Cross-Sectional Study on Prevalences of Psychiatric Disorders in Mutation Carriers of Huntington's Disease Compared With Mutation-Negative First-Degree Relatives

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Objective: To investigate the prevalences of formal DSM-IV diagnoses in pre–motor-symptomatic and motor-symptomatic mutation carriers at different stages of Huntington's disease compared to a control group of first-degree noncarrier relatives and the general population.

Method: Between May 2004 and August 2006, 154 verified mutation carriers and 56 verified noncarriers were recruited from the outpatient clinics of the Neurology and Clinical Genetics departments of Leiden University Medical Center and from a regional nursing home. To assess the 12-month prevalences of DSM-IV diagnoses, the sections for depression, mania, anxiety, obsessive-compulsive disorder, and psychosis/schizophrenia of the Composite International Diagnostic Interview were used. Prevalences in the Dutch general population were extracted from the Netherlands Mental Health Survey and Incidence Study (NEMESIS).

Results: Both presymptomatic and symptomatic mutation carriers portrayed significantly more major depressive disorder ($p = .001$ and $p < .001$, respectively) and obsessive-compulsive disorder ($p = .003$ and $p = .01$, respectively) than the general population. Symptomatic mutation carriers also showed an increased prevalence ($p = .01$) of nonaffective psychosis. Psychiatric disorders were more prevalent, although not significantly ($p = .06$), in mutation carriers compared to first-degree relatives who were noncarriers. Noncarriers did not differ from the general population.

Conclusion: Psychiatric disorders occur frequently in Huntington's disease, often before motor symptoms appear. In addition, first-degree noncarrier relatives do not show more psychiatric disorders compared to the general population, although they grew up in comparable, potentially stressful circumstances. Taking these findings together, psychopathology in Huntington's disease seems predominantly due to cerebral degeneration rather than to shared environmental risk factors.

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Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder resulting from an expanded trinucleotide CAG repeat, which codes for a polyglutamine in the IT15 gene on chromosome 4p16.3.[1] The pathogenesis in relation to the CAG repeat expansion has not yet been elucidated, but several processes have been suggested.[2] The mean age at onset is between 30 and 50 years. The first signs consist of involuntary movements (chorea, hypokinesia), cognitive deterioration, behavioral problems, and psychiatric disorders. There is no curative treatment for HD. Since 1993, presymptomatic gene testing has been available.[1] In The Netherlands, about 1200 to 1500 patients have symptoms of HD, 6000 to 9000 persons are at 50% risk for HD, and every year approximately 60 persons at 50% risk are tested gene-positive.

Psychiatric disorders may occur in all motor-symptomatic stages of HD and can also predate the onset of motor symptoms.[3–5] These disorders have an important negative impact on quality of life, add greatly to the suffering of patients and the burden of caregivers, increase the risk of institutionalization,[6,7] and may account for increased mortality and risk of suicide.[8,9] Little is known about true prevalences of psychiatric disorders in verified HD mutation carriers. This lack of information is due to small sample sizes, use of different methodologies, and

lack of adequate control groups.[10] We therefore aimed to investigate the 12-month prevalences of formally diagnosed psychiatric disorders in verified HD mutation carriers compared to a control group of verified first-degree noncarrier relatives and the general population.

Since being at risk for this incurable disorder and having been raised in an HD family is likely to have an impact on mental well-being,[11,12] we assumed that HD family members, regardless of their genetic status, would all show increased prevalences of psychiatric disorders compared to the general population.

