Chapter 7

Psychiatric disorders in Huntington's disease; a 2-year follow-up study.

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Abstract

Objective: This study investigates the presence and course of formal psychiatric disorders according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV) in 142 Huntington's disease (HD) mutation carriers in a two-year follow-up design.

Method: Of the 142 mutation carriers, 106 (75%) participated in the second measurement of an ongoing cohort study on psychopathology in HD. Presence of psychiatric disorders was assessed using the Composite International Diagnostic Interview.

Results: Of the 91 patients without a formal psychiatric disorder at baseline, 14 (15%) had a psychiatric disorder after two years, mostly a major depressive disorder (MDD) (64%). The baseline characteristics of lower education, having no children, a lower level of global daily functioning, a lifetime psychiatric diagnosis, and the use of psychotropic medication were predictive of incident psychiatric disorders after 2 years. Of the 15 patients with a psychiatric diagnosis at baseline, 8 (53%) no longer had a psychiatric disorder at follow-up. All 7 patients (47%) with a persistent psychiatric disorder were female and their most prevalent diagnosis was generalized anxiety disorder.

Conclusion: This cohort study confirms that psychiatric disorders, in particular MDD, frequently occur in patients with HD. Professionals working with HD patients should therefore be aware of the high risk of psychopathology in HD, because early diagnosis and treatment of psychiatric disorders may improve the quality of life of patients and their caregivers.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder caused by an expanded trinucleotide CAG repeat of the *HTT* gene on chromosome 4p16.3.[1] Clinical features of HD comprise motor abnormalities such as chorea and hypokinesia, cognitive dysfunction, as well as behavioral problems and psychiatric disorders. Behavioral and psychiatric symptoms often precede the manifestation of motor abnormalities of HD.[2,3] In most cases, the age of onset of HD is between 35 and 45 years, whereas the mean duration of disease is 16 years.[4,5] There is no cure for HD and only symptomatic treatment is available.

Depressed mood, anxiety, apathy and irritability are frequently reported neuropsychiatric symptoms in HD, with prevalence rates between 33% and 76%.[4] This broad range can be explained by the use of different assessment methods with varying definitions and cutoffs of neuropsychiatric phenomena in different stages of HD. Of these neuropsychiatric symptoms, only apathy seems to be positively related to the progression of HD.[6]

In a cross-sectional study, we found that both pre-motor symptomatic and symptomatic HD mutation carriers had more formal psychiatric disorders according to the *Diagnostic and Statistical Manual of mental disorders*, 4th edition (DSM-IV), especially major depressive disorder (MDD) and obsessive-compulsive disorder (OCD), compared to the general population.[4] Until now, there are no follow-up studies on the course of psychiatric disorders in HD.

For many patients and their relatives, psychiatric disorders are severely disabling manifestations of HD.[7] Diagnosing and acknowledging the presence of psychopathology in HD is of major importance and may help patients and their families to better cope with the severe symptoms of this progressive disease. Moreover, adequate symptomatic treatment can improve the quality of life of HD patients and their caretakers.

This follow-up study investigates the presence and course of formal psychiatric disorders according to the DSM-IV, as well as their predictors in verified HD mutation carriers.

