Psychopathology in Huntington's disease
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Chapter 4

Behavioral problems in Huntington’s disease using the Problem Behaviors Assessment

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Acknowledgments
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Abstract

Objective: To investigate behavioral problems in Huntington’s disease.
Method: In 152 Huntington’s disease mutation carriers and a control group of 56 non-carriers at initial 50% risk, the Dutch version of the Problem Behaviors Assessment was administered. Mutation carriers were divided into three groups according to the motor section of the Unified Huntington’s Disease Rating Scale: pre-motor symptomatic, early and advanced symptomatic subjects. The factor structure and interrater reliability of the Problem Behaviors Assessment were investigated.

Results: The clinically relevant interrater reliability of the Problem Behaviors Assessment was 0.82 for severity scores and 0.73 for frequency scores. The Problem Behaviors Assessment showed a three-factor solution: apathy, depression and irritability. Mutation carriers, including presymptomatic subjects, portrayed more apathy, depression and irritability than non-carriers. Early symptomatic subjects had more apathy, but not more depression or irritability, compared to presymptomatic subjects. Advanced symptomatic subjects had more apathy than early symptomatic subjects.

Conclusions: The Problem Behaviors Assessment is a reliable and sensitive instrument. Behavioral problems occur in all stages of Huntington’s disease and arise before the onset of motor symptoms. Apathy is related to disease severity, whereas depression and irritability are not. The broad clinical phenotype of Huntington’s disease therefore requires adequate service delivery with integrated and multidisciplinary patient care.

Introduction

Huntington’s disease is a progressive autosomal dominant neurodegenerative disorder with an elongated CAG repeat length on chromosome 4. It has an insidious onset (mean age 40 years) and varied clinical presentation.1 Huntington’s disease is traditionally characterized by movement disturbances whilst cognitive deterioration is now well documented.7 Increasingly, however, neuropsychiatric symptoms are recognized as much more distressing and disabling for both subjects and their caretakers, and are often the main reason for institutionalizing.3

A systematic review of the literature showed that the reported prevalences of depressed mood, anxiety, irritability and apathy vary from 33% to 76%, whereas obsessive compulsive symptoms and psychosis occur less often with a prevalence of 10–52% and 3–11%, respectively.4 An evaluation of available studies on psychopathology in Huntington’s disease is difficult because of different methodologies, small sample sizes and lack of control groups.5 Because Huntington’s disease is uncommon and complex, and behavioral symptoms are often not described as a major part of the disease process, the symptoms, course and management may be relatively unknown to health care professionals.

Some evidence exists that cognitive deterioration precedes the onset of motor symptoms in Huntington’s disease.6,7 Several retrospective studies indicate that the same might be the case for psychopathology.8–12 Only four cross-sectional studies comparing pre-motor symptomatic mutation carriers with non-carriers have been done so far.15–18 Although they found no difference for past or present psychiatric morbidity, they did find that presymptomatic mutation carriers differed from non-carriers on measures of irritability and anger/hostility. We therefore propose that behavioral problems, especially irritability, precede the onset of motor symptoms in Huntington’s disease.

The etiology of neuropsychiatric symptoms is likely to be complex, implicating firstly direct neuropathological effects by the disease itself17 and, secondly, social and environmental causal factors.9,10 An appropriate control group for genetically confirmed Huntington’s disease mutation carriers is therefore their mutation-negative siblings. They share the same psychosocial family background, often strongly influenced by an ill parent, as well as other risk factors that could contribute to the development of behavioral problems.9,15 These include being at-risk for many years, as well as participating in the presymptomatic testing procedure until the outcome is known. We suppose that part of the behavioral problems in Huntington’s disease is due to direct disease processes and therefore expect that mutation carriers portray more behavioral problems compared to their mutation-negative siblings.

