9)	5 (6)	8 (7)	5 (4)
Social phobia	3 (3)	2 (2)	2 (2)	2 (2)
Affective disorder	20 (23)	15 (17)	17 (15)	10 (9)
Major depression	18 (20)	13 (15)	14 (12)	9 (8)
Bipolar disorder	0 (0)	0 (0)	1 (1)	1 (1)
Dysthymic disorder	1 (1)	1 (1)	2 (2)	0 (0)
Cyclothymic disorder	1 (1)	1 (1)	0 (0)	0 (0)
Obsessive–compulsive disorder	4 (5)	2 (2)	2 (2)	2 (2)
Schizophrenia	1 (1)	1 (1)	0 (0)	0 (0)
Eating disorder	3 (3)	0 (0)	6 (5)	2 (2)
Tobacco abuse	34 (38)	18 (20)	37 (32)	24 (21)
Alcohol dependence	3 (3)	1 (1)	7 (6)	0 (0)

DSM-III, Diagnostic and Statistical Manual of Mental Disorders 3rd edition.

p<0.01). There was also a significant relationship between distance to onset and current prevalence of broadly defined depressive symptoms (z = 10.8, p<0.05). Current prevalence of affective disorder in each time to onset group was compared with that of non-carriers. Because of the small sample sizes, only individuals less than 1 year from clinical onset achieved a significantly higher prevalence rate of affective disorders compared with non-carriers ($\chi^2 = 20.2$, p<0.001).

Figure 2 shows prevalence rates of irritability symptoms for gene carriers and non-carriers. Irritability rates were raised in gene carriers up to 10 years before clinical onset but not in those who were further from onset at the time of interview. However, there was no significant relationship between proximity to onset and prevalence of irritability symptoms within the 10 year period before onset.

No other psychiatric disorder showed a significant temporal relationship with clinical onset.

DISCUSSION

Comparison of at risk individuals who carry the HD mutation with those who do not revealed no significant differences in terms of *lifetime* prevalence of psychiatric disorder. However, gene carriers did report a higher *current* prevalence of affective disturbance at the time of interview compared with non-carriers, and both the prevalence and severity of these affective symptoms appeared to be related to proximity to clinical onset of HD.

Contrary to the present findings, previous studies have found low rates of current psychiatric disorder in individuals at risk from HD.[10 13] A number of factors may explain these contrasting findings. Whereas previous studies have often excluded people with soft motor signs,[10 12 13] we chose to include such individuals allowing us to investigate psychiatric symptoms across the whole preclinical period. We found prevalence rates most marked in individuals who were closest to clinical onset of HD. Moreover, inclusion of more broadly defined psychiatric criteria enabled us to identify increased prevalence of subthreshold disturbances in gene carriers that would otherwise have remained undetected by more formal diagnostic classifications.

Our findings allow us to comment on the temporal evolution of affective symptoms in HD. High rates of affective disorder were observed in people who were 6–10 years from onset, increasing in severity in those who were 1–5 years from onset, with a further marked increase in those who were closest to clinical onset. However, only individuals who were less than 1 year from clinical onset reported a significantly higher rate compared with non-carriers. This clustering of affective symptoms around the time of motor onset is in keeping with some earlier reports. In a retrospective review of affected HD individuals, Shiwach[7] found that the onset of all cases of major depression occurred in the 8 years preceding or following motor onset, with 33% of depression cases occurring (on average 4 years) before neurological onset. Watt and Seller[11] also reported a clustering of minor depressive symptoms around the time of onset of motor chorea (using rather different criteria to our study), but attributed them to the stress of receiving a clinical diagnosis of HD. The present study extends these findings by demonstrating that depression remains highly prevalent even when knowledge of genetic status is not disclosed.

The nature of the observed affective changes deserves comment. In addition to depression, a large proportion of affective symptoms were recorded under the diagnostic entity of mania. However, these symptoms consisted principally of periods of increased irritability. Elevated mood, a core symptom of mania, was never reported, and associated manic symptoms were rarely observed. Moreover, unlike depression, irritability symptoms remained stable in relation to motor onset, both in terms of prevalence and severity, and did not converge to bipolar disorder. Although reports of mania have been described in HD, the precise nature is not clear, and given the present findings it is possible that what is being described is an increase in irritability. Irritability was present to some extent also in non-carriers, suggesting that concerns of being at risk and life stressors may contribute to the occurrence of this symptom. However, the data suggest that this may not be a sufficient explanation. There was a non-significant trend (p = 0.06) for a higher frequency of irritability in gene carriers. The increase in irritability appearing up to 10 years before onset raises the intriguing possibility that this might reflect a prodromal change occurring even earlier than major affective disorder and extending for a substantial period of time before motor onset.

