Psychopathology in Huntington's disease
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Chapter 5

Measurement of psychopathology in Huntington’s disease: the critical role of caregivers

E. van Dulijn, E.J. Giltay, F.G. Zitman, R.A.C. Roos, R.C. van der Mast

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Abstract

**Objective:** To investigate the concurrent validity of two dimensional rating scales that were designed for assessment of psychopathology in Huntington’s disease, with categorical DSM-IV diagnoses.

**Background:** Assessment of psychopathology in Huntington’s disease using formal criteria is complex due to the co-morbid somatic and cognitive disturbances, and diminished disease awareness.

**Method:** In 152 Huntington’s disease mutation carriers, test scores on the Problem Behaviors Assessment scale (PBA) and the behavioral section of the Unified Huntington’s Disease Rating Scale (UHDRS-b) were associated with DSM-IV diagnoses according to the Composite International Diagnostic Interview (CIDI).

**Results:** Both high PBA and UHDRS-b scores corresponded with presence of DSM-IV diagnoses. Receiver operating characteristic curves showed an area under the curve of 0.87 for the PBA and 0.91 for the UHDRS-b, demonstrating moderate to strong discriminatory power. Using caregiver information, subjects who were too cognitively impaired for CIDI assessment showed similar high PBA and UHDRS-b scores, with both a negative predictive value of 96% and a positive predictive value of 40% and 44% respectively, for the presence of formal psychiatric disorders.

**Conclusion:** The use of dimensional rating scales and caregiver information allows for the assessment of psychopathology in advanced stage Huntington’s disease, also in the presence of cognitive impairment.

Introduction

Huntington’s disease is a progressive neurodegenerative disorder with an autosomal dominant hereditary pattern, caused by an elongated CAG repeat on chromosome 4.1 Huntington’s disease is clinically characterized by progressive motor dysfunction, psychiatric disorders and cognitive dysfunction. Typically, first clinical symptoms appear between the age of 30 and 50 years, showing a progressive course and disease duration of 15 to 20 years.

The presence of psychiatric disorders in Huntington’s disease is associated with poor quality of life and increased caregiver distress, and it hastens admission to nursing homes.2,3 Depression is the most frequently reported psychiatric disorder, but neuropsychiatric symptoms such as irritability and apathy are also highly prevalent in Huntington’s disease.4,5 Because some of the non-emotional symptoms of psychiatric disorders overlap with the typical symptoms of Huntington’s disease, these may influence the validity of psychiatric assessment, e.g. weight loss may be a symptom of depression, but can also be an isolated symptom of Huntington’s disease.6 Besides, Huntington’s disease patients frequently show lack of insight in advanced stages, and may not be able to communicate.7,8 Assessment of psychiatric disorders may thereby be considerably hampered and even impossible, although in fact patients may suffer from gross psychopathology leading to severe functional impairments.

The current generally accepted diagnostic classification of psychiatric disorders is the Diagnostic and Statistical Manual, Fourth edition (DSM-IV-TR).9 The DSM utilizes a non-etiological, categorical approach according to a subset of strict criteria to assign a psychiatric diagnosis at a certain time. This approach is useful in physically healthy subjects, but has major limitations in patients with a neurodegenerative disorder.

These limitations raise the question whether diagnostic classification of psychiatric disorders according to the DSM is reliable and valid in Huntington’s disease. For that reason, the use of dimensional rating scales that use caregiver information for the assessment of psychopathology has been suggested as more appropriate in clinically affected Huntington’s disease patients.10,11 Such an approach may better reflect the range of symptoms across the spectrum of psychopathology than a DSM diagnosis.

In this study, we hypothesized that dimensional measurement using caregiver information is appropriate to detect psychopathology in advanced Huntington’s disease. We assessed the concurrent validity of two dimensional rating scales that were specifically designed for the assessment of psychopathology in Huntington’s disease, compared to a categorical assessment of psychiatric disorders as defined by DSM-IV criteria.

Methods

**Subjects**

Between May 2004 and August 2006, 152 consecutive Huntington’s disease mutation carriers with a repeat length of 36 or more were recruited from the out-patient departments of Clinical Genetics and Neurology of the Leiden University Medical Center (LUMC), and from a regional nursing home. The design of the study has been described in detail elsewhere.12 All subjects
Behavioral section of the Unified Huntington’s Disease Rating Scale

The behavioral section of the UHDRS (UHDRS-b) (See: Appendix B) consists of 11 items for the assessment of neuropsychiatric symptoms in a four weeks period. Severity and frequency of these symptoms are scored on a scale from 0 to 4, with higher numbers indicating more psychopathology. The sum of the product of severity and frequency scores of all items is the UHDRS-b score (range 0 - 176).

