Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/37384 holds various files of this Leiden University dissertation.

Author: Hubers, Anna Alida Maria (Marloes)
Title: Suicidality in Huntington's disease
Issue Date: 2016-01-21

Chapter 2

Suicidality in Huntington's disease

AAM Hubers, N Reedeker N, EJ Giltay, RAC Roos, E van Duijn, RC van der Mast

J Affect Disord 2012;136(3):550-557

Abstract

Background: In Huntington's disease (HD) the risk of suicide is increased. Since suicidality may precede suicide, this study investigates prevalence, clinical associations and predictors of suicidality in HD.

Methods: Suicidality was investigated in 152 mutation carriers and 56 non-carriers, and was considered present if the score on the item 'suicidal ideation' of the Problem Behaviours Assessment (PBA) was >1 point. After 2 years, 100 mutation carriers who were free of suicidality at baseline were re-assessed. Associations and predictors of suicidality were analysed using multivariate logistic regression analysis.

Results: Eleven (20%) pre-motor and 20 (20%) motor symptomatic mutation carriers were considered suicidal compared to none of the non-carriers. Cross-sectionally, suicidal mutation carriers were more likely to use antidepressants (odds ratio = 5.3), were more often apathetic (OR = 2.8), more often had a depressed mood according to the PBA (OR = 5.9), and were more often diagnosed with a DSM-IV depression diagnosis (OR = 4.7). Independent associations were more frequent use of antidepressants (OR = 4.0) and presence of a depressed mood (OR = 4.2). Longitudinally, depressed mood (OR = 10.6) at baseline was the only independent predictor of suicidality at follow-up.

Limitations: Selection bias might have occurred which could have affected the suicidality prevalence and incidence.

Conclusion: It is important to screen both pre-motor and motor symptomatic HD mutation carriers for suicidality. The presence of a depressed mood is both associated with and predictive of suicidality in HD and assessment of depressed mood can help to identify individuals with increased risk for suicide.

Introduction

Huntington's disease (HD) is a neurodegenerative, autosomal dominantly inherited disease.[1] An expanded CAG repeat on the short arm of chromosome 4 causes an expanded polyglutamine chain in the huntingtin protein.[2] Motor disorders, cognitive decline and both behavioural problems and psychiatric disorders are part of the clinical presentation of HD, with progression of symptoms over time. Some of these symptoms can be treated but the disease cannot be cured.

Behavioural problems and psychiatric disorders are major constituents of the clinical spectrum of HD;[3] many patients and their relatives consider these problems to be the most distressing aspect of the disease.[4] An important clinical aspect of HD is the increased risk of suicide, as was described by George Huntington in 1872.[5] Patients with HD were shown to commit suicide four to eight times more often than the general population.[6-8] A suicide risk of 5.7 suicides per 100 deaths has been reported in HD,[6] whereas the suicide risk in the general Dutch population is about 1 suicide per 100 deaths.[9] A study investigating suicidality over the previous thirty days reported a relatively high prevalence of 19% in motor symptomatic HD mutation carriers,[10] whereas the lifetime prevalence of suicidality in a mixed population of both pre-motor and motor symptomatic HD mutation carriers was 20%.[11] In comparison, 11% of the general Dutch population, aged 18 to 64 years, ever considered suicide and 3% ever performed a suicide attempt.[12] The increased prevalence of suicidality and suicide may be related to the emotional distress of having an incurable disease as well as the psychopathology that is common in HD.

In the HD population, sociodemographic and clinical characteristics such as having no offspring,[13;14] being unemployed,[15] the presence of a depressed mood[10;11;16] and a psychiatric history[15] were found to be of importance for suicidality and suicide. However, most studies investigating suicidality or suicide in HD were retrospective,[14] or cross-sectional[10;11;13] or they focused on persons undergoing predictive testing for HD.[6;7;15] The only prospective study investigating suicidality in HD focused on suicidal behaviour in prodromal HD.[16] Some studies used survey data obtained from family members[17] or included a low number of participants.[14] Also, several studies focused on completed suicide,[13;14;17] rather than on suicidal thoughts and attempts, whereas suicidal ideation may be of particular importance because it is a strong risk factor for and antecedent of completed suicide.[18;19]

The present study aimed to assess the prevalence of suicidality, defined as the presence of suicidal ideation or suicide attempt in the month preceding the interview, in HD mutation carriers and a control group of non-carriers. Cross-sectionally, we wanted to investigate possible

sociodemographic and clinical characteristics associated with suicidality and longitudinally we analysed the possible baseline predictors of suicidality at 2-year follow-up. We hypothesised that, similar to the general population, suicidality in HD is linked to psychopathology, in particular depression.