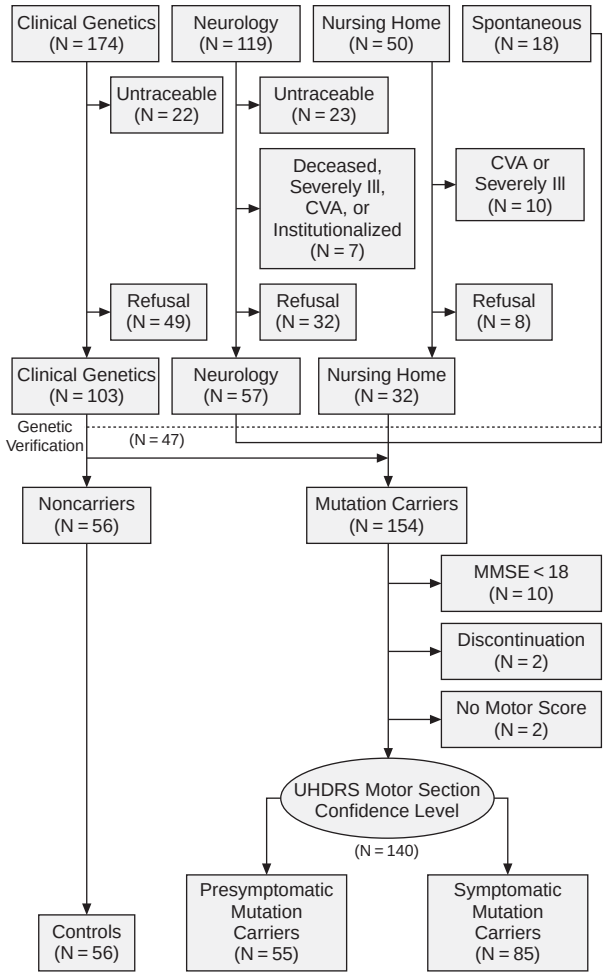
METHOD

Subjects

Between May 2004 and August 2006, 361 subjects were recruited from 4 sources (Figure 1). First, an invitational letter was sent to 174 subjects who had attended the Department of Clinical Genetics of Leiden University Medical Center between 1999 and 2004 for HD mutation analysis. Leiden University Medical Center is a Dutch teaching hospital and a national reference center for HD. Next to verified HD carriers, verified first-degree noncarrier relatives—with an a priori 50% risk for HD—were enrolled as a comparison group to control for environmental factors such as growing up with an ill parent in potentially harmful family circumstances, the knowledge of being at risk for HD, and participating in the predictive testing procedure. Second, an invitational letter was sent to all HD patients (N = 119) currently attending the outpatient clinic of the Department of Neurology of Leiden University Medical Center. Third, 1 nursing home (Overduin in Katwijk) in the area of Leiden with a specialized ward for HD patients was visited in order to include subjects in advanced stages of HD, both institutionalized and attending a day clinic. These subjects (N = 50) were selected on the basis of their physical and verbal capability to participate; severe dysarthric and severely demented subjects were not approached. Fourth, a minority of the subjects, called "spontaneous" participants (10 presymptomatic and 8 symptomatic), were included with help of the Dutch HD patients' association after posting an announcement on their Internet site and in their quarterly.

Subjects with juvenile-onset HD (N = 1) or concurrent diseases of the central nervous system (e.g., cerebrovascular accident) (N = 4) were excluded, as well as mutistic subjects (N = 8) and subjects who did not have a sufficient command of the Dutch language (N = 2). Forty-five outpatients were untraceable and 2 subjects were deceased. Of the remaining 299 subjects, 89 refused to participate because of various reasons including having no time, being too fatigued or too sick, and not wanting to be confronted with HD (response rate, 68.3%). Thus, we included 210 subjects, comprising 56 verified mutation-negative subjects and 154 verified mutation carriers. After the assessment, another 10 subjects were excluded because of severe cognitive disorders, 2 subjects declined during the study, and 2 more mutation carriers were excluded because of an absent motor assessment, leaving 56 noncarriers and 140 mutation carriers (Figure 1). The study was approved by the Medical Ethics Committee of Leiden University Medical Center, and all subjects gave informed consent.

Figure 1. Flowchart of Inclusion of Subjects



Abbreviations: CVA = cerebrovascular accident, MMSE = Mini-Mental State Examination, UHDRS = Unified Huntington's Disease Rating Scale.

