Behavioural complaints in participants who underwent predictive testing for Huntington’s disease

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LETTER TO JMG

Changes in mood and behaviour form the most variable symptoms of the clinical characteristics of Huntington’s disease (HD). Although the diagnosis is usually based on motor signs, behavioural changes occur as a first manifestation of HD in up to half of the patients. Irritable behaviour, aggression, and depression are most commonly seen in the first phase of the disease. Anxiety, obsessions, and apathy are also extremely common in HD. In certain families, major affective disorders may appear as early as 20 years before the onset of chorea and dementia. However, with regard to the manifestation of psychiatric signs, there is a known difficulty in distinguishing between an intrinsic and a reactive pattern. The action of the disease is often intertwined with the reaction to the disease in diagnosed patients but also in “asymptomatic” (that is, absence of motor signs) subjects carrying the expansion of the CAG triplet repeat (henceforth referred to as “carriers” compared to “non-carriers”). As far as we are aware, only two studies have been reported regarding psychiatric symptoms in asymptomatic carriers compared to non-carriers. A controlled psychiatric study reported by Shiwach and Norbury showed that there was no significant increase in affective disorder in the former group. However, the whole predictive tested group showed a higher prevalence of psychiatric episodes than their partners. According to the authors it is, therefore, not plausible that depression is an early sign of HD in asymptomatic carriers. Depression and feelings of helplessness are indeed usually seen as a consequence of stressful events related to HD, like predictive testing in both carriers and non-carriers, even years after the predictive test result. Many studies have been reported on mood changes as a reactive pattern in both carriers and non-carriers, but behavioural changes as a plausible first manifestation of HD have not been the subject of such extensive investigation. Only Berrios et al. reported higher measures of irritability in neurologically asymptomatic carriers, suggesting that this symptom can appear very early in the course of HD. The focus of most investigators in this group has been directed more towards cognitive and motor functioning.

Differentiating between the behavioural changes inherent in HD and the well known impact of DNA testing is important in view of studying early markers of the disease onset. This is in line with Paulsen et al. who stated “Careful study of neuropsychiatric symptoms associated with HD is essential to help distinguish features that are pathognomonic from behaviours that are sensitive but not specific of the disease”.

Therefore in the present explorative study, we investigated the following issues.

- Is there a difference between carriers and non-carriers in the outcome of the UHDRS behavioural assessment?
- Do age and gender play a role in developing behavioural complaints?
- Are a psychiatric history and the interval between DNA testing and first assessment associated with the development of behavioural complaints?
- Is there a change in behavioural complaints in carriers after 18 months? Do these differ from non-carriers?

Key points

- Huntington’s disease (HD) is characterised by involuntary movements, dementia, and psychiatric signs, the latter occurring as a first manifestation of the disease in up to half of the patients. However, diagnosis is usually based on the motor symptoms.
- In this explorative study, we compared the occurrence of behavioural complaints in 46 identified carriers for HD and in 88 non-carriers by single blind administration of the Unified Huntington’s Disease Rating Scale (UHDRS). Follow up was performed after 18 months in 114 participants.
- No significant differences were found between carriers and non-carriers in demographics or neurological motor signs according to the UHDRS.
- Carriers complained more than non-carriers about sadness, low self-esteem, aggressive behaviour, and compulsions. This was mostly seen in women and persons aged 30 to 49 years. Carriers in this age group did not express significantly more anxiety than non-carriers. Younger non-carriers (20-29 years) were found to be more anxious than older ones.
- A history of depression and the interval between predictive testing and first assessment were associated with behavioural complaints in the non-carrier group only.
- At follow up after 18 months, carriers still complained about aggression, while complaints about mood and low self-esteem had disappeared.
- We speculate that aggressive behaviour in our carrier group may be seen as an initial sign intrinsic to HD, while the presence of complaints about mood and low self-esteem seems to be related to the impact of the predictive test. However, owing to the explorative nature of our study, we do not suggest that phenoconversion has occurred. Research focusing on the early detection of behavioural changes, using a broader instrument, is still indispensable.

Longitudinal investigation is needed because of the diagnostic inaccuracy in cross sectional assessment of patients, one reason being the variability in presentation early in the disease. Also, knowledge about the progression of psychiatric, motor, and cognitive symptoms and their relationship is essential for research into neuroprotective treatments.