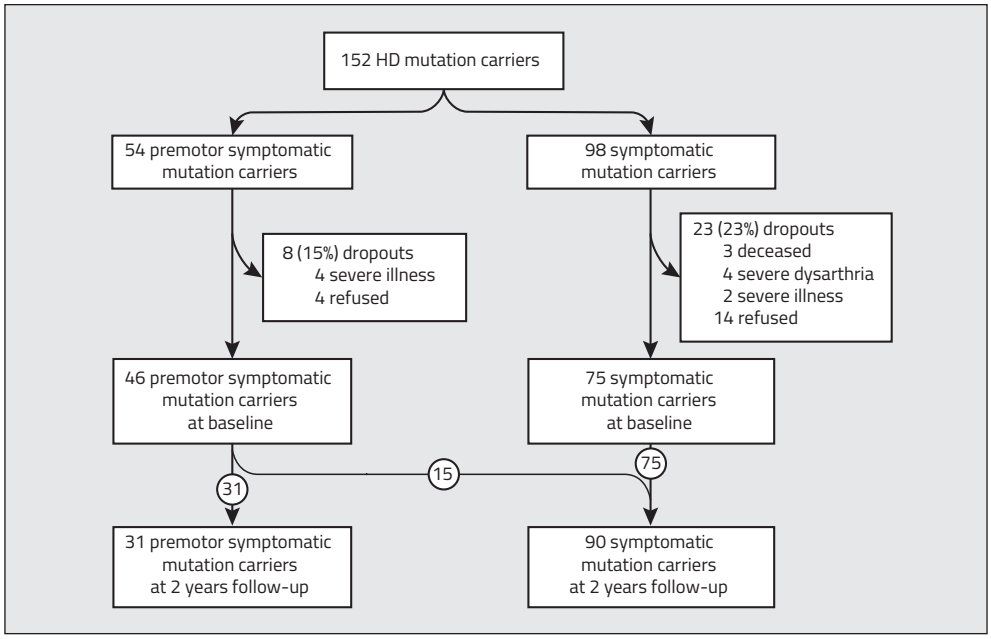
Method

Subjects

Subjects were recruited between May 2004 and August 2006 from the outpatient departments of Neurology and Clinical Genetics of the Leiden University Medical Center, and from a regional nursing home (Overduin in Katwijk) with a specialized ward for HD patients. A detailed description of the study design has been published earlier.[3] In short, this study included 142 verified HD mutation carriers, comprising 55 pre-motor symptomatic mutation carriers and 97 motor symptomatic HD patients. Two years after their initial visit, all subjects were approached for a second measurement. Three subjects were deceased, whereas 22 (15%) were excluded because of severe cognitive

dysfunctioning (n = 7), end-stage disease (n = 8), and severe dysarthria (n = 7). At follow-up, 11 subjects (10%) refused to participate for various other reasons. This resulted in 106 eligible subjects for the present study (Figure 1). The study was approved by the Medical Ethical Committee of the Leiden University Medical Center. All subjects gave written informed consent.

Figure 1. *Flowchart of the study population*



Instruments

Socio-demographic and clinical characteristics

Information on socio-demographic and clinical characteristics was collected using a standardized interview. The estimated age of onset was calculated according to the formula of Vassos et al.: ln [age of onset (years)] = 6.18 - 0.054 * [CAG repeats (number)].[8] Global daily functioning was assessed using the Total Functioning Capacity (TFC) scale, which is part of the Unified Huntington's Disease Rating Scale (UHDRS).[9] The TFC scale consists of five items and the total score ranges from 0 to 13 points, with lower scores indicating worse performance on daily functioning. Presence of motor symptoms was assessed by a neurologist with extensive experience of HD using the motor section of the UHDRS (UHDRS-m). The UHDRS-m ranges from 0 to 124 points, with higher scores indicating more severe motor impairment. On the basis of the clinical examination, the neurologist assigned a score indicating to what degree he was confident that the presence of the movement disorder in a subject was due to HD. This confidence level score ranges from 0 to 4 points. Mutation

carriers with a confidence level score of 0 (normal) or 1 point (nonspecific motor abnormalities [< 50% confidence]) were classified as pre-motor symptomatic. Mutation carriers with a score of 2 to 4 points (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 motor symptomatic. Use of psychotropic medication was registered.