Instruments

Demographic and clinical characteristics. Information on demographic and clinical characteristics was collected using a standardized interview. Global functioning was assessed using the Total Functioning Capacity (TFC) subscale of the Unified Huntington's Disease Rating Scale (UHDRS), a widely used standardized clinical rating scale for HD patients.[13] The TFC consists of 5 questions assessing employment; the capacity to handle

financial affairs, manage domestic chores, and perform activities of daily living; and the care level provided. The TFC ranges from 0 to 13 points, with lower scores indicating poorer functional abilities.[14]

CAG repeat length. The number of CAG repeats of all subjects was verified, except for 1 symptomatic subject who died during the study. Subjects with a normal repeat length containing 26 or fewer copies and those with an intermediate repeat number between 27 and 35 were considered noncarriers.[15] Since alleles in the 36 to 39 repeat range are unstable and are associated with the HD phenotype, these subjects were considered positive for HD in this study.

Assessment of motor functioning and disease stage. All subjects were examined for assessment of motor symptoms by a neurologist with experience of HD using the motor section of the UHDRS.[13] The neurologist was blinded to the genetic status and the results of all other assessments of the subjects. On the basis of the clinical examination, the neurologist assigned a score indicating to what degree he or she was confident that the presence of an extrapyramidal movement disorder in a subject may be due to HD. This confidence-level score ranged from 0 to 4. Mutation carriers with a confidence-level score of 0 (normal) or 1 (nonspecific motor abnormalities, < 50% confidence) were classified as presymptomatic (N = 55). The remaining mutation carriers (N = 85) with a score of 2 to 4 (2 = motor abnormalities that may be signs of HD [50%–89% confidence], 3 = likely signs of HD [90%–98% confidence], 4 = unequivocal signs of HD [≥ 99% confidence]) were considered symptomatic. We further stratified motor-symptomatic mutation carriers with confidence levels of 2 to 4 according to the total UHDRS motor scores as an "early disease stage" group and an "advanced disease stage" group using the median score (40 points) of the total UHDRS motor score (range, 0–124 points) as a cut-off.

Diagnosis of psychiatric disorders. The Composite International Diagnostic Interview (CIDI),[16] a fully structured, standardized psychiatric diagnostic interview for disease classification according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV),[17] was administered by the interviewers after certified training and under close supervision of a psychiatrist (E.v.D.).

The sections for depression, mania, anxiety, obsessive-compulsive disorder, and psychosis of the Dutch translation of the computerized edition of the CIDI, Version 2.1, were used to assess the presence of each disorder in the past 12 months. The interrater reliability of the CIDI is excellent, and the test-retest reliability and validity are good.[18] Because of lack of reliability in subjects with severe cognitive dysfunction, the CIDI was not administered in subjects with a score < 18 points on the Mini-Mental State Examination (MMSE)[19] (range, 0–30 points). Raters for psychiatric and cognitive functioning were deliberately informed about the genetic status of the participants, because nondisclosure on the side of the participant could considerably influence the subjects' answers to questions about symptoms that are directly related to their genetic status.

Prevalences of psychiatric disorders in the general population were extracted from the Netherlands Mental Health Survey and Incidence Study (NEMESIS),[20] a prospective study of the prevalence, incidence, and course of psychiatric disorders using the CIDI in a representative sample of 7076 noninstitutionalized Dutch adults aged 18 to 64 years.

Statistical analyses. Independent-samples t tests were used to compare group means of continuous variables, and Fisher exact tests were used for comparison of dichotomous demographic characteristics and for pairwise comparison of prevalences of psychiatric disorders. All analyses were carried out 2-sided, and, because of multiple testing, a significance level of $p < .01$ was applied.

Logistic regression analysis was applied to determine possible associations between various demographic and clinical characteristics (age, sex, having a partner, having children, higher education, psychiatric family history, CAG repeat length, total UHDRS motor score, and total MMSE score) and the presence of psychiatric disorders during the past 12 months in mutation carriers. Nonlinear generalized canonical correlation analysis was conducted to determine multiple clusters and the coincidence of symptomatic and presymptomatic subjects in each of the clusters.[21]

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) for Windows, release 12.0.1.[22]

