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Disease stage, but not sex, predicts depression and psychological distress in Huntington's disease: A European population study

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ABSTRACT

Objective: Depression and anxiety significantly affect morbidity in Huntington's disease. Mice. models of Huntington's disease have identified sex differences in mood-like behaviours that vary across disease lifespan, but this interaction has not previously been explored in humans with Huntington's disease. However, among certain medical populations, evidence of sex differences in mood across various disease stages has been found, reflecting trends among the general population that women tend to experience anxiety and depression 1.5 to 2 times more than men. The current study examined whether disease stage and sex, either separately or as an interaction term, predicted anxiety and depression in Huntington's disease.

Methods: A cross-sectional study of REGISTRY data involving 453 Huntington's disease participants from 12 European countries was undertaken using the Hospital Anxiety and Depression Scale. A series of multiple regression analyses were undertaken to discover to what extent disease stage and sex predicted anxiety, depression, and general distress after controlling for a number of known predictors of mood difficulties.

Results: Disease stage, but not sex, was found to predict depressive symptoms and general distress. Neither disease stage nor sex predicted anxiety. Furthermore, an interaction term computed for disease stage and sex did not contribute to the models tested.

Conclusion: In terms of considering risks to developing depression and anxiety in the Huntington's disease population, practitioners may need to pay special attention to disease stage progression (but not sex differences) to enable early detection and treatment of depression (but not anxiety).

1. Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease characterised by impairments in movement, cognition and emotion. The onset of the disease usually occurs in mid-adulthood, with a progressive functional decline over approximately 20 years resulting in premature death [1]. Although there is no sex difference in the probability of inheriting the HD gene mutation from a parent, children who have inherited the gene from their father tend to develop symptoms earlier, due to instability of the trinucleotide cytosine–adenine–guanine (CAG) expansion found in paternal transmission [2].

Prevalence estimates of anxiety and depression in HD range considerably due to variations in assessments and disease stages measured, with 13–71% for anxiety [3], and 15–69% for depression [4,5]. Also, the aetiology of these symptoms is complex, with contributions from the neurodegenerative process itself [6], and also from the life stresses of living with a terminal and debilitating illness [7]. Due to the familial nature of the disease, HD mutation carriers may also be at a higher risk for depression and anxiety from having to deal with challenges, perhaps from an early age, such as witnessing family members with, or dying from, the disease; caregiving duties for family members; decisions around reproductive choices; and concerns about informing others of genetic risk. Despite these additional stresses potentially increasing vulnerability to anxiety and depression, and the deleterious effects that mood difficulties have on morbidity and mortality in HD [8], evidence suggests anxiety and depression are under-treated in HD [9]. Therefore, understanding risk factors for anxiety and depression in HD is vital for adequate detection, treatment and, ideally, prevention.

One key focus for discussion regarding depression and anxiety in HD is disease stage. A model commonly used to describe functional decline in HD involves five stages, using ranges of Total Functional Capacity (TFC) scores of the United Huntington Disease Rating Scale (UHDRS) [10], based on the following criteria: engagement in occupation; capacity to handle financial affairs; ability to manage domestic responsibilities and perform activities of daily living; and extent of care provided [11]. Thus HD patients move from relative independence in Stage 1, through to the advanced stage of the disease (Stage 5), where patients are severely impaired in their capacity to perform activities of daily living.

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From the HD literature that has addressed disease stage, there are mixed results regarding critical periods for anxiety and depression, but suggest they do not necessarily follow a linear trend across disease stage [9,12–14]. One large study revealed a significant peak in anxiety and depression symptoms at Stage 2 of the disease, while the authors of a more recent study found prevalence of moderate to severe depression to be highest among stages 4–5 [9]. In order to develop the findings from previous studies, it is important to explore other variables that may impact on the risk of developing anxiety and depression, and interact with disease stage. In the current paper we focus on sex. We know that a consistent finding among the general population is that women are likely to experience anxiety and depression between 1.5 and 2 times more than men [15,16]. Explanations for these differences have included gender biases in diagnosis and treatment of mental health problems, socio-political contexts, hormonal differences, and differences in help-seeking behaviour among men and women [17].

Despite these theoretical and empirical differences, research into sex differences in mood in HD is limited. Of the limited human studies available, there is evidence to suggest that the usual ratio of discrepancy noted between men and women does not exist in HD [9,18]. More research regarding sex differences in anxiety and depressive-like behaviours in HD has been undertaken using various mice models [19]. Animal models of HD enable researchers to consider the aetiology of behavioural symptoms and also mechanisms underlying sex differences, as potential biological contributions can be tested in the absence of psychosocial issues affecting human gene carriers, such as the knowledge that they have a fatal neurodegenerative condition.