METHODS

Participants

Since the availability of direct mutation analysis between 1993 and 1998, 370 people with a 50% risk of developing
Huntington’s disease have travelled from all over The Netherlands to Leiden to undergo presymptomatic testing. Applicants were considered positive for HD when the number of (CAG) copies exceeded 35 repeats. Applicants with a repeat containing fewer than 27 copies were considered to be non-carriers. Those with a repeat number between 27 and 35 were considered intermediate.

Applicants who were or who became symptomatic and, consequently, for whom DNA testing was confirmatory, were not invited to participate in this study (n=10). Between November 1997 and January 1999, 134 subjects (36% of the total group tested) underwent the initial assessment in this single blind study. The percentage of carriers who participated was lower (34%) compared to the whole group who applied for DNA testing (44%). There were no demographic differences between this group and non-participants. However, there was a minority of carriers between 40 and 60 years in the group of non-carriers. Those with a repeat number between 27 and 35 were considered intermediate.

Twelve participants had previously undergone the linkage test and received direct testing after 1993. For seven participants, the study design was double blind because they did not yet know the outcome of their DNA test on entry. Three participants had an intermediate result (CAG repeats 30, 30, 34) and were included in the present study in the non-carrier group, as they are unlikely to develop the disease.

The study was approved by the Medical Ethics Committee of the LUMC and all participants gave their informed consent.

**Measures**

All participants were requested not to disclose the result of the predictive test to the investigators. The protocol consisted of using open questions about complaints in daily functioning, categorised by a psychological assistant and a psychologist (MNWA) into memory, concentration, motor, affect, behaviour, somatic, and others. Furthermore, the Unified Huntington’s Disease Rating Scale (UHDRS) and an extended neuropsychological assessment were evaluated. The protocol lasted for about four hours (break included). The second protocol was performed 18 months later with the exception of the medical history from the UHDRS, an intelligence test, and two memory tests. This shortened version of the protocol took about two hours.

**UHDRS**

The UHDRS comprises questions about medical history, a motor examination, a cognitive assessment, a behavioural assessment, an assessment of functional ability, and completion of a medication form. There is a high degree of internal consistency within each of the domains and it is a valid instrument for assessing the clinical features of HD. Furthermore, it appears to be appropriate for repeated administration during clinical studies and for tracking changes. The scores of the motor tests, assessed by a neurologist (JPPvV/RACR), were summed in a total motor score and a diagnosis was filled during clinical studies and for tracking changes. The scores of the motor tests, assessed by a neurologist (JPPvV/RACR), were summed in a total motor score and a diagnosis was filled during clinical studies and for tracking changes. The scores of the motor tests, assessed by a neurologist (JPPvV/RACR), were summed in a total motor score and a diagnosis was filled during clinical studies and for tracking changes.

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**Table 1** Group characteristics of 134 participants

<table>
<thead>
<tr>
<th>DNA test</th>
<th>Carriers (n=46)</th>
<th>Non-carriers (n=88)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>16/30</td>
<td>40/48</td>
<td>0.23*</td>
</tr>
<tr>
<td>Age at NPA, mean (range), years</td>
<td>39 (21–66)</td>
<td>42 (18–64)</td>
<td>0.16†</td>
</tr>
<tr>
<td>Education</td>
<td>4 (9%)</td>
<td>6 (7%)</td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>29 (63%)</td>
<td>56 (64%)</td>
<td>0.78‡</td>
</tr>
<tr>
<td>Number of CAG repeats, median (range)</td>
<td>13 (28%)</td>
<td>26 (30%)</td>
<td></td>
</tr>
<tr>
<td>Age in years at DNA result, mean (range)</td>
<td>39 (18–62)</td>
<td>36 (18–62)</td>
<td>0.09†</td>
</tr>
<tr>
<td>Time interval in months between DNA result and first NPA (n=127), median (range)</td>
<td>43 (1–60)</td>
<td>36 (0–61)</td>
<td>0.02‡</td>
</tr>
<tr>
<td>History of depression, yes/no¶</td>
<td>14/30</td>
<td>18/70</td>
<td>0.15*</td>
</tr>
<tr>
<td>Use of neuroleptics</td>
<td>0.15*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressive drugs</td>
<td>2 (4%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>Anxiolytic drugs</td>
<td>3 (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square test; †t-test; ‡Mann-Whitney test.
¶Seven DNA results not yet known at time of neuropsychological assessment (NPA).
†Two missing.