RESULTS

Demographic and Clinical Characteristics

The 56 noncarriers and 140 mutation carriers differed significantly in many demographic and clinical characteristics (Table 1). Seven noncarriers had an intermediate CAG repeat length (range, 27 to 35 repeats), and 3 mutation carriers had a CAG repeat length between 36 and 39 repeats, which is associated with a reduced penetrance. Subgroups of presymptomatic and symptomatic mutation carriers differed in age (mean = 40.8 years and 49.9 years, respectively), having any children (mean = 63.6% and 82.4%, respectively), use of psychotropic medication (mean = 21.8% and 55.3%, respectively), TFC score (mean = 12.0 points and 7.8 points, respectively), MMSE score (mean = 28.1 points and 25.9 points, respectively), and having had higher education (mean = 63.6% and 44.7%, respectively) (data not shown). Logistic regression analysis showed that only age ($p = .003$) and TFC ($p < .001$) were significant predictors, whereas the other covariates were not ($p > .30$).

Table 1. Sociodemographic and Clinical Characteristics of Study Subjects (N = 196)

Characteristic	Mutation Carriers (N = 140) N	%	Noncarriers (N = 56) N	%			p Value[a]
Male gender	64	45.7	25	44.6			1.00
Higher education[b]	73	52.1	38	67.9			.056
Married or with partner	99	70.7	46	82.1			.108
Any children	105	75.0	30	53.6			.006
High alcohol consumption[c]	18	12.9	8	14.3			.817
Use of psychotropic medication	59	42.1	3	5.4			< .001
Antidepressants	37	26.4	3	5.4			< .001
Neuroleptics[d]	26	18.6	0	0			< .001
Benzodiazepines	29	20.7	0	0			< .001
	Mean	SD	Mean	SD	t Statistic	df	p Value
Age, y	46.3	11.7	39.1	11.1	3.91	194	< .001
CAG repeats, no.	44.1[e]	3.6	21.5	4.1	–40.07	194	< .001
TFC score, points[f]	9.5	3.9	12.9	0.5	–10.15	150[g]	< .001
MMSE score, points[h]	27.0[i]	4.2	29.1	1.2	–6.97	193[g]	< .001

[a]The Fisher exact test (2-sided) was used for dichotomous variables, and the t test was used for continuous variables.
[b]Educational level was dichotomized into lower level (< 12 years) and higher level (≥ 12 years).
[c]Alcohol consumption was considered high if more than 14 glasses per week were consumed.
[d]Including tiapride, which was primarily given as a treatment for motor symptoms.
[e]CAG repeat length of 1 motor symptomatic subject with an HD-positive family history was not verified. Four subjects had an intermediate repeat length.
[f]The TFC scale has a range of 0 to 13 points, with lower scores indicating more severe functional impairment.
[g]Corrected for unequal variances.
[h]The MMSE has a range of 0 to 30 points, with a lower score indicating more severe cognitive dysfunctioning. Only subjects with an MMSE score ≥ 18 were included.
[i]One presymptomatic subject refused assessment of MMSE score.
Abbreviations: MMSE = Mini-Mental State Examination, TFC = Total Functional Capacity scale.

Table 2. 12-Month Prevalences of Psychiatric Disorders According to the Composite International Diagnostic Interview (CIDI) in Mutation Carriers and Noncarriers Compared to the Dutch General Population

Disorder	Mutation Carriers (N = 140) N	%	Noncarriers (N = 56) N	%	General Population (N = 7076), %	p Value[a,b]	p Value[a,c]	p Value[a,d]
All depressive disorders[e]	25	17.9	4	7.1	…	.07	…	…
Major depressive disorder	24	17.9	4	7.1	5.8	.08	< .001	.57
Dysthymia	3	2.1	0	0	2.3	.56	1.00	.64
Manic episode	3	2.1	0	0	1.1	.56	.21	1.00
All anxiety disorders[e]	22	15.7	4	7.1	…	.16	…	…
Panic disorder	6	4.3	2	3.6	2.2	1.00	.14	.35
Agoraphobia without panic	2	1.4	0	0	1.6	1.00	1.00	1.00
Generalized anxiety disorder	7	5.0	0	0	1.2	.20	.02	1.00
Social phobia	8	5.7	1	1.8	4.8	.45	.55	.52
Obsessive-compulsive disorder	6	4.3	1	1.8	0.5	.68	< .001	.25
Nonaffective psychosis	2	1.4	1	1.8	0.2	1.00	.04	.11
Any psychiatric disorder[e]	36	25.7	7	12.5	…	.06	…	…