Assessment of psychiatric disorders

Both at baseline and at follow-up, a computerized version of the Composite International Diagnostic Interview (CIDI) was used to assess the presence of MDD, dysthymia, mania, OCD, panic disorder, generalized anxiety disorder (GAD), social phobia, agoraphobia, and psychosis, according to the DSM-IV criteria.[10] The interrater reliability of the CIDI is excellent, and the test-retest reliability and validity are good,[11] except for patients with significant cognitive impairments. Therefore, the CIDI was not administered to subjects with a Mini-Mental State Examination (MMSE) score < 18 points. At baseline, a psychiatric disorder was considered present when the subject fulfilled the DSM-IV criteria on the day of the interview or in the prior month. When subjects reported a psychiatric disorder which ended before the month preceding the interview at baseline, this was considered a lifetime psychiatric diagnosis. After two years the same interview was repeated to assess the presence of a psychiatric disorder in the period between baseline and follow-up.

Neuropsychological assessment

The MMSE, Symbol Digit Modalities Test (SDMT), Verbal Fluency Test (VFT), and Stroop tests were administered to assess cognitive functioning. The MMSE was used to assess global cognitive functioning.[12] The SDMT examines attention, working memory, and visuo-verbal substitution speed.[13] The VFT is sensitive to frontal executive dysfunction and subtle degrees of semantic memory impairment.[14] The Stroop tests were used to measure a person's sustained attention in three conditions: color naming, word reading and naming the color of the ink of an incongruous color name (interference).[15]

Statistical analysis

Data are presented as numbers with percentages, means with standard deviations (SD), or medians with interquartile ranges (IQR) when appropriate. Unpaired *t*-test or non-parametric Mann-Whitney *U*-test, chi-square test, or Fisher's exact test were used when appropriate.

Baseline characteristics of subjects who were lost to follow-up were compared with participants who completed the study.

We categorized the subjects into four groups. The first group consisted of subjects without any psychiatric disorder at either measurement (no psychiatric disorder); the second group was free of psychiatric disorders at baseline, but had one or more psychiatric disorder(s) at follow-up (incident psychiatric disorder); the third group had one or more psychiatric disorder(s) both at baseline and

Table 1. *Baseline socio-demographic and clinical characteristics of 106 mutation carriers based on the presence/absence of psychiatric disorder(s) at two-year follow-up.*

	All Mutation carriers (n=106)	NP (n=77)	IP (n=14)	*p*-value	PP (n=7)	RP (n=8)	*p*-value
Socio-demographic characteristics							
Male gender (n, %)	48 (45)	38 (48)	6 (46)	0.60	0 (0)	5 (83)	0.20
Age (years ± SD)	46 ± 12	46 ± 12	45 ± 11	0.67	45 ± 10	47 ± 19	0.28
Higher education (n, %) [a]	69 (65)	55 (70)	6 (46)	0.001	5 (56)	3 (50)	0.80
Any children (n, %)	78 (74)	60 (76)	8 (62)	< 0.001	7 (78)	4 (67)	0.82
Married or living together (n, %)	80 (76)	58 (73)	10 (77)	0.10	7 (78)	5 (83)	0.17
Clinical characteristics							
CAG repeats (n ± SD)	44 ± 3	43 ± 3	45 ± 2	0.80	43 ± 3	43 ± 2	0.14
Estimated age of onset (years ± SD) [b]	46 ± 7	46 ± 8	44 ± 6	0.36	47 ± 4	48 ± 2	0.44
TFC (points, IQR) [c]	11 (8-13)	12 (9-13)	11 (7-13)	0.03	7 (5-12)	8 (7-10)	0.78
UHDRS-m (points, IQR) [d]	10 (1-32)	11 (1-34)	10 (3-41)	0.13	17 (1-40)	5 (2-21)	0.69
Lifetime psychiatric diagnosis (n, %)	44 (42)	21 (27)	9 (64)	0.01	7 (100)	7 (88)	0.99
Use of psychotropic medication (n, %)	41 (39)	23 (29)	8 (62)	0.002	5 (56)	5 (83)	0.20
MMSE (points, IQR) [e]	28 (26-29)	28 (26-29)	27 (26-29)	0.27	26 (24-28)	28 (25-30)	0.69
ExCog [f]	0.00	0.06	-0.27	0.93	0.14	-0.26	0.97

NP = no psychiatric disorder both at baseline and follow-up; IP = incident psychiatric disorder; PP = persistent psychiatric disorder; RP = remitted psychiatric disorder.
Data are presented as numbers (%), means (± SD) or medians (IQR) when appropriate. *P*-values are calculated by chi-square test, non-parametric Mann Whitney-U test and unpaired *t*-test.