Method

Participants

Between May 2004 and August 2006, 343 potential participants at initial 50% risk of HD were contacted through the departments of Neurology and Clinical Genetics of the Leiden University Medical Center and a nursing home specialised in the daily care of HD patients. Of these, 192 were willing and able to participate in this study. In addition, 16 participants were enrolled via the Dutch HD patients' association after posting an announcement on their internet site and in their quarterly. Finally, 152 mutation carriers (CAG repeat length ≥ 36) and 56 non-carriers were included in the cross-sectional analysis. The design of this study has been described in detail elsewhere.[20]

Two years after their initial visit, all participants were approached for a second measurement. Follow-up data from mutation carriers who were free of suicidality at baseline (n = 121) were used in the longitudinal analyses. Of them, 21 (17.4%) dropped out due to a variety of reasons. One person was deceased and one person was untraceable, whereas eight were excluded because of inability to speak, too severe symptomatology or other medical conditions. The remaining 11 persons refused to participate because they did not feel like it, or due to private circumstances. This resulted in 100 eligible mutation carriers for follow-up assessment (Figure 1).

This study was approved by the Medical Ethical Committee of the Leiden University Medical Center. Written informed consent was obtained from all participants. Because many institutionalised participants had cognitive deficiencies, special attention was paid to this important issue by contacting their physicians and asking them to thoroughly discuss study participation with these patients and their family members, before giving consent.

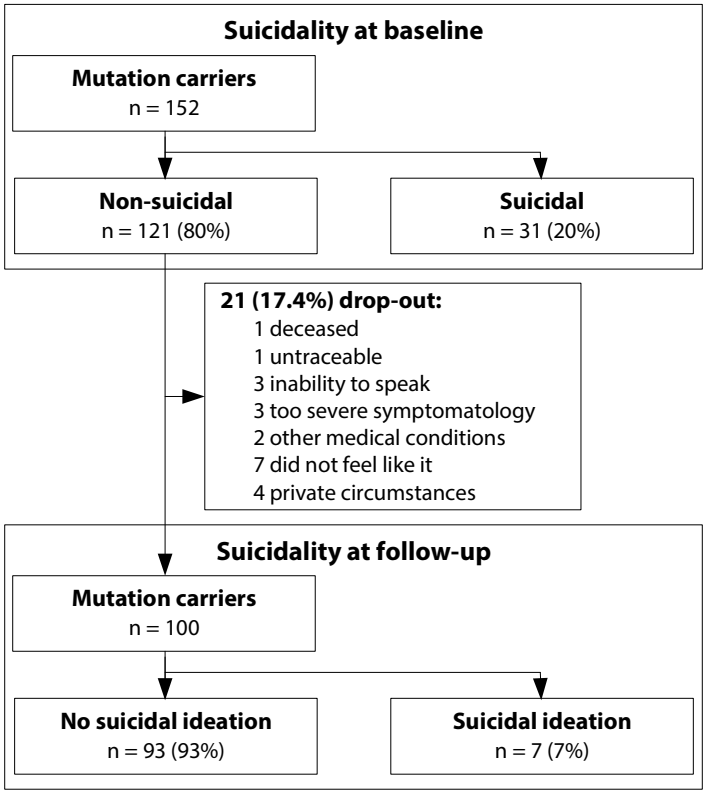


Figure 1. Flowchart of drop-outs in the present study.

Instruments

Assessment of suicidality

Suicidality was assessed using the validated Problem Behaviours Assessment (PBA).[21] The PBA is a semi-structured interview specifically designed for patients with HD, assessing the frequency and severity of 36 common behavioural problems. The interrater reliability of the PBA (Dutch translation) is 0.82 for severity scores and 0.73 for frequency scores.[22]

Severity and frequency of suicidality in the month preceding the interview were assessed with the item 'suicidal ideation' of the PBA (question 8) (Figure 2A). The total suicidality score is computed by multiplying the severity and frequency scores of this item, resulting in total scores ranging from 0 through 16. Based on clinical experience, a total (multiplied) suicidality score > 1 point was used to characterise suicidality (Figure 2B), meaning that participants

