Depression in Prodromal Huntigton Disease

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Introduction

The PREDICT-HD study is prospectively following individuals with the mutation for Huntington Disease prior to onset of motor symptoms. The presentation and treatment of depression in this population remains poorly understood, and the goal of this project is to ultimately improve its identification and clinical management. In this cohort, prior work to date has identified mildly elevated psychiatric symptoms, including depression.

Methods

802 individuals with prodromal HD (prHD) and 222 gene expansion-negative individuals were evaluated for symptoms of depression at their initial visit in the PREDICT-HD study. The Beck Depression Inventory II (BDI-II), UHDRS Behavioral Scale, and depression subscale of the Symptom Checklist 90 Revised (SCL-90R) were used. Antidepressant treatment at the first visit was reported. A factor analysis was completed among those with prHD and least mild symptoms on the BDI-II (N = 168). This included questions across all three assessments to identify the most significant domains of depressive symptoms in this population. Longitudinal changes were also evaluated between visits at baseline and year three.

Sample Demographics

	Expansion-Negative	Expansion-Positive
Number	222	802
Age (mean years)	44	40
Gender (%M/%F)	64%/36%	64%/36%

Beck Depression Inventory (BDI) - II Scores at Study Entry and Year 3

	Expansion-Negative	Far to Onset (>15 years)	Mid to Onset (9–15 years)	Near to Onset (<9 years)	HD Diagnosed
Baseline Visit	4.48 (5.22) N = 222	7.75 (8.39) N = 310	9.42 (9.53) N = 296	6.70 (8.13) N = 196	N.A.
Year 3 Visit	3.91 (5.22) N = 145	6.32 (7.62) N = 188	7.93 (9.17) N = 199	7.19 (8.46) N = 173	13.24 (13.97) N = 58

Each cell contains mean (with SD in parentheses) and sample size (N) for the BDI-II, a 21-question self-administered measure of depressive symptoms over the two weeks prior to taking the assessment. Each question is rated on a scale of 0 to 3, giving a maximum total of 63, with higher scores indicating more depressive symptoms. Results from baseline and year 3 PREDICT-HD visits are presented here in order to compare scores over time, as the year 3 visit maximizes the number of total participants and provides a diagnosed group for comparison. The expansion positive groups are stratified by predicted time to onset (Langbehn et al., 2004, Clin Genet 65:267–277). Overall, the expansion positive groups have higher depression scores; however, all group means are less than the standard cutoff for mild depressive symptoms (14). Analysis of annual change in symptoms from baseline to year 3 by linear regression did not identify significant differences among the groups.

Factor Analysis of Depressive Symptoms

Among the subset of 168 expansion-positive subjects with mild or greater symptoms of depression on the BDI-II (see figure to the right), a factor analysis was performed to identify possible common symptom domains. Questions from the BDI-II, the depression subscale of the Symptom Checklist 90 Revised (SCL-90R), and relevant depression questions from the UHDRS behavioral assessment were included. Eight separate factors were identified, with proposed names given based on the predominant symptoms measured in each factor.

Factor 1 - Low Self-Esteem
- BDI 3-Past Failure
- BDI 5-Guilty Feelings
- BDI 7-Self Dislike
- BDI 8-Self Criticalness
- BDI 14-Worthlessness
- SCL 26-Blaming Self
- SCL 79-Feeling of Worthlessness
- UHDRS 27a-Low Self-Esteem/Guilt Freq
- UHDRS 27b-Low Self-Esteem/Guilt Sev

Factor 2 - Physical Symptoms
- BDI 15-Loss of Energy
- BDI 16-Changes in Sleep
- BDI 18-Changes in Appetite
- BDI 19-Concentration Difficulty
- BDI 20-Tiredness/Fatigue
- SCL 14-Feeling Low in Energy
- SCL 32-Feeling no Interest in Things
- SCL 71-Feeling Everything is an Effort

Factor 3 - Isolation/Sadness
- SCL 20-Crying Easily
- SCL 22-Feeling Trapped
- SCL 26-Blaming Self
- SCL 29-Feeling Lonely
- SCL 30-Feeling Blue
- SCL 31-Worrying too Much
- SCL 79- Feeling of Worthlessness