The aim of our study was to investigate the prevalence of psychopathology and behavioral problems in (a) a sample of genetically and clinically confirmed Huntington’s disease mutation carriers, comprising both the early and advanced stages of the disease; (b) a group of presymptomatic mutation carriers; and (c) a control group of mutation-negative subjects at initial 50% risk. Because neuropsychiatric symptoms in subjects with neurodegenerative disorders cannot often be grouped according to formal psychiatric classifications,16 a dimensional approach may better be used to illuminate neuropsychiatric symptomatology.18 We therefore
use the Problem Behaviors Assessment (PBA) (See: Appendix A) to assess behavioral problems in this study. The PBA is a semi-structured interview specifically designed for a more reliable assessment and better understanding of behavioral problems in Huntington’s disease. Craufurd et al. described three clusters of symptoms — apathy, irritability and depression — based on a factor analysis using data from 78 subjects. They also reported an interrater reliability of 0.86 for severity scores and 0.84 for frequency scores.

The PBA is a promising instrument, but Craufurd et al. did not include a sufficiently large sample in their factor analysis. We therefore re-assess the factor structure and determine the interrater reliability of the Dutch translation of the PBA.

**Methods**

**Participants**

Between May 2004 and August 2006, 343 genetically tested subjects at initial 50% risk of Huntington’s disease were contacted via the Departments of Neurology and Clinical Genetics of the Leiden University Medical Centre and long-term care facility ‘Overduin’ in the Netherlands. One hundred and ninety-two subjects were willing and able to participate in this study. Subjects with a neurological condition other than Huntington’s Disease were excluded. An additional 18 subjects were recruited through other means, such as the Dutch Huntington’s Disease association, but two subjects were subsequently lost to follow-up. The remaining 280 subjects were divided into four groups based on (a) their genetic test result, which was obtained from their medical records, and (b) their Unified Huntington’s Disease Rating Scale (UHDRS) motor score (Figure 1). The Medical Ethical Committee of the Leiden University Medical Centre approved the study. All subjects gave informed consent.

**CAG repeat length**

The number of CAG repeats of all subjects was verified. Subjects with a normal repeat length containing 26 or less copies and those with an intermediate repeat number between 27 and 35 were considered non-carriers. Since alleles in the 36 to 39 repeat range are unstable and are associated with the Huntington’s disease phenotype, these subjects were considered positive for Huntington’s disease in this study.

**Interview**

All subjects were interviewed by trained interviewers who collected socio-demographic data and administered all measures, except for the motor section of the UHDRS. In a previous study, subjects who are mostly well informed about the symptoms accompanying disease onset tended to conceal symptoms from the interviewer if they were to keep their genetic status secret. Therefore interviewers were not blinded for the genetic status of participants, as this would result in an underreporting of behavioral problems.

**Assessment of motor functioning and disease stage**

The motor section of the UHDRS was assessed by a neurologist who was kept blind for the genetic status of the subject. Based on the clinical examination, the neurologist expressed his confidence that the presence of motor symptoms in a study subject is a sign of clinically manifest Huntington’s disease. Confidence level scores range from 0 to 4. All mutation carriers (n = 55) with confidence level scores of 0 and 1 were classified as presymptomatic. The remaining mutation carriers (n = 97) with score 2 to 4 were all considered symptomatic. The median score (40 points) of the total UHDRS motor score (range 0 - 124 points) was used for distinguishing early symptomatic (n = 47) from advanced symptomatic subjects (n = 50) (Figure 1).

**Figure 1. Flowchart of inclusion of subjects**

![Diagram of inclusion process](image)

CVA = Cerebrovascular accident; UHDRS-m = Unified Huntington’s Disease Rating Scale, motor section

**Assessment of neuropsychiatric symptoms**

Behavioral problems were assessed with the PBA which consists of 36 items covering nearly all behavioral problems present in Huntington’s disease. The 5-point PBA rating scales, one
subscale for severity and one for frequency, are modeled after the behavioral section of the UHDRS, using the scores 0 (absent), 1 (questionable), 2 (mild), 3 (moderate) and 4 (severe). Unlike the UHDRS, which rates behavior in the last 6 months, the PBA solely assesses behavioral problems in the 4 weeks prior to the interview.