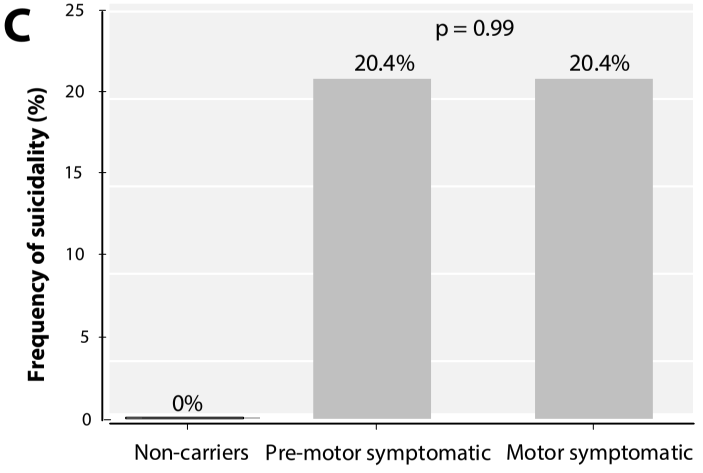
A **Frequency ratings for suicidality**

0 – **Never** or almost never
1 – **Seldom**; less than once a week
2 – **Sometimes**; at least once, up to three/four times a week
3 – **Frequently**; five, six or seven times a week
4 – **Every day**; or almost every day for most/all of the day

Severity ratings for suicidality

0 – **Absent**
1 – **Questionable**; also rate 1 if subject plans suicide at a later date when disease is more severe but obtains comfort from this as means to retain control of destiny
2 – **Mild**; sometimes very pessimistic with fleeting suicidality
3 – **Moderate**; subject has pervasive and distressing feelings of hopelessness and frequent suicidal ideation, but has not yet acted on this in any way
4 – **Severe**; subject has attempted or prepared suicide

C



B

Severity of suicidality	Frequency of suicidality				
	Absent (0)	**Seldom (1)**	**Sometimes (2)**	**Frequently (3)**	**Every day (4)**
Absent (0)	114 (75%)	0 (0%)	(0%)	0 (0%)	0 (0%)
Questionable (1)	0 (0%)	7 (4.6%)	5 (3.3%)	1 (0.7%)	5 (3.3%)
Mild (2)	0 (0%)	5 (3.3%)	4 (2.6%)	3 (2.0%)	1 (0.7%)
Moderate (3)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)	3 (2.0%)
Severe (4)	0 (0%)	1 (0.7%)	1 (0.7%)	0 (0%)	0 (0%)

Figure 2. Suicidality in the study population.

Box A shows the rating scale of suicidality according to item 8 of the Problem Behaviours Assessment, composed of severity and frequency ratings. The total suicidality score is calculated as the severity rating multiplied by the frequency rating. Participants scoring > 1 are considered suicidal. Box B shows the frequency and severity suicidality scores of all 152 mutation carriers. The shaded area indicates the suicidal mutation carriers (n = 31; 20.4%). Box C shows the frequency of suicidality in the study population according to categories of non-carriers, pre-motor symptomatic (UHDRS motor score confidence level ≤ 1) and motor symptomatic mutation carriers (UHDRS motor score confidence level > 1).

scoring a total score of 1 on the 'suicidal ideation' item were not considered suicidal, since suicidal ideation is then 'questionable and seldom' present according to the participant or interviewer. When participants were very pessimistic with fleeting suicidal thoughts, although 'seldom' (less than once a week), they scored 2 points on the 'suicidal ideation' item. These participants were categorised as being suicidal. The cut-off value also implies that participants who were not actively suicidal at the time of assessment, but 'sometimes' (at least once a week) considered suicide as an option for a later date, were categorised as being suicidal.

Sociodemographic and clinical characteristics
Information on sociodemographics and clinical characteristics, and use of psychotropics was collected using a standardised interview.

Total Functioning Capacity (TFC) subscale of the Unified Huntington's Disease Rating Scale (UHDRS) was used to assess global functioning.[23] Scores range from 0 through 13 points, with lower scores indicating poorer global functioning.[24]

Motor function was assessed by an experienced neurologist using the motor scale of the UHDRS.[23] This scale includes the rating of 15 motor symptoms on a scale from 0 (normal) to 4 (severe). The total UHDRS motor score is the sum of these 15 individual items. Total scores range from 0 through 124 points, with higher scores indicating worse motor functioning. The diagnostic Confidence Level (CL) of this UHDRS motor scale[23] was used to define mutation carriers as pre-motor symptomatic (CL score 0 or 1 point) or motor symptomatic (CL score 2 through 4 points).

Neuropsychiatric characteristics
Apathy was assessed using the Apathy Scale (AS).[25] This semi-structured interview consists of 14 questions to determine the level of apathy, with scores ranging from 0 through 3, with a maximum total score of 42 points. A cutoff score ≥ 14 points was used to indicate presence of apathy.[25;26]

The item 'depressed mood' from the PBA[21] was used to assess severity and frequency of a depressed mood in the month preceding the interview, with both severity and frequency scores ranging from 0 (normal/never) to 4 (severe/always). Based on clinical experience, a total (multiplied) depressed mood score > 1 point was used to characterise the participant as having a depressed mood, since a total score of 1 on the 'depressed mood' item is scored when the presence of a depressed mood is questionable and seldom according to the participant or interviewer.