[a] Higher education = > 12 years of education;
[b] Estimated age of onset is computed according to the Vassos formula;[7]
[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance;
[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms;
[e] MMSE = Mini-Mental State Examination: range 0-30 points;
[f] ExCog = executive cognitive function is defined by 5 index *z*-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, with lower score indicating worse performance.

at follow-up, independent of the type of psychiatric disorder (persistent psychiatric disorder); and the fourth group had one or more psychiatric disorders at baseline, but none at follow-up (remitted psychiatric disorder).

Because of the low numbers of incident, persistent, and remitted psychiatric disorders, we mainly used simple descriptive statistics for the presence and course of psychiatric disorders, since formal statistical comparison of these groups was hampered by a low statistical power and a high risk of type I errors.

A composite variable for executive cognitive functioning (ExCog) was computed because of strong collinearity (r > 0.80) between the SDMT, VFT, and three Stroop tests. This variable was computed by averaging the standardized *z*-scores of these 5 tests total scores (i.e. subtracting the mean from an individual raw score and then dividing the difference by the SD).

To analyze possible differences in socio-demographic and clinical characteristics, we compared the baseline characteristics of the group with incident psychiatric diagnoses with the group without psychiatric diagnoses at follow-up. All tests were two-tailed with $p < 0.05$ denoting statistically significance. SPSS 17.0 for Windows (SPSS Inc., Chicago, Ill) was used for the statistical analyses.

Results

Table 1 presents the baseline characteristics of all participating mutation carriers combined, as well as the four follow-up groups separately. Of the 91 subjects without a psychiatric diagnosis at baseline, 14 (15%) had one or more incident psychiatric disorder(s) over the two-year follow-up period. Of these, 3 subjects had more than one psychiatric disorder. All 7 subjects with a persistent psychiatric disorder were female, and GAD was the most prevalent disorder in this group. Of the 15 subjects with one or more psychiatric disorder(s) at baseline, 8 had a remission of the psychiatric disorder(s) at follow-up.

The baseline characteristics low education ($p = 0.001$), having no children ($p < 0.001$), lower TFC score ($p = 0.03$), a lifetime psychiatric diagnosis, and the use of psychotropic medication ($p = 0.002$) were predictive of incidence of psychiatric disorders, as compared to the group without psychiatric disorders at both baseline and follow-up. No significant differences were found between the persistent and remitted groups.
The 36 (25%) subjects who were lost to follow up (Figure 1) had a similar baseline prevalence rate of psychopathology as compared to the participants (22% and 26%, respectively). These drop-outs showed a higher median UHDRS-m score (37 points versus 10 points; $p < 0.001$), a lower median MMSE score (26 points versus 28 points; $p = 0.008$), and a lower median TFC score (7 points versus 11 points; $p = 0.001$), compared to the participating subjects, indicating that they were in a more advanced disease stage at baseline (data not shown).

Incident psychiatric disorders
Of the 14 subjects with an incident psychiatric disorder in the follow-up period, 9 (64%) had a MDD. Two subjects with MDD had one (panic disorder) or two (GAD and social phobia) comorbid psychiatric disorder(s). Furthermore, one subject had psychosis, one panic disorder and comorbid mania, one social phobia, one OCD, and one subject had agoraphobia (Table 2). Ten subjects with an incident psychiatric disorder used psychotropic medication at follow-up, whereas four subjects with MDD did not use psychotropic medication. Eight subjects were already using psychotropic medication at baseline, despite the fact that they did not fulfill the criteria for a formal DSM-IV diagnosis at that time. Nine subjects showed a decline of 3 points or more on the TFC scale in the two-year follow-up, indicating a deterioration of their functioning over time. Nine subjects were pre-motor symptomatic at baseline, of whom two became motor symptomatic during the follow-up period.