Where possible, subjects were interviewed in the presence of a knowledgeable informant. If not, we conducted a telephone interview with an informant. Both the informant and the subject were given the opportunity to speak with the interviewer separately, in order to acquire information that might have been kept from us in the presence of the other person. Scores were determined by the interviewer based on the combination of information gathered, which included clinical observations.

In order to assess the interrater reliability of the PBA, a random subset of 63 subjects and their informants were interviewed a second time on the same day by a different interviewer. For the methodological evaluation [principal component analysis (PCA)] of the PBA, the PBAs of 152 mutation carriers only were used. These were augmented with a further group of 25 PBAs of mutation carriers who were assessed as part of ordinary monitoring. This resulted in a total of 177 PBAs for the methodological evaluation.

For this study a Dutch translation of the PBA was created. The Dutch PBA was translated back into English by a native English speaker which resulted in a few linguistic changes only.

**Other clinical characteristics**

Information on sociodemographic and clinical characteristics was obtained during a standardized interview. The estimated age of onset was calculated according to the following equation: log (age) = α + β (CAG number repeats), where α = 6.15 and β = −0.053.23

The Total Functional Capacity (TFC) scale was administered to assess general functioning. The TFC is widely used in Huntington's disease research, with scores ranging from 0 to 13 points.24 A lower score indicates worse general functioning. The Mini-Mental State Examination (MMSE) was used to assess global cognitive functioning. A score below 25 (out of 30) is used as indication of cognitive impairment.25

**Statistical analysis**

Group differences on demographic and clinical characteristics were determined using one-way ANOVA. Post hoc comparisons were carried out with the Scheffé method for differences between groups for continuous data. Chi-square tests with adjusted standardized residuals were used for analysis of dichotomous data.

Interrater reliability of the PBA was assessed using weighted kappas. A kappa of more than 0.6 is considered acceptable and a kappa of more than 0.8 is considered good.26 Because we only considered differences of more than 1 point between the raters as clinically relevant, a 'clinically relevant’ kappa was calculated, which only included differences that were larger than 1 point.

The factor structure of the PBA was determined using PCA with varimax rotation. Items occurring in less than 10% of subjects were excluded (i.e., change in food preference, obsessions, somatization, sexually disinhibited behavior, sexually demanding behavior, delusions, jealousy and all forms of hallucinations). The PBA scores (the product of severity and frequency scores) of the resulting 28 items were entered into an analysis of 177 cases. The solution was checked for robustness by randomly deleting 10% of the cases, which was repeated five times. The quantity of factors was based on a Monte Carlo analysis and a scree plot. Based on the results of the PCA, three internally consistent subscales were computed. Alpha maximization was used as a criterion for including items in a subscale. The subscale scores were computed as the mean of the included items, resulting in a theoretical range from 0 to 16. The subscale scores of the different groups were compared using analyses of covariance (ANCOVA), with sex, education and psychiatric history as covariates, to distinguish between the groups. Because these scores are not normally distributed, a square root transformation was applied. Significance for all tests was set at p < 0.05. Kappas were computed in Microsoft Excel. All other analyses were carried out in Statistical Package for Social Sciences v. 12.0.1.

**Results**

Socio-demographic and clinical characteristics The main socio-demographic and clinical characteristics of the study population are given in Table 1. A significantly lower CAG repeat length was found in presymptomatic compared to symptomatic mutation carriers (p < 0.05). The calculated mean number of years to the estimated age of onset in presymptomatic mutation carriers was 8 years. Both early and advanced symptomatic mutation carriers had significantly lower mean MMSE scores than presymptomatic mutation carriers and non-carriers (p < 0.05). All groups differed significantly from each other with respect to TFC and the use of psychotropic drugs. Presymptomatic mutation carriers significantly more often reported a psychiatric history than the other three groups. This was corrected for in the subsequent analyses (ANCOVA).