**Table 2** Mean of complaints assessed using the behavioural part of the UHDRS

<table>
<thead>
<tr>
<th>DNA test</th>
<th>Carriers (n=45)</th>
<th>Non-carriers (n=88)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHDRS behavioural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadness</td>
<td>2.58 (3.56), 0–16</td>
<td>1.33 (2.77), 0–16</td>
<td>0.01</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>2.18 (4.04), 0–16</td>
<td>0.74 (2.09), 0–9</td>
<td>0.007</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.51 (2.94), 0–12</td>
<td>1.21 (0.63), 0–10</td>
<td>0.76</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>0.42 (1.64), 0–9</td>
<td>0.03 (0.24), 0–2</td>
<td>0.08</td>
</tr>
<tr>
<td>Aggression</td>
<td>1.51 (3.48), 0–16</td>
<td>0.38 (1.5), 0–9</td>
<td>0.04</td>
</tr>
<tr>
<td>Irritable behaviour</td>
<td>1.56 (3.37), 0–16</td>
<td>1.15 (2.65), 0–16</td>
<td>0.98</td>
</tr>
<tr>
<td>Obsessions</td>
<td>0.69 (2.35), 0–12</td>
<td>0.34 (1.65), 0–9</td>
<td>0.07</td>
</tr>
<tr>
<td>Compulsions</td>
<td>0.64 (2.29), 0–12</td>
<td>0.23 (1.75), 0–16</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Mann-Whitney test.
sometimes; 3 = frequently; 4 = almost always). The behavioural part was reported orally by the participant only. The assessment was structurally performed by a trained psychological assistant and afterwards discussed under the supervision of a psychologist (MNWA).

Statistical analysis
Data were analysed using the Statistical Package for Social Sciences (SPSS), version 10. To reduce the number of variables, the products of severity and frequency were calculated for each symptom. Variables that were not normally distributed were analysed with non-parametric tests. Differences between carriers and non-carriers during baseline and follow up were examined with Student’s t test, chi-square test, Fisher’s exact test, and Mann-Whitney U test, where appropriate. Spearman’s rank correlation was calculated to analyse behavioural complaints in relation to motor functioning and age and with the interval between DNA testing and first assessment. Age was kept for this purpose as a continuous variable. Afterwards, age was classified into three subgroups (<29 years, 30-49 years, ≥50 years) for further investigation of the group close to probable age of onset. The Wilcoxon signed ranks test was used to study changes within groups after 18 months. The Mann-Whitney U test was performed to investigate differences over time between carriers and non-carriers. Significance level was set at 0.01 while marginal findings are reported with a more liberal p level (<0.05).

RESULTS
Group characteristics
The group characteristics are described in table 1. The time interval between DNA testing and this study was marginally longer in carriers compared to non-carriers. Neither group showed significant differences in other variables.

Assessment of spontaneously reported complaints in daily functioning showed marginal differences in affect (15% carriers and 5% non-carriers) and behaviour (9% of the carriers reported irritability and/or aggression while 1% non-carriers mentioned anxiety) (Fisher’s exact test, p=0.05).

Carriers did not differ significantly from non-carriers with respect to the diagnosis based on the UHDRS motor assessment (n = 124, Mann-Whitney U test, p=0.15).11

Comparison between carriers and non-carriers in behavioural complaints
Table 2 shows that carriers complained significantly more than non-carriers of sadness and low self-esteem and marginally in aggression and compulsions. Means are reported because the value of nearly all medians was zero. None of the participants complained about delusions or hallucinations. Spearman’s rank correlation was performed to ensure that the differences found between the two groups were not because of the few carriers discovered to be motor affected. Marginal association with diagnosis based on the motor assessment and the total motor score was only found in non-carriers for low self-esteem (r=0.22, p=0.05; r=0.25, p=0.02).

The role of age and gender in the occurrence of behavioural complaints
Age
In carriers no correlation was found between age and behavioural complaints. However, in the age category 30-49 years, carriers (n=30) complained significantly more about low self-esteem and guilt (p=0.008) and marginally about aggression (p=0.03) compared to non-carriers (n=46). Older carriers (>50 years, n=8) reported significantly more complaints concerning sadness (p=0.007) and obsessions (p=0.009) than older non-carriers (n=27). Younger carriers (<29 years, n=7) reported marginally more irritable behaviour (p=0.04) compared to non-carriers of similar age (n=15).