The present study sheds light on the aetiological mechanisms underlying psychiatric disorder in preclinical HD. It has been suggested that preclinical psychiatric symptoms arise from early expression of the HD gene.[2 8] The finding that lifetime psychiatric symptoms were reported as frequently in individuals without the HD mutation as those with, contests this interpretation. Both gene carrier and non-carrier groups reported high rates of major affective disorder compared with lifetime estimates of 8%,[22] suggesting that higher rates of adverse life events or early social deprivation associated with a family history of HD may predispose some at risk individuals to develop depression. However, this observation should be interpreted with a degree of caution. A recent epidemiological study using an updated version of the CIDI found that the rate of affective disorder in a European population (14%) was similar to that observed in non-carriers in the present study (15%).[23] Although the present study was carried out in the

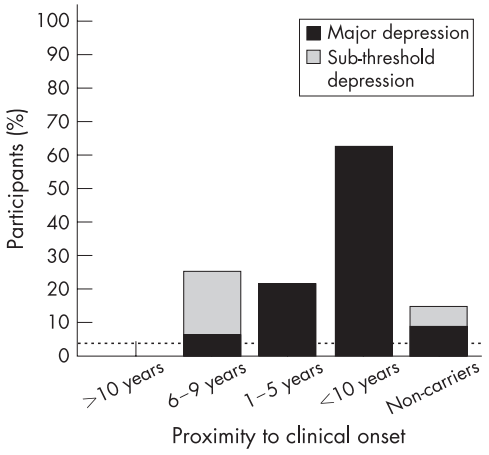

Figure 1 Current prevalence of affective disorder and closeness to onset. *Broken reference line indicates 1 year prevalence of major affective disorder, as reported in the Epidemiological Catchment Area Study (ECA) study.[22]

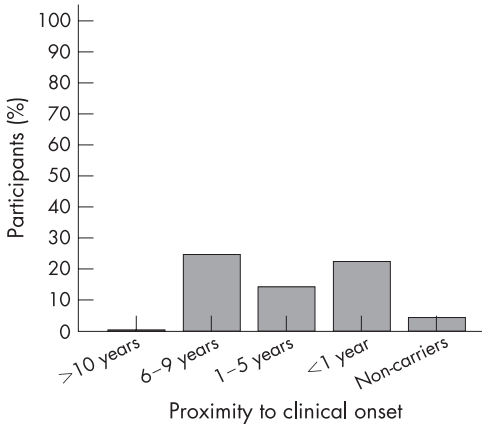

Figure 2 Current prevalence of irritability and closeness to onset.

same time period and used the same diagnostic classification (DSM-III) as the American study,[22] our participants may share more cultural characteristics with the population sampled in the European study.

In addition to the possibility of increased lifetime prevalence of psychiatric disorders, the present study shows that mood disorder is a salient characteristic of the prodromal stage of HD. The clear temporal relationship between symptoms of depression and the onset of neurological signs offers two interpretations. One possibility is that the high rate of depression observed close to clinical onset reflects an emotional response to increasing awareness of emerging motor impairment. Indeed, although cases of definite HD were excluded from the study, several participants displayed soft neurological signs on examination and could arguably have been aware of them. However, it is well recognised that, even in the early stages, HD patients lack subjective awareness of their movement disorder and that this denial of symptoms is likely to have a physiological, rather than a psychological, basis.[24] The fact that subjects in our study requested a presymptomatic genetic test rather than a diagnostic test and, furthermore, that they all denied motor symptoms on interview, indicates that, at least on a conscious level, they were not aware of emerging motor deficits. Moreover, the finding that high rates of depression were also observed in patients who were further from clinical onset and had a normal neurological presentation argues against an explanation in purely reactive terms and suggests a common neural substrate for depression and motor impairment. The observation that affective symptoms may anticipate clinical motor onset by several years suggests that depression is an early manifestation of neuronal dysfunction. That subtle neuropathological changes can occur before any detectable motor impairment is supported by evidence from structural[25 26] and functional[27] imaging studies as well as neuropathological investigations[28] showing early changes in the striatum in presymptomatic HD gene carriers. Moreover, studies have linked depressive symptoms in HD to dysfunction of frontal-striatal pathways[29 30] implicated in reward mediated behaviours.[31] The present findings also mirror our data showing that mild cognitive change represents an early feature of striatal dysfunction in preclinical HD.[32]

To our knowledge, this is the largest study to investigate psychiatric disorder in preclinical HD. The double blind design allowed direct comparison of gene carriers and non-carriers, controlling for social factors and investigator bias. Subsequent follow-up of gene carriers allowed us to document the evolution of psychiatric disorder across the preclinical period. The present study indicates that affective disorder is a salient characteristic of the prodromal stages of HD and highlights the strong temporal relationship between depression and onset of clinical motor symptoms. Longitudinal studies will be essential to further characterise the evolution of affective disorder as the disease progresses.

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