The Dutch translation of the computerised version of the Composite International Diagnostic Interview (CIDI, Version 2.1)[27] was used to assess the presence of a psychiatric disorder according to the criteria of the Diagnostic Statistical Manual (DSM) of mental disorders, version IV.[28] The CIDI is a completely structured and standardised psychiatric diagnostic interview. The CIDI was not administered in participants scoring < 18 points on the Mini-Mental State Examination, since the CIDI cannot be reliably administered in participants with such severe cognitive dysfunction.

Cognitive characteristics

The Mini-Mental State Examination (MMSE) was used to determine global cognitive functioning. The ExCog was used as a measure for executive cognitive function. This composite variable was obtained by averaging the standardised z-scores of the cognitive subscales of the UHDRS,[23] including the Verbal Fluency Test (VFT),[29] the Symbol Digit Modalities Test (SDMT)[30] and the Stroop tests.[31]

Statistical analyses

Data are presented as n (%), mean (±SD) or median (interquartile range, IQR) when appropriate. Sociodemographic and clinical characteristics of HD mutation carriers and non-carriers were compared by chi-squared tests for categorical data, t-tests for independent samples with normal distributions, or non-parametric Whitney-U tests for continuous variables without normal distributions.

Suicidal mutation carriers were compared with non-suicidal mutation carriers using univariate logistic regression analysis. Scores on the independent variables TFC, UHDRS-motor, MMSE and ExCog were dichotomised at the median. The independent cross-sectional associations of suicidality in HD were determined by multiple forward logistic regression analysis. Variables included in this analysis had a p-value ≤ 0.10 in the univariate logistic regression and we also adjusted for sex and age (being forced into the model). The overall use of psychotropic medication was not included in the analysis because of overlap with the use of antidepressants. The presence of a formal DSM-IV diagnosis of depression according to the CIDI was not included in the original models because the CIDI could not be administered in 12 participants scoring < 18 points on the MMSE.

Non-suicidal mutation carriers at baseline, who became suicidal at follow-up, were compared with those mutation carriers who did not become suicidal at follow-up using univariate logistic regression analyses. Since only 7 mutation carriers had incident suicidality at the 2-year follow-up that resulted in low power, the multivariate cross-sectional model was the only one tested

using the longitudinal data in which the significant associations of suicidality in the cross-sectional model (use of antidepressants and presence of a depressed mood according to the PBA) and sex and age were entered. A p-value < 0.05 was considered statistically significant. SPSS version 16.0 was used.

Results

Mutations carriers versus non-carriers

Compared with the 56 non-carriers, the 152 mutation carriers were significantly older and more often had a depressed mood according to the PBA, although there was no significant difference in the presence of a formal DSM-IV diagnosis of depression. Mutation carriers also had worse cognitive scores on all cognitive tests compared with non-carriers (data not shown). Suicidality was only present in mutation carriers (Figure 2C).

Comparison of Huntington's disease mutation carriers with and without suicidality

At baseline, 31 mutation carriers (20%) were considered suicidal according to the PBA, whereas 121 mutation carriers (80%) were not (Table 1, Figure 2B, C). There was no significant difference in the prevalence of suicidality between pre-motor symptomatic (CL ≤ 1) and motor symptomatic (CL ≥ 2) mutation carriers (Figure 2C). Also, there was no significant difference in presence of suicidality between participants who received their genetic test result in the year preceding the interview and those who received their genetic test result more than a year prior to the interview (data not shown).

Univariate analyses showed a significantly higher use of psychotropics (specifically antidepressants) in suicidal mutation carriers compared with non-suicidal mutation carriers. Suicidal mutation carriers were more often apathetic, more often had a depressed mood according to the PBA, and were more often diagnosed with a formal DSM-IV diagnosis of depression. There was no significant difference between the two groups in cognitive functioning (Table 1).