In non-carriers, age correlated marginally with anxiety (r=-0.23, p=0.03). The percentage of younger non-carriers reporting this complaint was higher than those over 50 years of age (50% vs 11%).

Gender
Gender differences were not apparent in the total group, nor when we looked at carriers and non-carriers separately. No differences were found between male carriers and male non-carriers. Female carriers, however, complained marginally more about sadness (p=0.03), low self-esteem (p=0.01), and aggression (p=0.02) than female non-carriers.

Influence of psychiatric history on the development of behavioural complaints
Participants were asked about the presence of a psychiatric history for depression, obsessive-compulsive disorder, psychosis, suicidal ideation, and suicidal attempt (UHDRS items 34-36, yes/no answer). Thirty-two percent of the carriers reported a history of depression and 21% of the non-carriers (NS) (table 1). Five carriers (11%) and four non-carriers (5%) used medication (table 1). There was no significant relationship between intake of neuroleptics and history of depression (r=0.005, p=0.96).

Fig 1 illustrates the mean occurrence of behavioural complaints among participants with and without a history of depression. A history of depression was only associated with behavioural complaints among the non-carriers. Participants from this group with a history of depression differed significantly from participants without as far as sadness (p=0.008), low self-esteem (p=0.000), and anxiety (p=0.000) were concerned, and marginally in obsessions (p=0.02). Suicidal ideation in the past did not differ between the groups. A history of obsessive-compulsive disorder, psychosis, or attempted suicide was never reported.

Influence of time interval between DNA testing and first assessment
In the non-carriers, significant positive correlations were seen with aggressive behaviour (r=0.29, p=0.007) and with irritable behaviour (r=0.36, p=0.001). No correlations were found in the carrier group between time since DNA testing and behavioural complaints.
Comparison of behavioural complaints between baseline and follow up for both carriers and non-carriers

After 18 months, 114 (85%) participants had returned to our department for follow up. Reasons for drop out were the following: no response to second recruitment (four carriers and six non-carriers), private circumstances (one non-carrier), the protocol was too demanding (two carriers), it was of no use to do it (two carriers), no time (one non-carrier), no benefit (one non-carrier), not tracked down (one non-carrier), no reason (one carrier), and dead (one carrier). Three of the carriers who dropped out were rated during baseline as either having probable or unquestionable motor symptoms characteristic of HD.

There were no significant differences in demographics between carriers (n=36) and non-carriers (n=78). The shorter duration of the protocol meant that the neurologists had less of an opportunity to attend the investigation. Consequently, a motor performance was assessed on 28 carriers and 53 non-carriers. Carriers differed marginally in the diagnosis (p=0.04). This group showed slightly more “minor soft motor signs” than during the first protocol (24% instead of 21%) while non-carriers showed fewer “minor soft motor signs” (14% instead of 21%). Three of the carriers who dropped out were rated during baseline as either having probable or unquestionable motor symptoms characteristic of HD.

Table 3 Mean change of behavioural complaints in carriers and non-carriers 18 months after baseline

<table>
<thead>
<tr>
<th>DNA test</th>
<th>Carriers (n=35)</th>
<th>Mean* (SD), range</th>
<th>Non-carriers (n=78)</th>
<th>Mean* (SD), range</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHDRS behavioural</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadness</td>
<td>0.66 (3.09), −6−7</td>
<td>0.28 (3.15), −12−16</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-esteem‡†</td>
<td>1.09 (2.67), −1−12</td>
<td>0.32 (2.04), −4−9</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.02 (4.22), −12−12</td>
<td>0.22 (3.62), −12−16</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>0.01 (0.87), −4−3</td>
<td>0.01 (0.34), −2−2</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td>0.29 (2.48), −8−9</td>
<td>0.03 (3.77), −4−9</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable behaviour</td>
<td>0.11 (3.03), −6−9</td>
<td>0.15 (2.66), −6−9</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsessions</td>
<td>−0.37 (2.09), −9−5</td>
<td>0.08 (2.29), −12−9</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsions</td>
<td>0.29 (3.2), −10−12</td>
<td>−0.14 (2.36), −9−16</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Higher score = fewer complaints (baseline minus follow up).
†Mean changes over time between the two groups (Mann-Whitney test).
‡Significantly fewer complaints in carriers (Wilcoxon signed ranks test: p=0.007).