**Assessment of PBA**

The interrater reliability of the PBA was 0.82 (95% CI = 0.65 – 1.00) for severity scores and 0.73 (95% CI = 0.47 – 1.00) for frequency scores, as measured with a ‘clinically relevant kappa’.

Factor analysis revealed three components that together explained 38.6% of the variance (Table 2). Although Monte Carlo analysis allowed for four principal components, the scree plot indicated three components comprising coherent items. Based on the PCA three internally consistent subscales — apathy, depression and irritability — were computed. Alpha maximization was used as criterion for including items in a subscale. Internal consistencies expressed as Cronbach’s α were 0.84 for apathy, 0.81 for depression and 0.67 for irritability. The subscales turned out to be sufficiently stable. In the five tests performing a PCA on random subsamples of 90% of the cases, the same components emerged. Some minor shifts of items to another component were observed; one or two in each test. These items included ‘insomnia’ (4x), ‘impaired judgment’ (2x), ‘loss of energy’ (2x), and ‘self-centeredness’ (1x). Only this last item was used in the construction of a subscale (irritability).
Table 1. Demographic and clinical characteristics of study subjects (n = 208)

<table>
<thead>
<tr>
<th></th>
<th>Non-carriers</th>
<th>Presymptomatic mutation carriers</th>
<th>Early symptomatic mutation carriers</th>
<th>Advanced symptomatic mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 56</td>
<td>n = 55</td>
<td>n = 47</td>
<td>n = 50</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>25 (45%)</td>
<td>24 (44%)</td>
<td>22 (47%)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Age in years (mean, SD)</td>
<td>39 (11.1)</td>
<td>41 (10.4)</td>
<td>47 (10.7)</td>
<td>54 (11.0)</td>
</tr>
<tr>
<td>Education in years (mean, SD)</td>
<td>14 (3.5)</td>
<td>14 (3.9)</td>
<td>14 (4.1)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>CAG repeat length (mean, SD)</td>
<td>22 (4.1)</td>
<td>43 (2.3)</td>
<td>45 (3.2)</td>
<td>45 (3.6)</td>
</tr>
<tr>
<td>Estimated age of onset (mean, SD)</td>
<td>N/A</td>
<td>49 (5.9)</td>
<td>45 (7.1)</td>
<td>43 (7.5)</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric history (n, %)</td>
<td>18 (32%)</td>
<td>28 (51%)</td>
<td>19 (40%)</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Use of psychopharmaca, (n, %)</td>
<td>3 (5%)</td>
<td>12 (22%)</td>
<td>19 (40%)</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>High alcohol consumption (mean, %)</td>
<td>8 (14%)</td>
<td>10 (18%)</td>
<td>5 (11%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>MMSE (mean, SD)</td>
<td>29.1 (1.2)</td>
<td>28.7 (1.4)</td>
<td>26.9 (2.7)</td>
<td>21.5 (6.9)</td>
</tr>
<tr>
<td>TFC (mean, SD)</td>
<td>12.9 (0.5)</td>
<td>12.0 (1.4)</td>
<td>10.1 (2.8)</td>
<td>4.1 (3.4)</td>
</tr>
<tr>
<td>UHDRS-motor score (mean, SD)</td>
<td>2.2 (2.6)</td>
<td>2.3 (3.1)</td>
<td>19.3 (11.3)</td>
<td>61.1 (15.1)</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination; TFC = Total Functional Capacity; UHDRS = Unified Huntington's Disease Rating Scale; NA = not-applicable.

Non-carriers and presymptomatic mutation carriers versus early symptomatic versus advanced symptomatic mutation carriers: p < 0.05.

Advanced symptomatic mutation carriers compared to all other groups: p < 0.05.

Non-carriers compared to all other groups: p < 0.001, and pre-symptomatic mutation carriers versus early and advanced symptomatic mutation carriers: p < 0.05.

Non-symptomatic mutation carriers versus early and advanced symptomatic mutation carriers: p < 0.005.

Pre-symptomatic mutation carriers compared to all other groups: p < 0.05.