Table 1. Sociodemographic and clinical characteristics as associations of suicidality in Huntington's disease mutation carriers.[a]

	Non-suicidal (n = 121)	**Suicidal** (n = 31)	**Odds Ratio**[b]	**95% CI**[b]	**p-value**[b]
Sociodemographic characteristics					
Male gender (n, %)	55 (46%)	14 (45%)	0.99	0.45 – 2.18	0.98
Age (years ± SD)	47.9 ± 11.5	47.2 ± 13.2	1.00	0.96 – 1.03	0.79
Married or with partner (n, %)	89 (74%)	22 (71%)	0.88	0.37 – 2.11	0.77
Children (n, %)	95 (80%)	19 (68%)	0.53	0.22 – 1.33	0.18
Institutionalised (n, %)	10 (8%)	4 (13%)	1.64	0.48 – 5.65	0.43
Clinical characteristics					
CAG repeats (number ± SD)	44.1 ± 3.2	43.9 ± 2.9	0.98	0.86 – 1.11	0.70
Estimated duration of disease[c] (years ± SD)	2.6 ± 11.4	1.5 ± 13.5	0.99	0.96 – 1.03	0.64
TFC score[d] ≤ 10.5 points (n, %)	57 (47%)	19 (61%)	1.78	0.79 – 3.98	0.16
UHDRS-motor[e] ≥ 15 points (n, %)	62 (51%)	16 (52%)	1.02	0.46 – 2.24	0.97
Pre-motor symptomatic disease stage[f] (n, %)	43 (36%)	11 (36%)	1.00	0.44 – 2.28	0.99
Use of psychotropic medication (n, %)	42 (35%)	20 (65%)	3.42	1.50 – 7.81	0.004
Use of antidepressants (n, %)	25 (21%)	18 (58%)	5.32	2.30 – 12.3	<0.001
Use of benzodiazepines (n, %)	25 (21%)	11 (36%)	2.11	0.90 – 4.98	0.09
Use of antipsychotics (n, %)	13 (11%)	5 (16%)	1.60	0.52 – 4.88	0.41

Neuropsychiatric characteristics					
Apathy Scale score[g] ≥ 14 points (n, %)	33 (27%)	16 (52%)	2.84	1.27 – 6.40	0.01
Depressed mood to PBA[h] score > 1 point (n, %)	50 (41%)	25 (81%)	5.92	2.26 – 15.5	<0.001
Any psychiatric disorder to CIDI[i] (n, %)	13/113 (12%)	6/27 (22%)	2.20	0.75 – 6.44	0.15
Depressive disorder to CIDI[i] (n, %)	4/113 (4%)	4/27 (15%)	4.74	1.10 – 20.3	0.04
Cognitive characteristics					
MMSE[j] score ≤ 27 points (n, %)	63 (52%)	19 (61%)	1.46	0.65 – 3.26	0.36
ExCog[k] ≤ 0.04 (n, %)	62 (51%)	14 (45%)	0.78	0.36 – 1.73	0.55

[a] Cross-sectional analysis using univariate logistic regression.
[b] Odds ratio, 95% CI and p-value by binary logistic regression.
[c] Estimated duration of disease is calculated by the current age minus the estimated age of onset (calculated using the formula of Vassos et al).[34] Estimated duration of disease can be negative.
[d] TFC score: Total Functional Capacity score, scores ranging from 0 t0 13 points; higher scores indicating better total functioning.
[e] UHDRS-motor: Unified Huntington's Disease Rating Scale motor section, scores ranging from 0 through 124 points; higher scores indicating more motor disorders.
[f] Pre-motor symptomatic mutation carriers are defined as HD mutation carriers with a UHDRS confidence level ≤ 1 point. HD mutation carriers with a UHDRS confidence level > 1 point are considered to be motor symptomatic.
[g] Apathy Scale score: scores ranging from 0 through 42 points; higher scores indicating more apathy.
[h] Depressed mood score of the Problem Behaviours Assessment (question 1), consisting of the severity and frequency score for depressed mood. Scores ranging from 0 through 16 points.
[i] CIDI: Composite International Diagnostic Interview to assess the presence of a depressive disorder and a psychiatric disorder in the last month. Could not be completed in 12 participants because of a MMSE score < 18 points.
[j] MMSE score: Mini-Mental State Examination, scores ranging from 0 through 30 points; higher scores indicating better mental state.
[k] ExCog: executive cognition; higher scores indicating better cognitive function.

Using multivariate analyses, the use of antidepressants (odds ratio (OR) = 3.96; 95% confidence interval (CI) = 1.59–9.87) and the presence of a depressed mood according to the PBA (OR = 4.17; 95% CI = 1.52–11.5) were independently associated with suicidality (Table 2).

In addition, sensitivity analyses were conducted to evaluate the robustness of the model. All participants scoring 1 (non-suicidal) or 2 (suicidal) on the suicidality item were excluded from the analysis. This sensitivity analysis confirmed our findings with higher OR on the covariates, whereas the TFC score (OR = 2.88; 95% CI = 1.04–7.95) and use of benzodiazepines (OR = 3.14; 95% CI = 1.18–8.37) also showed a significant difference between the suicidal and non-suicidal groups (data not shown). In the multivariate model, the presence of a depressed mood and use of antidepressants remained the only independent associations of suicidality (data not shown).