Caregivers

Ratings of the PBA and the UHDRS-b are based on the reports of the subject and his/her caregiver, together with the clinical impression of the interviewer. Caregivers of the subjects who were too cognitively impaired for the CIDI consisted of nurses (58%), partners (25%), and children (17%). Caregivers of the other subjects were partners (60%), siblings (13%), parents (10%), children (7%), and the remaining 10% were assessed in the absence of a caregiver.

Statistical analyses

The three study groups were compared using independent samples t-tests for continuous variables and chi-square (χ²) tests for dichotomous variables and for pair-wise comparison. All analyses were carried out two-sided with a significance level of p < 0.05. Non-parametric Kruskal-Wallis one-way analysis of variance was applied for testing differences between the groups for variables with skewed distributions.

Receiver operating characteristic (ROC) analysis was done to compare the results with the PBA as well as the UHDRS-b to classification of subjects according to DSM-IV diagnosis as assessed with the CIDI, and to select optimal cut-off scores for screening and diagnostic purposes of these two scales. ROC curves were plotted for Huntington’s disease patients with a DSM-IV diagnosis, as well as for the combined group of Huntington’s disease patients with a DSM-IV diagnosis and Huntington’s disease patients in whom formal CIDI assessment was not possible. These curves yielded the ‘sensitivity’ versus ‘1 minus the specificity’ for each possible cut-off point. Optimal cut-off points were determined by assessing which score combined maximum sensitivity and specificity. The area under the ROC curve (AUC) was used as an indicator of diagnostic test’s discriminatory power to distinguish between subjects with and without a DSM-IV diagnosis. An AUC < 0.75 was considered not clinically useful.

Results

Demographic and clinical characteristics

Nineteen (13.6%) of the 140 subjects had one or more psychiatric disorders according to the CIDI (Table 1). Ten of them (52.6%) of the 19 subjects with a psychiatric diagnosis had a single psychiatric disorder; five subjects (26.3%) had two psychiatric disorders, three subjects (15.8%) had three psychiatric disorders, and one subject (5.3%) had even four. Most frequently reported psychiatric disorders were major depressive disorder (n = 8) and obsessive-compulsive disorder (n = 7).

Table 1 shows the demographic and clinical characteristics of 121 subjects without a formal DSM-IV diagnosis, 19 subjects with a formal DSM-IV diagnosis, and 12 subjects that were too cognitively impaired. These latter subjects showed characteristics of advanced Huntington’s...
### Table 1. Sociodemographic, clinical, and functional characteristics of the three study groups among 152 HD mutation carriers

<table>
<thead>
<tr>
<th>Sociodemographics</th>
<th>Subjects without DSM-IV diagnosis (n = 121)</th>
<th>Subjects with DSM-IV diagnosis (n = 19)</th>
<th>Subjects in whom CIDI was not possible&lt;sup&gt;a&lt;/sup&gt; (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n, %)</td>
<td>57 (47.1)</td>
<td>7 (36.8)</td>
<td>5 (41.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>47 (11.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44 (12.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57 (10.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.008</td>
</tr>
<tr>
<td>Married or partner (n, %)</td>
<td>87 (71.9)</td>
<td>12 (63.2)</td>
<td>7 (58.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Any children (n, %)</td>
<td>89 (73.6)</td>
<td>16 (84.2)</td>
<td>11 (91.7)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

### Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Subjects without DSM-IV diagnosis (n = 121)</th>
<th>Subjects with DSM-IV diagnosis (n = 19)</th>
<th>Subjects in whom CIDI was not possible&lt;sup&gt;a&lt;/sup&gt; (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated age of onset (mean, SD)</td>
<td>45 (7.9)</td>
<td>47 (4.7)</td>
<td>45 (6.0)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.64</td>
</tr>
<tr>
<td>CAG repeats (mean, SD)</td>
<td>44 (3.5)</td>
<td>43 (2.2)</td>
<td>44 (2.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.55</td>
</tr>
<tr>
<td>High alcohol consumption (n, %)</td>
<td>18 (14.9)</td>
<td>0</td>
<td>0</td>
<td>0.07</td>
</tr>
</tbody>
</table>