Persistent psychiatric disorders
Seven HD mutation carriers, all female, had one or more persistent psychiatric disorder(s) at follow-up, although in five subjects the diagnosis was changed into another psychiatric disorder during the

Table 2. *Socio-demographic and clinical characteristics of 14 mutation carriers (I-XIV) with incident psychiatric disorder(s) at two-year follow-up.*

Incident psychiatric disorder	I MDD	II MDD	III MDD	IV MDD	V MDD	VI MDD	VII MDD, PD	VIII MDD, GAD, SPH	IX MDD	X PSY	XI PD, M	XII SPH	XIII OCD	XIV APH
Socio-demographic characteristics														
Gender	m	f	m	f	m	f	f	f	m	f	M	f	m	m
Age (years)	32	33	35	38	40	40	46	53	63	48	44	50	66	69
Higher education[a]	-	+	+	-	+	+	-	-	-	-	+	-	-	+
Children	0	2	0	0	1	2	0	1	2	3	3	4	0	0
Married or living together	-	+	+	+	+	-	+	+	+	+	+	-	-	+
Clinical characteristics														
CAG repeats	47	45	45	45	44	47	43	46	44	46	40	51	41	42
Estimated age of onset (years)[b]	38	43	43	43	45	38	47	40	45	36	56	31	53	50
TFC at baseline (points)[c]	13	12	13	11	9	13	7	7	6	2	12	4	3	13
TFC at follow-up (points)	8	13	7	8	3	13	6	3	3	5	5	0	2	9
UHDRS-m at baseline (points)[d]	10	2	0	10	24	4	9	36	46	54	0	47	67	4
UHDRS-m at follow-up (points)	9	2	3	7	32	17	7	56	47	81	8	34	65	10
Motor symptomatic at baseline[e]	+	-	-	+	+	+	-	+	+	+	-	+	+	-
Lifetime psychiatric diagnosis	-	MDD	MDD, GAD	OCD	MDD	-	MDD, GAD, PD	MDD, DYS, PD	MDD, PSY	-	PD	DYS	-	-
Use of psychotropic medication at baseline[f]	-	-	SSRI	B	SSRI	-	-	SSRI, B	Tiap, SSRI	SSRI	SSRI	SSRI, AAP	-	-
Use of psychotropics at follow-up	-	-	SSRI	AAP, B	SSRI	-	-	SSRI, AAP, B	Tiap, SSRI	SSRI, AAP, B	SSRI, AAP, B	SSRI, AAP, B	AAP	B
MMSE at baseline (points)[g]	25	29	29	25	27	26	28	29	27	18	27	27	27	28
MMSE at follow-up (points)	28	30	29	28	26	28	30	28	29	21	29	22	20	29
ExCog decline[h]	+	-	-	-	+	+	-	-	-	-	+	-	-	-

MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; SPH = social phobia; PSY = psychosis; M = mania; OCD = obsessive-compulsive disorder; APH = agoraphobia.

[a] Higher education ≥ 12 years of education.

[b] Estimated age of onset is computed according to the Vassos formula.[7]

[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance.

[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms.

[e] '-' = pre-motor symptomatic (Confidence Level score: 0 - 1); '+' = motor symptomatic (Confidence Level score: 2 - 4).

[f] SSRI = selective serotonin re-uptake inhibitors; AAP = atypical antipsychotics; B = benzodiazepines, Tiap = tiapridal.

[g] MMSE = Mini-Mental State Examination: range 0-30 points.

[h] ExCog = executive cognitive function: '+' = decline, '-' = incline. ExCog is defined by 5 index *z*-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, lower score indicating worse performance.