Anxiety-like behaviours in mice include avoidance of open spaces, heights or light in tests such as the open field test, elevated plus maze and light/dark box test. These tests have revealed some evidence of male HD mice demonstrating more anxiety-like behaviour [20,21]. Depression-like behaviours in rodents are measured by such paradigms as the sucrose test, whereby HD mice are considered to illustrate anhedonia when they exhibit a reduced preference for sucrose solution. The forced swimming test is another measure that may represent depressive-like behaviour through reduced swimming and climbing activity. In these tests, female mice have been shown to demonstrate more behaviours suggestive of depression [22–24]. Therefore, collectively, there is evidence of sexual dimorphism of anxiety and depressive-like behaviours in rodent models of HD, with suggestion of a potential interaction between sex differences and stage of disease progression [19], an area that has not been examined in humans.

This study therefore examines whether, in humans, disease stage interacts with sex to predict depression and anxiety symptoms in HD. This is important because across disease stages, men and women face different life challenges that may impact on emotional health, such as concerns about the ability to start or maintain a family, changes in social support, or peak changes in reproductive and hormonal processes (e.g. menopause) [25–27]. Furthermore, recent findings suggest complex sex effects in the clinical phenotype of HD, with women demonstrating more severe symptoms and faster rate of progression, particularly in terms of motor and functional abilities [18]. Consequently, improved understanding of any sex differences regarding the emotional component of the disease, and the interactions with disease stage, may help identify stages of critical risk for men and women in terms of mental health, and inform the design of future disease-modifying clinical trials [18]. Finally, such a consideration would add to research that have examined these as key factors in other medical conditions, where an interaction between sex and disease-stage was found to influence mood symptoms among those in certain diseases [28,29], but not others [30].

In the current study, we aimed to examine the influence of disease stage and sex on anxiety and depression and to test the veracity of any relationship between sex and disease stage by controlling for several known predictors of anxiety and depression. Specifically we hypothesised that: i) disease stage would not independently predict anxiety and depression symptoms; ii) there would be a sex difference in depression and anxiety, with women reporting more symptoms than men; iii) there would be an interaction effect between sex and disease stage in HD for depression and anxiety.

2. Method

2.1. Sample

Our sample comprised 453 verified HD mutation carriers, from across 12 European countries, who were REGISTRY 3 study participants. REGISTRY is a multi-national, prospective study examining the natural history of HD (http://www.euro-hd.net/html/registry). Ethical approval was gained locally via ethics committees for all study sites contributing to REGISTRY.

2.2. Data

We requested all available Hospital Anxiety and Depression Scale (HADS) [31] data from the European HD Network (EHDN), following approval of the research proposal by the EHDN Scientific and Bioethics Advisory Committee. As the data set included some repeat measures, we used only cross-sectional data based on participants' first visit, covering the period 27 June 2011 to 27 June 2013, which led to an initial study cohort size of $n = 496$ who had a CAG repeat of ≥39. As there were only 4 participants in Stage 5, we excluded this group from the analysis. We also excluded those with juvenile HD, defined by a CAG repeat ≥55 on the larger allele, due to potential phenotypical differences from adult-onset HD [32] ($n = 3$). A further 36 participants were excluded due to missing data (history of depression) [$n = 8$], current medication use [$n = 12$], current alcohol and cigarette intake [$n = 13$], age [$n = 1$] and education years [$n = 2$]) resulting in our total 453 (203 males, 250 females) participants, aged from 22 years to 86 years (mean age = 53.00, SD = 11.9). Participants were from the following European countries: Austria (9), Finland (2), France (116), Germany (86), Italy (10), Norway (43), Poland (88), Portugal (9), Spain (29), Sweden (12), Switzerland (2), and UK (47). The sex breakdown by disease severity stage was Stage 1 (75 males, 114 females), Stage 2 (71 males, 57 females), Stage 3 (48 males, 60 females), and Stage 4 (9 males, 19 females).

The outcome variables (depression and anxiety) were assessed using the HADS, a 14-item self-report tool comprising two 7-item measures relating to anxiety and depression symptoms, with both scores combined to create a measure of general psychological distress. Each item is scored on a 4 point scale (0–3, with scores ranging from 0 to 21 on each subscale, with higher scores representing higher levels of distress). The HADS has been shown to be a reliable, sensitive and precise instrument across a wide range of populations [33] and has previously been found to have excellent screening properties for identifying clinical cases of depression in HD compared to a "gold standard" diagnostic measure of depression with the total HADS score of 13/14 (sensitivity 1.00, specificity 0.79) and for the HADS-D, a 6/7 cut-off (sensitivity 1.00, specificity 0.82) [34]. We used total scores for HADS, the HADS anxiety subscale, and the HADS depression subscale to examine symptomatology.

As one of our key predictor variables, disease stage was defined using scores from the TFC scale of the UHDRS [10,11]: Stage 1 (11–13), Stage 2 (7–10), Stage 3 (3–6), Stage 4 (1–2) and Stage 5(0) (noting we excluded this latter group). We also included a number of other variables so we could control for several known predictors of depression and anxiety. These included: years in education, as a longer period in education has been found to be related to lower levels of depression in later life [35]; certain medications (antidepressants, anxiolytics, mood stabilisers/anti-epileptics, neuroleptics, sleeping tablets, betablockers and tetrabenazine, the latter of which can have side-effects of anxiety and depression [36]); past use of antidepressants and anxiolytics, and history of depression (no assessment of history of anxiety is included