Difference between all groups: p > 0.05.

Alcohol consumption was considered high if more than 14 glasses a week were consumed.

Table 2. Principal Component Analysis on PDA items

<table>
<thead>
<tr>
<th>Component</th>
<th>Component Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0.75</td>
</tr>
<tr>
<td>Depression</td>
<td>0.52</td>
</tr>
<tr>
<td>Component Items</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>3.00</td>
</tr>
<tr>
<td>4.00</td>
<td>7.00</td>
</tr>
<tr>
<td>11.00</td>
<td>14.00</td>
</tr>
<tr>
<td>17.00</td>
<td>20.00</td>
</tr>
<tr>
<td>23.00</td>
<td>26.00</td>
</tr>
<tr>
<td>29.00</td>
<td>32.00</td>
</tr>
<tr>
<td>35.00</td>
<td>38.00</td>
</tr>
<tr>
<td>41.00</td>
<td>44.00</td>
</tr>
<tr>
<td>47.00</td>
<td>50.00</td>
</tr>
<tr>
<td>53.00</td>
<td>56.00</td>
</tr>
<tr>
<td>59.00</td>
<td>62.00</td>
</tr>
<tr>
<td>65.00</td>
<td>68.00</td>
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<tr>
<td>71.00</td>
<td>74.00</td>
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<tr>
<td>77.00</td>
<td>80.00</td>
</tr>
<tr>
<td>83.00</td>
<td>86.00</td>
</tr>
<tr>
<td>89.00</td>
<td>92.00</td>
</tr>
<tr>
<td>95.00</td>
<td>98.00</td>
</tr>
</tbody>
</table>

Note: The Principal Component Analysis (PCA) was performed on the principal components derived from 177 possible clinical symptoms of disease. The items that are used in this analysis are in boldface.

*Authors.*
### Table 3. Subscale scores for the different study groups.

<table>
<thead>
<tr>
<th></th>
<th>Non-carriers</th>
<th>Presymptomatic carriers</th>
<th>Symptomatic carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Advanced</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td>n = 55</td>
<td>n = 50</td>
<td>n = 47</td>
</tr>
<tr>
<td>Apathy (mean, SD)</td>
<td>0.11 (0.40)</td>
<td>1.01 (1.96)</td>
<td>2.07 (3.07)</td>
</tr>
<tr>
<td>Depression (mean, SD)</td>
<td>1.32 (1.94)</td>
<td>2.54 (2.71)</td>
<td>2.79 (2.92)</td>
</tr>
<tr>
<td>Irritability (mean, SD)</td>
<td>0.81 (1.73)</td>
<td>1.53 (1.88)</td>
<td>1.80 (2.63)</td>
</tr>
</tbody>
</table>

Analysis of variance, with Bonferroni pairwise and Helmert contrasts. Subscales scores are presented as mean (SD) with analyses adjusted for age at time of testing.

### Behavioral problems in Huntington’s disease

Comparison of the subscale scores of the different study groups revealed significantly more apathy, depression and irritability in all mutation carriers than in non-carriers (Table 3). Presymptomatic mutation carriers showed more apathy, depression and irritability compared to non-carriers, whereas they differed from early symptomatic mutation carriers on measures of apathy only. Advanced mutation carriers revealed more apathy than the earlier disease stage groups, but not more depression and irritability (Table 3).

No significant relationships were found between the three subscale scores and the estimated age of onset of motor symptoms in mutation carriers.

### Discussion

The PBA appears to be a promising instrument for the assessment of behavioral symptoms in Huntington’s disease. The instrument shows a good interrater reliability, is easy to administer and covers a broad range of behavioral problems. The PBA also facilitates a dimensional approach, which seems appropriate for the assessment of behavioral problems in Huntington’s disease. 26

The PCA conducted on this instrument gives a robust solution. It features three subscales: apathy, depression and irritability. Our subscales are roughly similar to the factors found by Craufurd et al., 27 although their sample was rather small for a reliable factor analysis. 27 Measuring the correlation between external measures of apathy, depression, irritability and the relevant factors on the PBA could provide further evidence for the existence of different neuropsychiatric syndromes in Huntington’s disease.

