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Research paper

Suicidal ideation and suicidal behavior according to the C-SSRS in a European cohort of Huntington's disease gene expansion carriers

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ABSTRACT

Background: Huntington's disease (HD) gene expansion carriers are at an increased risk of suicide, but so far, no studies have investigated the full spectrum of suicidality, including suicidal ideation, suicidal behavior and self-injurious behavior.
Methods: We included 1451 HD gene expansion carriers (age 48.4 years (SD 14.0), 54.8% female) of the REGISTRY study of the European Huntington's Disease Network. Lifetime suicidal ideation and suicidal behavior were assessed with the Columbia-Suicidal Severity Rating Scale. Motor symptoms and disease stage were assessed using subscales of the Unified Huntington's Disease Rating Scale, and depressed mood and irritability were assessed by the Problem Behaviors Assessment.
Results: Lifetime passive suicidal ideation was reported by 21.2%. Participants in stage II showed the highest prevalence rate of suicidal ideation, while participants in stage IV/V showed the highest prevalence of suicidal behavior. A lifetime suicide attempt was reported by 6.5% of the HD gene expansion carriers. In multivariate regression analyses, both suicidal ideation and suicidal behavior were associated with a depressed mood, and to a lesser extend to irritability.
Limitations: Results may have been affected by denial or recall bias and no conclusions can be made about the temporal and causal relationships with depressed mood and irritability because of the cross-sectional analyses.
Conclusions: Given the high prevalence of suicidal ideation and suicidal behavior in all stages of HD, it is important to screen HD gene expansion carriers for suicidal ideation and suicidal behavior on a regular basis in clinical practice.

1. Introduction

Huntington's disease (HD) is a neurodegenerative disorder with an autosomal-dominant inheritance pattern. The genetic defect is a CAG expansion in the *HTT* gene on chromosome 4. In most HD gene expansion carriers, symptoms become manifest in the third or fourth decade of their lives, with an average survival time of 20 years. Movement symptoms, like chorea and dyskinesia, are the most prominent symptoms, but many patients already have psychiatric and neurocognitive symptoms before movement symptoms appear. Depression, anxiety, irritability, apathy, and obsessive compulsive behaviors are the frequent psychiatric symptoms that can be present in all stages of the disease, though only apathy is clearly related to disease progression. Currently, there are only symptomatic treatments for chorea and psychiatric symptoms available.

HD patients are at an increased risk of suicide. Among a group of 452 deceased HD expansion gene carriers from the National Huntington Disease Research Roster, 5.7% of the deaths resulted from suicide (Farrer, 1986). A similar frequency (5.6%) was reported in a Danish HD population (Sørensen and Fenger, 1992), but higher frequencies have also been described (Di Maio et al., 1993). A follow-up study reported an incidence of 0.4% for attempted suicide and 0.03% for completed suicide among prodromal HD gene expansion carriers per year (Fiedorowicz et al., 2011), whereas the lifetime risk of suicide attempts in the general population ranges between 0.5% and 4.6% (Bernal et al., 2007; Kessler et al., 1999; Scoccoa et al., 2008; ten Have et al., 2013) and the life-time risk of completed suicide is about 1% (ten Have et al., 2013).

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A study investigating suicidal ideation over the previous month reported a rate of 19% in motor symptomatic HD expansion carriers (Wetzel et al., 2011), while the lifetime prevalence of suicidal ideation in a mixed population of both premotor and motor symptomatic HD gene expansion carriers was 20% (Orth et al., 2010). Another study showed no difference between premotor symptomatic and motor symptomatic HD gene expansion carriers (both 20%) (Paulsen et al., 2005). In comparison, in the general Dutch population, aged 18–64 years, the lifetime prevalence of suicidal ideation, plan, and attempt was 8.3%, 3.0%, and 2.2%, respectively (ten Have et al., 2013).

Findings suggest two critical periods for the highest increased risk of suicide in HD. The first critical period is immediately before receiving a clinical diagnosis of HD, and the second when personal independence diminishes (Paulsen et al., 2005). The increased rate of suicidal ideation, suicidal behavior, 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 two longitudinal studies, a depressed mood was found to be predictive of suicidal ideation in a mixed group of premotor and motor symptomatic HD gene expansion carriers (Hubers et al., 2012), and predicted suicide attempts and completed suicide in the prodromal stage of HD (Fiedorowicz et al., 2011).

So far, no studies have investigated the full spectrum of suicidality in HD, from fleeting non-active suicidal ideations to active suicidal behavior with preparatory acts and completed suicide. The majority of the studies used only a single item to assess the presence of suicidal ideation or suicidal behavior, often with a Likert-scale to assess severity or frequency. Relevant information about different aspects related to suicidal ideation and suicidal behavior like the existence of a plan or aborted attempts is lacking in HD. Most suicide risk screening measures do not inquire about aborted and interrupted suicide attempts, whereas earlier research has suggested that individuals with aborted suicide attempts (Barber et al., 1998) and interrupted suicide attempts (Steer et al., 1988) did not differ in their intent to die in planning their attempt in relation to those who actually carried out the act, highlighting the importance of the assessment of these at face value less severe forms of suicidal behavior (Burke et al., 2016). Assessment of specific types of suicidal ideation and suicidal behavior will give more detailed information about the full spectrum of suicidality and can attain a better understanding of risk for future suicidal behavior.