Next, the DSM-IV diagnosis of depression was forced into the cross-sectional multivariate model. The presence of a depressed mood and use of antidepressants remained the independent associations of suicidality (data not shown).

Table 1 shows that 8 participants had a formal DSM-IV diagnosis of depression (4 in the non-suicidal and 4 in the suicidal group). After exclusion of these 8 participants, the presence of a depressed mood according to the PBA and use of antidepressants again remained the only independent associations of suicidality (data not shown).

Predictors of suicidality at follow-up

Of the 121 participants free of suicidality at baseline (all had a suicidality score of 0), 100 were available for re-assessment after 2 years. The 21 drop-outs (17.4%) showed no significant differences on any of the baseline variables compared with the 100 participants that were followed up (data not shown). Seven (7%) of these 100 participants were suicidal at follow-up. Four of these 7 mutation carriers scored ≥ 4 on the suicidality item at follow-up, indicating moderate to severe suicidality. At baseline, these suicidal mutation carriers more often had a depressed mood according to the PBA (OR = 10.4; 95% CI = 1.20–90.2) and a formal DSM-IV psychiatric diagnosis (OR = 6.58; 95% CI = 1.27–34.2), although not particularly of depression (data not shown). Assessment of the CIDI at baseline was not possible in 5 of the 100 participants who were followed up because of severe cognitive impairment.

Using multivariate analysis in which sex, age, use of antidepressants and depressed mood were entered, depressed mood (OR = 10.6; 95% CI = 1.17–97.0) was the only significant independent predictor of suicidality (Table 2).

Table 2. Independent associations and predictors of suicidality in Huntington's disease mutation carriers.

Cross-sectional analysis (n = 152) *(31/152 were suicidal at baseline)*			
Baseline variable	**Odds Ratio**[a]	**95% CI**[a]	**p-value**[a]
Male gender	0.82	0.34 – 1.99	0.66
Age (years)	0.99	0.96 – 1.03	0.67
Use of antidepressants	3.96	1.59 – 9.87	0.003
Depressed mood[b]	4.17	1.52 – 11.5	0.006
Longitudinal analysis (n = 100) *(7/100 were suicidal at follow-up)*			
Baseline variable	**Odds Ratio**[a]	**95% CI**[a]	**p-value**[a]
Male gender	0.16	0.02 – 1.54	0.11
Age (years)	1.01	0.94 – 1.09	0.71
Use of antidepressants	1.33	0.21 – 8.48	0.76
Depressed mood[b]	10.6	1.17 – 97.0	0.04

Covariates cross-sectional analysis (forward model): use of antidepressants, use of benzodiazepines, Apathy Scale score, and depressed mood according to the PBA. Adjustment for sex and age.
Entered longitudinal analysis (enter model): sex, age, use of antidepressants, and depressed mood according to the PBA.
[a] Odds ratio, 95% CI and p-value by binary logistic regression.
[b] Depressed mood score of the Problem Behaviours Assessment (question 1), consisting of the severity and frequency score for depressed mood. Scores ranging from 0 through 16 points.

Discussion

The results of this study confirm that suicidality frequently occurred in this HD study group with a prevalence of 20% in mutation carriers compared with 0% in non-carriers. No difference was found in suicidality prevalence between pre-motor symptomatic and motor symptomatic mutation carriers. Cross-sectionally, suicidal mutation carriers were more likely to be depressed than non-suicidal mutation carriers, as shown by the higher use of antidepressants, the higher prevalence of apathy, possibly being a symptom of depression, the increased prevalence of a depressed mood according to the PBA and a more frequent formal DSM-IV diagnosis of depression. Longitudinally, these results were confirmed since the presence of a depressed mood was the only predictor of suicidality.

The prevalence of 20% suicidality among mutation carriers as found in our study is in accordance with a recent multi-site HD study reporting a suicidality month prevalence of 19% among motor symptomatic HD carriers, while the suicidality prevalence among pre-motor symptomatic mutation carriers was not investigated.[10] A large European cross-sectional study (Registry) also reported a suicidality prevalence of 19.9% among pre-motor and motor symptomatic mutation carriers.[11] However, the Registry study reported lifetime prevalence of suicidal ideation or suicidal attempts, assessed as present or absent, whereas our study focused on suicidality prevalence in the previous month, assessed by a score ranging from 0 through 16. This lifetime prevalence in the Registry study may be an underestimation of the true suicidality prevalence in HD due to recall bias in that study, and because the presence of suicidality was not investigated in a detailed psychopathology interview but in a general questionnaire on medical history.