[a]The Fisher exact test for significance (2-sided) was used.
[b]Mutation carriers versus noncarriers.
[c]Mutation carriers versus general population.
[d]Noncarriers versus general population.
[e]Comparison with the general population was not possible for "all depressive disorders" and "all anxiety disorders," since "all depressive disorders" was not mentioned as a separate category in the Netherlands Mental Health Survey and Incidence Study (NEMESIS); nor was it possible to compare "all anxiety disorders" and the prevalence of "any psychiatric disorder," since we did not assess the prevalence of specific phobias, posttraumatic stress disorder, eating disorder, and alcohol or drug abuse, which were included in the NEMESIS.
Symbol: … = not applicable.

12-Month Prevalences of Psychiatric Disorders

As is shown in Table 2, mutation carriers had significantly increased prevalences of major depressive disorder and obsessive-compulsive disorder compared to the Dutch general population. Additionally, a trend of an increased prevalence of generalized anxiety disorder was found in mutation carriers compared to the general population (p = .02). Psychiatric disorders were more prevalent, although not statistically significant, in mutation carriers compared to noncarriers. Noncarriers did not differ from the general population in prevalences of psychiatric disorders.

The majority (N = 19, 52.8%) of the 36 mutation carriers with a psychiatric diagnosis had a single psychiatric

Table 3. 12-Month Prevalences of Psychiatric Disorders According to the Composite International Diagnostic Interview (CIDI) in Presymptomatic Mutation Carriers, Symptomatic Mutation Carriers, and Noncarriers Compared to the Dutch General Population[a]

	Presymptomatic Mutation Carriers (N = 55)		Symptomatic Mutation Carriers (N = 85)		Noncarriers (N = 56)		General Population (N = 7076),			
Disorder	N	%	N	%	N	%	%	p Value[b,c]	p Value[b,d]	p Value[b,e]
All depressive disorders[f]	11	20.0	14	16.5	4	7.1	…	.06	…	…
Major depressive disorder	10	18.2	14	16.5	4	7.1	5.8	.09	.001	< .001
Dysthymia	1	1.8	2	2.4	0	0	2.3	.50	1.00	.72
Manic episode	1	1.8	2	2.4	0	0	1.1	.50	.46	.25
All anxiety disorders[f]	8	14.5	14	16.5	4	7.1	…	.24	…	…
Panic disorder	2	3.6	4	4.7	2	3.6	2.2	1.00	.35	.13
Agoraphobia without panic	1	1.8	1	1.2	0	0	1.6	.50	.59	1.00
Generalized anxiety disorder	3	5.5	4	4.7	0	0	1.2	.12	.03	.02
Social phobia	3	5.5	5	5.9	1	1.8	4.8	.36	.75	.61
Obsessive-compulsive disorder	3	5.5	3	3.5	1	1.8	0.5	.36	.003	.01
Nonaffective psychosis	0	0	2	2.4	1	1.8	0.2	1.00	1.00	.01
Any psychiatric disorder[f]	15	27.3	21	24.7	7	12.5	…	.06	…	…

[a]No significant differences were found comparing presymptomatic versus symptomatic mutation carriers (all $p > .5$), nor were significant differences found comparing symptomatic mutation carriers versus noncarriers (all $p \geq .09$).
[b]The Fisher exact test for significance (2-sided) was used.
[c]Presymptomatic mutation carriers versus noncarriers.
[d]Presymptomatic mutation carriers versus general population.
[e]Symptomatic mutation carriers versus general population.
[f]Comparison with the general population was not possible for "all depressive disorders" and "all anxiety disorders," since "all depressive disorders" was not mentioned as a separate category in the Netherlands Mental Health Survey and Incidence Study (NEMESIS); nor was it possible to compare "all anxiety disorders" and the prevalence of "any psychiatric disorder," since we did not assess the prevalence of specific phobias, posttraumatic stress disorder, eating disorder, and alcohol or drug abuse, which were included in the NEMESIS.
Symbol: … = not applicable.

disorder, 10 subjects had 2 psychiatric disorders, 6 subjects had 3 psychiatric disorders, and 1 subject had 4 psychiatric disorders.