A disadvantage of the PBA is its comparative length, but the instrument can be considerably reduced whilst retaining most of the advantages listed. We recommend leaving out all the items that have been excluded from the factor analysis, which reduces the amount of items from 36 to 28. If necessary the PBA could be reduced to the 14 items that constitute the three factors. Because the PBA does not generate formal psychiatric diagnoses, the instrument may be used alongside traditional psychiatric measures. The PBA is very likely to have a greater sensitivity for behavioral problems in Huntington’s disease, whereas formal psychiatric diagnostic instruments provide greater specificity.

A comparison of symptomatic and presymptomatic mutation carriers and a control group consisting of non-carriers at initial 50% risk shows that all mutation carriers portray more apathy, depression and irritability than the control group. This difference is apparent even before motor symptoms arise. Although some psychopathology in the mutation carrier group may be due to knowledge of a Huntington’s disease positive test result, a negative result also produces psychological problems, such as survivors’ guilt. No substantial long-term effects of test results have been found. 28 Therefore the difference between mutation carriers and the control group is directly due to neuropathology, rather than to psychosocial stressors such as a disturbed childhood and anxiety about test results.

These findings give strong evidence that behavioral problems are amongst the first disease
symptoms in Huntington’s disease and, in keeping with our hypothesis, can precede the onset of motor symptoms. Since our presymptomatic group also had reduced total functional capacity compared to non-carriers, clinically manifest Huntington’s disease can present itself before the onset of motor symptoms. This contradicts previous literature, which only found a difference between presymptomatic and non-carriers for irritability.13,14 The PBA, facilitating a multidimensional approach, may have been more sensitive than the instruments used in other studies.

Recognition and acknowledgement of these behavioral changes as part of the clinical phenotype of Huntington’s disease will help carriers and their families cope with this disease. General practitioners should be aware of these specific characteristics in subjects at risk for Huntington’s disease, because in many carriers the negative impact of Huntington’s disease may start long before the first motor symptoms occur. Possible interventions in general practice are family support and psycho-education about the broad spectrum of disorders in Huntington’s disease. Furthermore, multidisciplinary treatment with general practitioners, psychiatrists, psychologists, neurologists, nurses and social workers will contribute to the care of these patients and the quality of their lives.15

Presymptomatic and early symptomatic mutation carriers differed on measures of apathy only, as do early and advanced symptomatic mutation carriers. This confirms earlier evidence that apathy is strongly correlated to disease progression.16,17,18 Depression and irritability appear to be not related to disease stage at all, with consistent levels found in pre-, early and advanced symptomatic subjects.

A possible limitation of our study is that both interviewers and study subjects had knowledge of their mutation status. This may have contributed to increased scores of behavioral problems in mutation carriers. Blinding interviewers to the genetic status of the participant requires subjects to keep their status secret. Experience has shown that this would generate a biased response on questions about emotional problems which could be related to genetic status or be perceived by the subject or informant as related to disease onset. The interviewers were aware of this limitation, and in order to guarantee objectivity, frequent interrater sessions were held and disease progression was assessed separately, and blindly, by a neuropsychologist.

This is the first study that incorporates various Huntington’s disease stages and a control group of non-carriers at initial 50% risk and gives clear evidence for the early emergence of behavioral problems in Huntington’s disease. These symptoms are at least partly due directly to neuropathological processes. Since behavioral problems are amongst the most distressing symptoms for caregivers and patients,7 recognition and multidisciplinary treatment are vital. The PBA seems to be an appropriately sensitive instrument for assessment of behavioral problems. Overall, these findings provide strong support for increasing the emphasis on neuropsychiatric symptoms in Huntington’s disease in both research and clinical care.

References

Chapter 5
Measurement of psychopathology in Huntington’s disease: the critical role of caregivers

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