Table 3. *Socio-demographic and clinical characteristics of 7 mutation carriers (I-VII) with persistent psychiatric disorder(s) at two-year follow-up.*

	I	II	III	IV	V	VI	VII
Socio-demographic characteristics							
Gender	f	f	F	f	f	f	f
Age (years)	54	51	44	31	29	55	53
Higher education[a]	+	-	+	+	+	-	-
Children	0	1	2	1	0	2	2
Married or living together	+	+	+	+	-	+	+
Clinical characteristics							
Psychiatric disorder at baseline	MDD, PD	MDD, DYS, SPH	OCD	GAD, SPH	MDD, GAD, SPH	GAD, PD	MDD
Psychiatric diagnosis at follow-up	APH	MDD, GAD, PD	MDD, OCD	MDD, DYS, GAD, SPH	GAD, SPH	GAD, PD	MDD
CAG repeats	42	43	43	45	45	44	41
Estimated age of onset (years)[b]	50	47	47	42	42	45	53
TFC at baseline (points)[c]	9	7	5	13	10	6	4
TFC at follow-up (points)	8	4	2	11	12	6	4
UHDRS-m at baseline (points)[d]	17	31	4	0	2	60	30
UHDRS-m at follow-up (points)	42	19	23	5	3	59	48
Motor symptomatic at baseline[e]	+	+	-	-	-	+	+
Lifetime psychiatric diagnosis	DYS, GAD, PD	MDD, DYS, SPH	MDD, GAD, OCD	MDD, GAD, SPH	MDD, GAD, SPH	GAD, PD	MDD, PD
Psychotropic medication at baseline[f]	SSRI	TCA, AAP, B	-	-	SSRI, B	-	SSRI, B
Psychotropics at follow-up	SSRI	TCA, AAP, B	SSRI, Tiap, B	SSRI	SSRI	B	SSRI, AAP, B
MMSE at baseline (points)[g]	30	22	25	25	30	26	26
MMSE at follow-up (points)	28	24	28	27	30	28	24
ExCog decline[h]	-	-	+	+	+	+	+

MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; PSY = psychosis; SPH = social phobia; OCD = obsessive-compulsive disorder; APH = agoraphobia; M = mania.

[a] Higher education ≥ 12 years of education.

[b] Estimated age of onset is computed according to the Vassos formula.[7]

[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance.

[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms.

[e] '-' = pre-motor symptomatic (Confidence Level score: 0 - 1); '+' = motor symptomatic (Confidence Level score: 2-4).

[f] SSRI = selective serotonin re-uptake inhibitors; AAP = atypical antipsychotics; B = benzodiazepines, Tiap = tiapridal.

[g] MMSE = Mini-Mental State Examination: range 0-30 points.

[h] ExCog = executive cognitive function: '+' = decline, '-' = incline. ExCog is defined by 5 index *z*-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, lower score indicating worse performance.

Table 4. *Socio-demographic and clinical characteristics of 8 mutation carriers (I-VIII) with remitted psychiatric disorder(s) at two-year follow-up.*