Analyzing presymptomatic and symptomatic mutation carriers apart, both groups showed significantly increased prevalences of major depressive disorder ($p = .001$ and $p < .001$, respectively) and obsessive-compulsive disorder ($p = .003$ and $p = .01$, respectively) compared to the general population but not to noncarriers. In symptomatic subjects, prevalence of nonaffective psychosis was also significantly increased ($p = .01$). A trend was found for an increased prevalence of generalized anxiety disorder in both presymptomatic and symptomatic mutation carriers ($p = .03$ and $p = .02$, respectively) compared to the general population (Table 3).

Symptomatic mutation carriers did not differ in prevalences of psychiatric disorders from presymptomatic mutation carriers (all $p > .5$). Discriminating symptomatic mutation carriers into "early" and "advanced" symptomatic subjects according to their UHDRS motor score revealed no significant differences either (data not shown, all $p > .2$).

Demographic and Clinical Characteristics Associated With Presence of Psychiatric Disorders

Using logistic regression analysis, we found no significant associations between demographic and clinical characteristics and the presence of psychiatric disorders among all mutation carriers. Among presymptomatic mutation carriers only, a trend was found that subjects with a psychiatric disorder were younger compared to subjects without a psychiatric disorder (mean [SD] = 37.6 [8.8] years and 42.0 [10.7] years, respectively; $p = .04$). In addition, a somewhat higher mean UHDRS total motor score was found in presymptomatic mutation carriers with a psychiatric disorder compared to presymptomatic mutation carriers without a psychiatric disorder (mean [SD] = 3.5 [3.4] points and 1.9 [2.9] points, respectively; $p = .02$).

Using nonlinear generalized canonical correlation analyses, we found no clustering of demographics, clinical characteristics, disease stage, and presence of psychiatric diagnoses.

DISCUSSION

This study, using a fully standardized psychiatric interview, demonstrates that both presymptomatic and symptomatic HD mutation carriers had significantly more formal DSM-IV diagnoses than the general population. Psychiatric disorders were also more prevalent in mutation carriers compared to noncarriers, although not statistically significant, probably due to a lack of power caused by the small groups. Contrary to our assumption, however, noncarriers did not differ from the general population, although noncarriers shared the same potentially stressful environment with mutation carriers.

Affective Disorder

Our study confirms an increased prevalence of depression in mutation carriers compared to the general

population. Most earlier studies, however, measured symptoms of depression and not major depressive disorder meeting formal DSM criteria.[10] Although presymptomatic mutation carriers showed a higher prevalence of major depressive disorder than did the population at large, the difference with noncarriers did not reach statistical significance (p = .06). This is in accordance with the only other study that used the CIDI in HD. This study reported an increased rate of current depressive symptoms but not formal depressive disorder in presymptomatic mutation carriers compared to noncarriers.[23]

To date, the relationship between psychiatric phenotype and HD stage is unclear. Some research indicates a decreased prevalence of depression in advanced disease stage compared to presymptomatic stage.[4,24] However, psychiatric assessment in the advanced stage of HD may be hampered by cognitive deterioration and the increase of physical symptoms. For example, weight loss and disturbed sleeping could be symptoms of neuroendocrine disturbances in HD as well as symptoms of depression. Therefore, in advanced symptomatic HD patients, other diagnostic tools like observation of behavior and relatives' information should be part of the clinical examination.