Factor 4 - Irritability & Agitation
- BDI 11-Agitation
- BDI 17-Irritability
- UHDRS 29a-Anxiety Freq
- UHDRS 29b-Anxiety Sev
- UHDRS 30a-Irritable Behavior Freq
- UHDRS $_{30b\text{-}Irritable}$ Behavior Sev
- UHDRS 31a-Aggressive Behavior Freq
- UHDRS 31b-Aggressive Behavior Sev

Factor 5 - Suicidality
- BDI 9-Suicidal Thoughts
- SCL 15-Thoughts of Ending Life
- SCL 54-Feeling Hopeless About Future
- UHDRS 28a-Suicidal Thoughts Freq
- UHDRS 28b-Suicidal Thoughts Sev

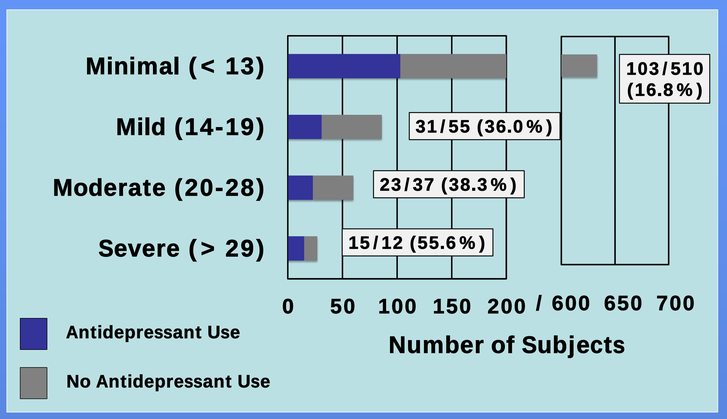
Factor 6 - Low Mood/Apathy
- UHDRS 25a-Depressed Mood Freq
- UHDRS 25b-Depressed Mood Sev
- UHDRS 26a-Apathy Freq
- UHDRS 26b-Apathy Sev
- UHDRS 27b-Low Self-Esteem/Guilt Sev
- UHDRS 29b-Anxiety Sev

Factor 7 - Loss of Interest
- BDI 2-Pessimism
- BDI 4-Loss of Pleasure
- BDI 12-Loss of Interest
- BDI 13-Indecisiveness
- SCL 32-Feeling no Interest in Things

Factor 8 - Low Sexual Interest
- BDI 21-Loss of Interest in Sex
- SCL 5-Loss of Sexual Interest

Using responses to questions on depression from the BDI-II (21 items), SCL-90R (13 items), and UHDRS behavioral assessment (14 items), a factor analysis was conducted with principal component analysis as the method of extracting initial factors. Orthogonal factor rotation was then applied to facilitate the interpretation of extracted factors. The number of factors was determined based on both the magnitude of eigenvalues and the scree plot. Any variable with factor loading larger than 0.4 was retained in the corresponding factor. Each symptom assessed in the UHDRS has a separate Frequency (Freq, a) and Severity (Sev, b) question.

Severity of Depression (BDI-II) and Antidepressant Use



HD expansion-positive subjects with available data on antidepressant use (784) were stratified according to standard BDI-II cutoffs for severity of depressive symptoms and whether they were taking an antidepressant at their initial PREDICT-HD visit. Values next to each bar represent the number of individuals taking or not taking antidepressants and percentage of the total taking antidepressants in parentheses.

Conclusions

Significant depressive symptoms were present in a minority of prHD subjects, but a large proportion of individuals with more severe symptoms did not report antidepressant use.

A factor analysis identified eight of the most prominent domains of symptoms among the group of individuals reporting at least mild levels of symptoms.

Reported symptoms of depression decreased from baseline to year three, but the overall trend was not significant.

Future Directions

- Further characterize specific symptoms of depression and the use of treatment.
- Identify factors related to the presentation of depression, including the potential associations of any symptoms or markers of HD.
- Analyze longitudinal data using all follow-up data and different methodolgies.

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