### Use of psychotropic medication (n, %)

<table>
<thead>
<tr>
<th></th>
<th>Subjects without DSM-IV diagnosis (n = 121)</th>
<th>Subjects with DSM-IV diagnosis (n = 19)</th>
<th>Subjects in whom CIDI was not possible&lt;sup&gt;a&lt;/sup&gt; (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>46 (38.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 (68.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (83.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>26 (21.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11 (57.9)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (50.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>23 (19.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (15.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (58.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.006</td>
</tr>
</tbody>
</table>

### Functional measures

<table>
<thead>
<tr>
<th></th>
<th>Subjects without DSM-IV diagnosis (n = 121)</th>
<th>Subjects with DSM-IV diagnosis (n = 19)</th>
<th>Subjects in whom CIDI was not possible&lt;sup&gt;a&lt;/sup&gt; (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFC (median, IQR)</td>
<td>17 (11-31)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (2-31)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80 (67-88)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE (median, IQR)</td>
<td>28 (25-29)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (7-17)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26 (23-30)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UHDRS-m (median, IQR)</td>
<td>21 (17-28)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (4-10)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (1-2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> CIDI was not possible because of severe cognitive dysfunction (two subjects with MMSE score <18 points and two subjects who did not understand the questions, though MMSE scores were 19 and 20 points, respectively).

<sup>b</sup> These calculations were based on n = 11.

Because of their skewed distribution, median and Interquartile Range (IQR: P<sub>25</sub> - P<sub>75</sub>) are given for TFC, MMSE, and UHDRS-m. P values are calculated by non-parametric Kruskal-Wallis tests.

### Table 2. Median PBA (sub)scores and UHDRS-b scores for the three study groups among 152 HD mutation carriers

<table>
<thead>
<tr>
<th></th>
<th>Subjects without DSM-IV diagnosis (n = 121)</th>
<th>Subjects with DSM-IV diagnosis (n = 19)</th>
<th>Subjects in whom CIDI was not possible&lt;sup&gt;a&lt;/sup&gt; (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBA score (median, IQR)</td>
<td>46 (26-85)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>134 (92-164)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>126 (78-166)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> PBA was not possible because of severe cognitive impairment (two subjects with MMSE score <18 points and two subjects who did not understand the questions, though MMSE scores were 19 and 21 points).

<sup>b</sup> PBA score ranges from 0 - 576 points, with higher scores indicating more behavioral problems. Apathy subscore ranges from 0 - 66 points; depression subscore ranges from 0 - 80 points; irritability subscore ranges from 0 - 80 points; UHDRS-b score ranges from 0 - 76, with higher scores indicating more behavioral problems.

Because of their positively skewed distribution, median and Interquartile Range (IQR: P<sub>25</sub> - P<sub>75</sub>) are given.

<sup>a</sup> <sup>b</sup> Values in the same row with different superscript letters are significantly different at p < 0.05 by non-parametric Kruskal-Wallis tests.
disease stage including decreased TFC score, increased total UHDRS-motor (UHDRS-m) score, and the use of significantly more neuroleptics in comparison with the two other study groups.

**PBA and UHDRS-b scores in relation to presence of DSM-IV diagnoses**

There was a significant difference between the three study groups for both the PBA (sub) scores and the UHDRS-b score (Table 2). All median PBA (sub) scores and the UHDRS-b score were significantly higher in subjects with a DSM-IV diagnosis compared to subjects without a DSM-IV diagnosis (all \( p < 0.05 \)). Also, subjects to whom the CIDI could not be administered because of severe cognitive dysfunction showed a significantly higher total PBA score, PBA apathy subscore, and UHDRS-b score compared to those without a DSM-IV diagnosis. No statistically significant differences were found between the cognitively compromised group and subjects with a DSM-IV diagnosis. As is shown in Figure 1A, high PBA and UHDRS-b scores indicate severe and frequent psychopathology in the cognitively compromised group.

**Figure 1.** Histograms and ROC curves for the PBA and UHDRS-b scores of the three study groups among 152 Huntington’s disease mutation carriers.

**Validity of PBA and UHDRS-b compared to DSM-IV**

To assess the concurrent validity of the two Huntington’s disease specific rating scales, the CIDI was considered to be the gold-standard. The ROC curves showed an AUC for the group with a DSM-IV diagnosis of 0.87 for the PBA and 0.91 for the UHDRS-b (Figure 1B), demonstrating moderate to strong discriminatory power. Next, adding the group without a CIDI assessment due to cognitive impairment to the group of subjects with a formal DSM-IV diagnosis, the AUC remained almost equal (0.86) for the PBA, but slightly decreased (0.86) using the UHDRS-b. The discriminatory power was therefore considered to be moderate and of similar strength for both rating scales in cognitively impaired subjects with Huntington’s disease.