In our study group, female carriers differed marginally from female non-carriers in sadness, low self-esteem, and aggressive behaviour and the interval since DNA testing to HD, as expected by these test participants. Other studies showed that the test result in some non-carriers did not alleviate problems or worries not related to HD, as expected by these test participants.

The occurrence of a history of depression was similar in the two groups. This may represent “regular” depression found in a large proportion of the population. Studies showed that people with a psychiatric history were more at risk of maladjustment following the test. (Vancouver group in Evers-Kiebooms and Decruyenaere). However, the contribution of a history of depression in developing behavioural complaints was only evident in non-carriers (sadness, low self-esteem,
and anxiety). Surprisingly, in our study carriers with a history 
did not differ from carriers without one. These findings, again, 
might be because of lesser power of the subgroup. Another 
possible explanation would be in line with Berrios et al.30 who 
reported discrepancies in factor structure of the psychiatric 
morbidity found in carriers, comprising “personality” (extra-
punitive, dominance, intrapunitive, outward and inward 
irritability) and non-carriers, comprising “anxiety”. The 
authors suggest that the psychiatric morbidity affecting carri-
ers may be the result of a subtle interaction between genetic 
factors and environment (for example, disturbed upbringing) 
whereas non-carriers would only be subjected to the latter, 
which would include anxiety.

The interval between predictive testing and the time of our 
study was not significantly associated with the presence of 
behavioural complaints in the carrier group. Other studies 
have reported that post-test intrusion level, hopelessness, and 
depressive symptoms disappear after one year.16 17 Also, 
carriers and non-carriers were reported not to differ signifi-
cantly in the long term (three years after disclosure of the 
DNA test) with regard to change from baseline on the investi-
gated psychological variables (intrusive thoughts, avoidance 
of thoughts, and hopelessness).16 17 These authors are in line 
with Wiggins et al.18 who concluded that predictive testing has 
maintained or even improved the psychological well being of 
carriers. The test result reduced uncertainty and provided an 
opportunity for appropriate planning.19 Codori et al.20 21 suggest 
that those who ask for the test are self-selected and believe 
they can cope better with a bad result. However, participants 
who underwent the direct mutation test had more depressive 
symptoms at all follow ups than those tested for linkage, even 
in the non-carrier group.17

In summary, owing to the explorative nature of our study, 
we can only speculate that aggressive behaviour in our carrier 
group may be seen as an initial sign intrinsic to HD while 
mood and low self-esteem complaints are more likely to be a 
reaction to the predictive test. Of course, as shown in other 
published reports, depression is a clinical manifestation of 
HD,22 but unfavourable genetic information does not generally 
produce syndromes of clinical depression.11 The participants in 
our study did not present with these characteristics. The high-
est percentages in our group of carriers were seen in the cat-
egories slight and mild with the exception of low self-esteem 
and aggression, which showed approximately the same 
percentage in the categories slight, mild, moderate, and severe. 
Our findings about the occurrence of aggression in our carrier 
group are not as striking as reported by Berrios et al.,16 and we 
do not suggest that phenocconversion has already occurred. In 
this study, we wanted to assert the fact that research in early 
detection of psychiatric signs is indispensable so that patients 
and family can be informed how to cope with these stressful 
manifestations of HD. Until now, this issue has been in the 
background compared to research in motor and cognitive 
functioning. This was the reason that our study was limited to 
the behavioural assessment of the UHDRS. The recent 
development of the Problem Behaviours Assessment for 
Huntington Disease (PBA-HD)23 may well resolve the lack, so 
of, a broader instrument than the UHDRS. This semi-

terview appears to be more suitable for investigating and 
descending the prevalence of behavioural symptoms. A review 
by Naarding et al.24 shows that most published studies on this 
subject are disappointing because of the lack of diagnostic 
criteria and adequate rating scales. The investigation of carri-
ers and the comparison with patients at different stages of the 
disease, relating behavioural complaints to cognitive and 
motor signs, should further enhance our insight into the early 
disease processes.

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