The Columbia-Suicide Severity Rating Scale (C-SSRS) assesses both suicidal ideation (passive and active suicidal ideation) and suicidal behavior (i.e., actual attempts, interrupted attempts, aborted attempts, preparatory acts or behavior, and self-injurious behavior) (Posner et al., 2011), and is recommend by the Federal and Drug Administration to assess the occurrence of treatment-emergent suicidal ideation and behavior in clinical trials (http://www.fda.gov/downloads/Drugs/…/Guidances/UCM225130.pdf). However, reference data is essential for clinical trials, but not yet available for HD.

The principal aim of our study is to assess lifetime prevalence of various levels of suicidal ideation and suicidal behavior, using the C-SSRS in order to be able to compare results of future trials in HD populations with naturalistic reference data. A secondary aim of our study is to assess associations between current clinical characteristics and previous suicidal ideation and suicidal behavior.

2. Methods

2.1. Participants

For this study, HD gene expansion carriers (CAG > 36 repeats) who participated in the REGISTRY study of the European Huntington's Disease Network (EHDN), and with complete C-SSRS and Unified Huntington's Disease Rating Scale behavior section (Huntington Study Group, 1996) scores, were analyzed, resulting in 1451 participants. If applicable, of each included participant only the first C-SSRS was used for analysis. REGISTRY is a large prospective study observing the natural course, clinical spectrum and management of HD in a large number of European countries (Orth et al., 2010). More information on the REGISTRY study can be found at http://www.euro-hd.net/html/registry. Full ethical approval for the REGISTRY study was obtained in each of the participating countries, and all participants gave written consent prior to their inclusion in the study.

2.2. Sociodemographic and clinical characteristics

HD gene expansion carriers in various disease stages from 17 countries participated. Data on sociodemographic and clinical characteristics, including psychiatric history and use of psychotropic medication, were collected by trained interviewers using detailed electronic case report forms. The motor section of the UDHRS was used to rate the presence of motor symptoms (total motor score (TMS): range 0–124), and the UHDRS diagnostic confidence level was used to define premotor symptomatic (score 0–1) and motor symptomatic (score ≥ 2) HD gene expansion carriers (Huntington Study Group, 1996). The Total Functional Capacity (TFC) scale was used to define five disease stages in motor symptomatic HD gene expansion carriers: score 13–11 (stage I), score 10 – 7 (stage II), score 6 – 3 (stage III), score 2 – 1 (stage IV) and score 0 (stage V) (Shoulson, 1981). Stages IV and V were collapsed in the analyses because of small group sizes.

2.3. Measurement of suicidal ideation and suicidal behavior

The C-SSRS, a semistructured interview, was used to assess suicidal ideation and suicidal behavior. For statistical reasons, we summed 5 dichotomous (absent = 0; present = 1) items and used this score to rate suicidal ideation, comprising the following items: (1) passive wish to be dead, (2) nonspecific active thoughts of suicide, (3) active suicidal ideation with any methods (not plan) without intent to act, (4) active suicidal ideation with some intent to act, without a specific plan, and (5) active suicidal ideation with specific plan and intent. Similarly, a 4-point scale was used to rate suicidal behavior, comprising the following items: (1) preparatory acts, (2) interrupted attempts, (3) aborted attempts, and (4) actual attempts. Interrupted suicide attempts occur when individuals initiate action to end their lives but are stopped by someone or something external to the individual before actually carrying out the act. Aborted suicide attempts occur when individuals start to do something to try to end their lives but stop themselves before actually harming themselves. Non-suicidal self-injurious behavior was assessed separately. Additionally, the severity score of the 'suicidal ideation' item of the Problem Behaviors Assessment (PBA), that actually assesses both suicidal ideation and suicidal behavior, was included to assess the correlation with the C-SSRS.

2.4. Measurement of depressed mood and irritability

We analyzed the association with depressed mood and irritability using the UHDRS behavioral section, since these two symptoms have repeatedly been associated with suicidal ideation and suicidal behavior and are frequent neuropsychiatric symptoms that occur in all stages of HD (Anderson et al., 2016; Hubers et al., 2013).

2.5. Statistical analysis

Descriptive statistics were used to characterize the study sample. Chi-squared ($\chi 2$) tests were used to compare the prevalence of suicidal ideation and suicidal behavior between groups. Suicidal ideation score and suicidal behavior score were calculated by adding all of their 5 and 4 component items for each individual participant. Chi-squared ($\chi 2$) tests were also used to analyze the association between depressed mood and irritability. Post-hoc Sidak comparisons were used to identify significant subgroup differences. The variables sex, age, depressed mood and irritability were entered in the multivariate regression analysis,

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