**Sensitivity and specificity of the PBA and UHDRS-b for the presence of DSM-IV psychopathology**

The PBA demonstrated an optimal sensitivity and specificity (respectively 79% [95% confidence interval (CI): 61 - 97%] and 81% [95% CI: 74 - 88%]) for psychopathology according to DSM-IV at a cut-off of 91 points for the total PBA score. The corresponding negative and positive predictive values were 96% [95% CI: 92 - 100%] and 40% [95% CI: 24 - 55%], respectively. The optimal sensitivity and specificity of the UHDRS-b (respectively 79% [95% CI: 61 - 97%] and 84% [95% CI: 78 - 91%]) was at a cut-off of 27 points for the total UHDRS-b score. The corresponding negative and positive predictive values were 96% [95% CI: 93 - 100] and 44% [95% CI: 27 - 61%], respectively.

**Discussion**

We showed that both high PBA and UHDRS-b scores corresponded with the presence of a psychiatric disorder according to DSM-IV criteria as assessed with the CIDI. Importantly, making use of caregiver information, subjects in whom formal assessment of DSM-IV diagnosis according to the CIDI was impossible because of cognitive impairment also showed high PBA and UHDRS-b scores. This finding confirms the face validity of these instruments suggesting severe and frequent psychopathology in patients in advanced disease stage.

Our finding that assessment using the PBA and UHDRS-b with caregiver information, was able to encompass psychopathology in all disease stages of Huntington’s disease, is in line with the suggestions done by others. The use of formal DSM diagnosis, instead of a dimensional measure, may explain why in some earlier studies the published rates of psychiatric disorders in the advanced stage of Huntington’s disease were relatively low compared to earlier disease stages. Especially in advanced stage of Huntington’s disease, when communication and insight may become so impaired that subjects are no longer able to express or to judge their symptoms, reported rates of psychiatric disorders appeared to decrease. In this stage, the PBA and the UHDRS-b may be particularly useful, since they include caregiver information. This contributes to a more accurate assessment of psychopathology than a patient assessment alone.

Furthermore, the PBA and the UHDRS-b showed similar psychometric performances, with similar negative and positive predictive values. The positive predictive values were rather low, due to the relative high number of subjects in whom the CIDI assessment was not possible.

The PBA has already shown an interrater reliability of 0.82 for severity scores and 0.73 for frequency scores. Although the UHDRS is widely used, we are not aware of any study on
the interrater reliability of the UHDRS-b which is a possible limitation of our study. A second limitation is that we did not assess the degree of insight, next to cognitive functioning, whereas lack of insight may already have been present before severe cognitive impairment. This may have compromised outcomes of the CIDI, since the use of the CIDI does not require information of the caregivers. A third limitation is that there is no agreement on the concept of psychopathology in patients with advanced neurodegenerative disorders. Consequently, high PBA and UHDRS-b scores may not represent the presence of DSM-IV disorders, though they indicate the presence of psychopathology. Finally, the number of patients with a formal DSM diagnosis was rather small, and therefore our results should be confirmed in other larger and therefore international cohorts of Huntington’s disease patients.

Whereas the assessment of psychopathology in advanced stages of Huntington’s disease is difficult, it may be even more difficult to measure the effectiveness of pharmacotherapy of neuropsychiatric symptoms. Still, monitoring the effect of a pharmacological treatment is compulsory to avoid the use of various non-indicated psychotropic medications. In our study, a high percentage of the patients used different psychotropic medications, especially those with cognitive impairments. Although the high PBA and UHDRS-b scores among these patients seem to justify the use of psychotropic medication, medication interactions and side effects may at the same time worsen motor symptoms. Furthermore, despite the frequent use of psychotropic medication, neuropsychiatric symptoms were still highly prevalent in this group.

In conclusion, the use of dimensional rating scales allows for the assessment of psychopathology, and for regular evaluation of psychiatric pharmacotherapy, making use of information of patients, caregivers and clinical parameters. The PBA and the UHDRS-b are particularly useful in the advanced stage of Huntington’s disease being indicative for initiation and (dis)continuation of psychiatric pharmacotherapy.

References
Chapter 6

Correlates of apathy in Huntington’s disease

E. van Duijn, N. Reedeker, E.J. Giltay, R.A.C. Roos, R.C. van der Mast
Journal of Neuropsychiatry and Clinical Neurosciences, in press