Prevalences of dysthymia, mania, or bipolar disorder did not differ between our study groups, nor has a difference been reported in earlier studies. One study using DSM criteria reported an increased prevalence of manic symptoms in presymptomatic mutation carriers compared to noncarriers, but these symptoms did not fulfill diagnostic criteria for bipolar disorder.[23]

Anxiety Disorder

Several studies reported increased prevalence of anxiety,[10] but in this study we found only a nonsignificant trend of an increased prevalence of formal generalized anxiety disorder in HD. Most studies, though, used measures with general questions about anxiety, worrying, and tensed feelings, e.g., the behavioral section of the UHDRS,[13] resulting in rates of anxiety symptoms as high as 34% to 61%.[10]

Obsessive-Compulsive Disorders

We found an increased prevalence of obsessive-compulsive disorder in mutation carriers compared to the general population, both in presymptomatic and in symptomatic mutation carriers, whereas until now, occurrence of formal obsessive-compulsive disorder has been described only in case reports, both before[25–27] and after[28] the onset of motor symptoms. Increased prevalences of obsessive and compulsive symptoms, however, have been reported previously.[29–31] Especially in later stages of HD, a more than 3 times greater probability of obsessive-compulsive symptoms in comparison to subjects at 50% risk has been described.[32]

Psychosis

Contrary to the literature[10] and our expectations, the prevalence of nonaffective psychosis in symptomatic mutation carriers in our study was rather low. This may be due to the use of strict DSM-IV criteria, our predominantly outpatient population, and the exclusion of subjects in an advanced disease stage with serious cognitive deterioration. Furthermore, symptomatic mutation carriers used much more psychotropic medication than presymptomatic mutation carriers, which could have suppressed psychiatric symptoms. In particular, the use of the neuroleptic tiapride in symptomatic mutation carriers, which is prescribed for motor symptoms, may have effectively reduced psychotic phenomena.[33,34] This fact would lead to an underestimation of psychosis, particularly in symptomatic mutation carriers.

Environmental and Biological Factors

We could not confirm our assumption that HD family members who were not genetically compromised had more psychiatric disorders than the general population, although they shared a potentially stressful environment. Early life experiences, such as insecure parental binding, the stress of being at risk, and the familial disease burden, do not make them more susceptible to psychiatric disorders compared to the general population. This finding indicates a predominantly neurodegenerative origin of psychiatric disorders in HD.

As the HD mutation itself does not show a full penetrance for the presence of psychiatric disorders, future research should focus on the contribution of other factors, both environmental and biological. Besides playing a part in the risk profile for psychiatric disorders, biological factors may also be markers for disease progression. Since presymptomatic mutation carriers with a psychiatric disorder have a significantly higher UHDRS total motor score compared to presymptomatic mutation carriers without a psychiatric disorder, research on early neuroendocrine and neuroanatomical changes in relation to the occurrence of psychiatric disorders—before the manifestation of movement disorders—is warranted. Although imaging studies on psychopathology in HD are rare, a decreased metabolic activity in orbital frontal-inferior prefrontal regions has been described in depressed HD patients,[35] and disturbed anatomical connections between the basal ganglia and the limbic system have been suggested in HD patients with obsessive-compulsive disorder,[36] all of which require further research.

To our knowledge, this is one of the largest studies among HD mutation carriers in which a validated and fully structured instrument was used to estimate the prevalences of psychiatric disorders according to DSM-IV classification. The use of a control group of first-degree noncarrier relatives is an important strength of this study. A possible limitation of our study is that both interviewers

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and study subjects had knowledge of their genetic status. In a previous study, subjects who were mostly well informed about the symptoms accompanying disease onset tended to conceal symptoms from the interviewer to avoid disclosure of their genetic status.[37] Therefore, interviewers were not blinded for the genetic status of participants, as this would potentially generate a biased response (underreport) on questions about psychiatric symptoms. This may have contributed to increased scores of psychiatric symptoms in mutation carriers. On the other hand, the prevalences of psychiatric disorders might have been underestimated, since those with psychiatric symptoms might have been more likely to refuse participation.[38] Furthermore, relatively small sample sizes and low rates of psychiatric disorders may have compromised the power to detect differences between the study groups.

This study highlights the importance of exploring the full clinical phenotype of HD before motor symptoms arise. The presence of a potentially treatable psychiatric disorder contributes greatly to disease burden and should therefore be a constant point of attention for all who work with HD patients and their families.

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