Remarkably, both in pre-motor symptomatic and motor symptomatic mutation carriers the baseline suicidality prevalence was 20%. This is in line with previous studies that suggested two critical periods of suicide risk in HD. This first critical period for suicidality occurs when genetically at-risk individuals are in the period immediately before diagnosis when they start to experience symptoms of HD,[8;17;32] while they only have non-specific neurological signs and not yet unequivocal signs of HD.[32] Suicidal pre-motor symptomatic mutation carriers in our study population belong to this first critical period of suicidality. A similar suicidality prevalence was found among motor symptomatic mutation carriers, who belonged to the second critical period for suicide risk occurring when patients with unequivocal motor symptoms of HD become more dependent on others for daily activities, as assessed by the TFC.[32] In contrast to others,[32] we found no relationship between TFC and suicidality. Various phenomena may contribute to the equal suicidality prevalence in both pre-motor and motor symptomatic mutation carriers

in the present study. First, before motor symptoms even appear, psychopathology (in particular depression) often arises.[22;33] This may contribute to the relatively high prevalence of suicidality in pre-motor symptomatic mutation carriers since the presence of a depressed mood seems to be the most important predictor of suicidality. Furthermore, the emotional distress of having an incurable disease with a devastating course might also contribute to the relatively high suicidality prevalence already in pre-motor symptomatic mutation carriers. Moreover, diminished support from and increased mortality rates among affected family members could also lead to complicated grief, depression and suicidality.

The most important correlate and predictor of suicidality in HD mutation carriers was the presence of a depressed mood according to the PBA, despite that not all these participants had a formal DSM-IV diagnosis of depression. Cross-sectionally, an association between a depression subscale and suicidality was found in the Registry study and the multi-site HD study, whereas in these studies motor and cognitive subscores of the UHDRS were not associated with suicidality.[10;11] Longitudinally, depressed mood was found to be predictive of suicidal attempts and completed suicide in prodromal HD.[16] Both our cross-sectional and longitudinal findings are in line with these latter results.

Besides having a depressed mood, suicidal mutation carriers were cross-sectionally more likely to use antidepressants. The percentage of participants using antidepressants was much higher than the percentage of participants officially diagnosed with a DSM-IV diagnosis of depression. However, antidepressants may already be prescribed before a patient meets the official criteria of a DSM-IV diagnosis of depression, or because of a depression in remission. Furthermore, in HD antidepressants are also prescribed for anxiety and irritability.[3] Since use of antidepressants was only associated with suicidality in the cross-sectional analysis, it is unlikely that the use of antidepressants causes suicidality.

The strengths of this study are the combination of cross-sectional and longitudinal analyses, the use of a comparison group (consisting of first-degree non-carriers at risk for HD), and the use of specific and validated measurement tools in a standardised interview.

Some limitations also warrant discussion. First, the study population available for follow-up was relatively small since HD is a rare disease; the use of larger databases will improve reliability. Despite the relatively small number of participants, all analyses consistently indicated a strong relationship of suicidality with depressed mood. Further, many of the variables included in this study were dichotomised because of their skewed distributions, which adversely affected the statistical power. Third, variables previously found to be associated with suicidality in HD, like

pessimism, hopelessness,[7] aggression,[10] unemployment[15] and a history of suicide attempt,[16] were not included in our analyses. Finally, selection bias might have occurred since suicidal and/or depressed participants might have been more likely to refuse participation, which may have caused an underestimation of the true suicidality prevalence and incidence in HD.

Given the elevated suicidality prevalence in the HD population, it is important to regularly screen both pre-motor and motor symptomatic HD mutation carriers for suicidal ideation during clinical assessment. We found that the presence of a depressed mood was the main risk factor for suicidality in HD. Assessment of suicidal ideation is a priority in those with a depressed mood, and strategies of support and treatment should certainly be available for this subgroup of patients.

Acknowledgments

We thank N.A. Aziz, S.J.A. Bogaard, and Y.A.M. Grimbergen, neurologists for performing UHDRS motor score.

References

(1) Walker FO. Huntington's disease. Lancet 2007;369:218-228.

(2) Hoogeveen AT, Willemsen R, Meyer N et al. Characterization and localization of the Huntington disease gene product. Hum Mol Genet 1993;2:2069-2073.

(3) van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci 2007;19:441-448.

(4) Hamilton JM, Salmon DP, Corey-Bloom J et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry 2003;74:120-122.

(5) Huntington G. On Chorea. The Medical and Surgical Reporter: A Weekly Journal 1872;26:317-321.