Psychiatric disorder at baseline	I OCD	II MDD, OCD	III GAD, SPH, APH	IV SPH	V PD, OCD	VI SPH	VII MDD	VIII MDD
Socio-demographic characteristics								
Gender	f	m	m	m	F	M	F	m
Age (years)	43	72	31	57	41	37	24	60
Higher education[a]	-	-	-	+	+	+	+	-
Children	1	0	0	2	2	1	1	2
Married or living together	-	+	-	+	+	+	+	+
Clinical characteristics								
CAG repeats	41	43	43	43	43	43	44	42
Estimated age of onset (years)[b]	53	47	47	47	47	47	45	50
TFC at baseline (points)[c]	13	4	8	8	3	11	8	10
TFC at follow-up (points)	11	1	12	5	2	12	12	10
UHDRS-m at baseline (points)[d]	0	65	2	6	49	4	0	5
UHDRS-m at follow-up (points)	4	59	18	8	60	9	-	16
Motor symptomatic at baseline[e]	-	+	-	+	+	+	-	-
Lifetime psychiatric diagnosis	MDD, OCD	OCD	DYS, GAD, SPH, APH	GAD, SPH	MDD, PD, OCD	SPH	-	MDD
Psychotropic medication at baseline[f]	-	SSRI, AAP, B	-	SSRI	SSRI, B	SSRI, B	B	B
Psychotropic medication at follow-up	-	SSRI	SSRI	SSRI, Tiap	SSRI, AAP, B	SSRI, B	B	SSRI, AAP, B
MMSE at baseline (points)[g]	26	23	30	28	22	28	30	26
MMSE at follow-up (points)	26	25	29	27	20	30	30	25
ExCog decline[h]	-	+	+	+	+	-	-	-

MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; PSY = psychosis; SPH = social phobia; OCD = obsessive-compulsive disorder; APH = agoraphobia; M = mania.

[a] Higher education ≥ 12 years of education.

[b] Estimated age of onset is computed according to the Vassos formula.[7]

[c] TFC = Total Functioning Capacity: range 0-13 points, with lower score indicating worse performance.

[d] UHDRS-m = Unified Huntington's Disease Rating Scale motor section: range 0-124 points, with higher score indicating more neurological symptoms.

[e] '-' = pre-motor symptomatic (Confidence Level score: 0 - 1); '+' = motor symptomatic (Confidence Level score: 2-4).

[f] SSRI = selective serotonin re-uptake inhibitors; AAP = atypical antipsychotics; B = benzodiazepines, Tiap = tiapridal.

[g] MMSE = Mini-Mental State Examination: range 0-30 points.

[h] ExCog = executive cognitive function: '+' = decline, '-' = incline. ExCog is defined by 5 index z-scores derived from SDMT, VFT, and 3 Stroop tests in SD from the mean, lower score indicating worse performance.

follow-up period (Table 3). MDD (n=3 at baseline, and n=3 at follow-up) and GAD (n=3 at baseline, and n=4 at follow-up) were the most frequently occurring psychiatric disorders in this group. Three subjects with a persistent psychiatric disorder did not use psychotropic medication at baseline, but all 7 received psychotropic medication at follow-up.

Remitted psychiatric disorders
Eight HD mutation carriers had one or more psychiatric disorder(s) at baseline, but no longer after two years (Table 4). The most frequent remitted psychiatric disorders in this group were MDD (n=3), OCD (n=3), and social phobia (n=3). Six subjects used psychotropic medication at baseline, and only one did not receive psychotropic medication at follow-up. This medication-free subject had a remitted OCD.

Discussion

In this prospective cohort study among HD mutation carriers, 15% of the subjects without a psychiatric disorder at baseline had a formal psychiatric disorder after two years, mostly a MDD (64%). Baseline predictors for these subjects with incident psychopathology were lower education, less often having children, poorer daily global functioning, a lifetime psychiatric diagnosis, and the use of psychotropic medication. Of the 15 subjects with a psychiatric diagnosis at baseline, 8 (53%) no longer had a psychiatric disorder at follow-up. All 7 subjects (47%) with a persistent psychiatric disorder were female and GAD was their most prevalent diagnosis; some of these affected women were diagnosed with different psychiatric disorders after two years of follow-up. Most subjects with a psychiatric diagnosis at follow-up received psychopharmacological treatment, although not always adequately.