(6) Farrer LA. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. Am J Med Genet 1986;24:305-311.

(7) Robins Wahlin TB, Backman L, Lundin A, Haegermark A, Winblad B, Anvret M. High suicidal ideation in persons testing for Huntington's disease. Acta Neurol Scand 2000;102:150-161.

(8) Schoenfeld M, Myers RH, Cupples LA, Berkman B, Sax DS, Clark E. Increased rate of suicide among patients with Huntington's disease. J Neurol Neurosurg Psychiatry 1984;47:1283-1287.

(9) van Heeringen K, Hengeveld MW. Suïcidaal gedrag. In: Hengeveld MW, van Balkom AJLM, eds. Leerboek Psychiatrie. 2nd ed. Utrecht, the Netherlands: De Tijdstroom; 2009:493-501.

(10) Wetzel HH, Gehl CR, Dellefave-Castillo L, Schiffman JF, Shannon KM, Paulsen JS. Suicidal ideation in Huntington disease: the role of comorbidity. Psychiatry Res 2011;188:372-376.

(11) Orth M, Handley OJ, Schwenke C et al. Observing Huntington's Disease: the European Huntington's Disease Network's REGISTRY. PLoS Curr 2010;2:RRN1184.

(12) ten Have M, de Graaf R, van Dorsselear S, Verdurmen J, van 't Land H, Vollebergh W. Suïcidaliteit in de algemene bevolking: gedachten en pogingen. Utrecht, the Netherlands: Trimbos Instituut; 2006.

(13) Baliko L, Csala B, Czopf J. Suicide in Hungarian Huntington's disease patients. Neuroepidemiology 2004;23:258-260.

(14) Lipe H, Schultz A, Bird TD. Risk factors for suicide in Huntingtons disease: a retrospective case controlled study. Am J Med Genet 1993;48:231-233.

(15) Almqvist EW, Bloch M, Brinkman R, Craufurd D, Hayden MR. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. Am J Hum Genet 1999;64:1293-1304.

(16) Fiedorowicz JG, Mills JA, Ruggle A, Langbehn D, Paulsen JS. Suicidal behaviour in prodromal Huntington disease. Neurodegener Dis 2011;8:483-490.

(17) Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM. Suicide risk in Huntington's disease. J Med Genet 1993;30:293-295.

(18) Suominen K, Isometsa E, Suokas J, Haukka J, Achte K, Lonnqvist J. Completed suicide after a suicide attempt: a 37-year follow-up study. Am J Psychiatry 2004;161:562-563.

(19) Wang AG, Mortensen G. Core features of repeated suicidal behaviour: a long-term follow-up after suicide attempts in a low-suicide-incidence population. Soc Psychiatry Psychiatr Epidemiol 2006;41:103-107.

(20) van Duijn E, Kingma EM, Timman R et al. Cross-sectional study on prevalences of psychiatric disorders in mutation carriers of Huntington's disease compared with mutation-negative first-degree relatives. J Clin Psychiatry 2008;69:1804-1810.

(21) Craufurd D, Thompson JC, Snowden JS. Behavioural changes in Huntington's disease. Neuropsychiatry Neuropsychol Behav Neurol 2001;14:219-226.

(22) Kingma EM, van Duijn E, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. Gen Hosp Psychiatry 2008;30:155-161.

(23) Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136-142.

(24) Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.

(25) Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;4:134-139.

(26) Kirsch-Darrow L, Fernandez HH, Marsiske M, Okun MS, Bowers D. Dissociating apathy and depression in Parkinson disease. Neurology 2006;67:33-38.

(27) World Health Organization. Composite International Diagnostic Interview [computer program]. Geneva, Switzerland: World Health Organization; 1997. Translation: ter Smitten MH, Smeets RMW, van den Brink W.

(28) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC, USA: American Psychiatric Association; 2000.

(29) Hodges JR. Initiation: verbal fluency tests. In: Cognitive Assessment for Clinicians. Oxford, UK: Oxford University Press; 2003:118-119.

(30) Smith A. The Symbol Digit Modalities Test: a neuropsychologic test for economic screening of learning and other cerebral disorders. Learning Disorders 1968;3:83-91.

(31) Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology 1935;18:643-662.

(32) Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. Am J Psychiatry 2005;162:725-731.

(33) Gargiulo M, Lejeune S, Tanguy ML et al. Long-term outcome of presymptomatic testing in Huntington disease. Eur J Hum Genet 2009;17:165-171.

(34) Vassos E, Panas M, Kladi A, Vassilopoulos D. Effect of CAG repeat length on psychiatric disorders in Huntington's disease. J Psychiatr Res 2008;42:544-549.