Because of the small number of subjects with psychopathology and a subsequent lack of power for further analysis, our results need to be interpreted with caution. Nevertheless, we have confirmed the high incidence of MDD in HD. Although longitudinal studies are lacking, this result is consistent with reported high prevalences of MDD of up to 30%.[4,16] This result contrasts with incidence rates found in other neurodegenerative disease, i.e. Parkinson's disease, in which an incidence rate of MDD of 2% per year is reported,[17,18] and with incidence rates found among the general population, as the two-year incidence rates of psychopathology among the general population are around 4%.[19] No follow-up studies on the incidence of formal psychiatric disorders in HD have been published, but some studies assessed the incidence and course of psychiatric symptoms and behavioral problems during the progression of HD.[20-22] Large multi-center studies are currently in progress to assess the course of HD in more detail, including psychiatric symptoms and behavioral problems.[23-25]

In the present study, some subjects with a persistent psychiatric disorder switched to another psychiatric disorder after two years. These transitions between specific psychiatric diagnoses and the occurrence of comorbid psychiatric disorders indicate diagnostic instability. There are several explanations for this instability in HD. First, diagnostic instability may be due to profound fluctuations in disease manifestations over time, or merely to a consequence of rigid diagnostic criteria. Consequently, the features and course of psychopathology in HD are probably not fully captured with the formal DSM-IV criteria, as has been reported for other neurodegenerative diseases.[26,27] Moreover, the presence of physical symptoms of HD (such as chorea, weight loss, and sleeping problems) may interfere with the psychiatric diagnosis. Second, assessing psychopathology in patients with moderate to severe HD is often challenging due to a possible lack of insight or poor disease awareness, combined with comorbid cognitive impairments. Caregivers or other informants are often needed to provide information during the assessment of psychopathology in advanced symptomatic HD patients, which may lead to information that is inconsistent with that elicited by patients and to overestimated prevalences of psychiatric disorders.

Although it was not the focus of this study, only 57% of the subjects with an incident psychiatric disorder at follow-up appeared to receive adequate psychopharmacological treatment according to the Dutch treatment protocols. However, it remains unclear whether this was related to a lack of recognition of psychopathology in HD. Nevertheless, adequate treatment is important to induce remission of the psychiatric disorder, to improve the quality of life, and to reduce the risk of suicide. All subjects with a persistent psychiatric disorder used some kind of psychotropic medication that is indicated for the distinct disorders. Selective serotonin reuptake inhibitors (SSRI) were the most often used antidepressants, whereas almost no tricyclic antidepressants were used; this is in line with recommendation made in an earlier review.(28) However, we do not know whether subjects received non-pharmacological interventions (e.g., psychotherapy) instead of – or parallel to – medication, although the efficacy of psychotherapy has scarcely been studied in HD. Psychotropic medication was also used by 29% of the subjects free of a psychiatric diagnosis at baseline. This group may have had a psychiatric diagnosis prior to baseline, being adequately treated.

The group with incident psychopathology had a slightly, but significantly, lower baseline TFC score compared to the group without psychiatric diagnoses at both measurements. Since the persistent and remitted groups also had lower baseline TFC scores, this indicates that having a psychiatric disorder is inversely associated with global daily functioning. This is in line with a recent study reporting that motor, cognitive, and mood symptoms are highly associated with poorer general function.[29]

We found no association between baseline measures of motor functioning or global cognitive functioning and transitions in the presence of psychiatric disorders. This confirms the results of earlier studies, in which no associations were found between psychopathology (such as depressive or anxiety symptoms), and cognitive or motor deterioration, or CAG length.[30,31]

The strength of this study is its prospective design and the use of validated and fully structured instruments to assess formal psychiatric disorders in HD mutation carriers. Limitations of the study are the relatively low number of subjects and the high number of drop-outs. Although the prevalence rates of psychiatric disorders at baseline were similar in the participating group versus drop-outs, different forms of bias cannot be ruled out.

We conclude that professionals working with HD patients should be aware of the high risk of psychopathology in HD. Adequate and early diagnosis and treatment of psychiatric disorders may improve the quality of life of patients and their caregivers, and lower suicide risk. Larger longitudinal studies are needed to confirm our findings, and to assess the independent predictors for incident psychiatric disorders in HD.

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