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

M-N W Witjes-Ané, A H Zwinderman, A Tibben, G-J B van Ommen, R A C Roos

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 intrinsically 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?

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

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.
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 in (normal, minor soft signs, probable HD, or unquestionable HD). The motor assessment has an excellent degree of inter-rater reliability.

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 in (normal, minor soft signs, probable HD, or unquestionable HD). The motor assessment has an excellent degree of inter-rater reliability.

#### Complaints

Complaints about affect and behavioural changes were investigated with the behavioural part of the UHDRS. Frequency and severity of complaints about mood/sadness, low self-esteem or guilt, anxiety, suicidal thoughts, disruptive or aggressive behaviour, irritable behaviour, obsessions, compulsions, delusions, and hallucinations were scored in five categories with respect to severity (0 = absent; 1 = slight, questionable; 2 = mild; 3 = moderate; 4 = severe) and frequency (0 = almost never; 1 = seldom; 2 =

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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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than secondary school</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>Higher than secondary school/university</td>
<td>13 (28%)</td>
<td>26 (30%)</td>
<td></td>
</tr>
<tr>
<td>Number of CAG repeats, median (range)</td>
<td>43 (39–51)</td>
<td>19 (14–34)</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>1 (2%)</td>
<td>3 (4%)</td>
<td>0.15*</td>
</tr>
<tr>
<td>Anxiolytic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (7%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Antidepressive drugs</td>
<td>2 (4%)</td>
<td>4 (5%)</td>
<td>0.78‡</td>
</tr>
</tbody>
</table>

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

### 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 [2.62], 0–16</td>
<td>0.076</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.
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, with 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), 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 no reason (one carrier), and dead (one carrier). Three of the participants who dropped out of the study, because no differences in behavioural complaints were found between this group and the group who participated in our follow up (results not shown). Our results on aggression and depression are similar to a recently published study by Berrios et al. These authors compared neurologically asymptomatic carriers with non-carriers in a double blind study. The groups did not differ in measures about depression but they did so in inwardly and outwardly directed irritability (that is, the possibility of self-harm and the possibility of angry action, respectively), suggesting that this symptom can occur very early in the course of HD.

In contrast to Decruyenaere et al and Codori et al, we could not confirm that carriers approaching age of onset are more anxious and manifest a higher post-test depression level. However, the presence of anxiety in younger non-carriers indicates that the impact of the DNA test could still be present in this group. Younger non-carriers could be more actively thinking about the consequence of the test result. Some non-carriers may have expected a different test result and they may have to rethink their plans for their future. Symptoms of depression and anxiety after predictive testing are indeed more likely in those who received a test result contradictory to the expected outcome (Vancouver group in Decruyenaere et al.). 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. This could also explain the positive relationship we found between irritable and aggressive behaviour and the interval since DNA testing in the non-carrier group.

In our study group, female carriers differed marginally from female non-carriers in sadness, low self-esteem, and aggression. The lack of significant differences between male carriers and non-carriers might be because of less power in the subgroups because the number of males was smaller. The fact that no gender differences were found in our study is in line with Codori et al, who suggested that women were just as well adjusted as men, but in contrast to Dudok de Wit et al, who reported that being a woman was one of the factors associated with a higher level of post-test distress.

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,

**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>Non-carriers (n=78)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean* (SD), range</td>
<td>Mean* (SD), range</td>
<td></td>
</tr>
<tr>
<td>UHDRS behavioural</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>
</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>
</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>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>0 (0.87), −4−3</td>
<td>0.01 (0.34), −2−2</td>
<td>0.73</td>
</tr>
<tr>
<td>Aggression</td>
<td>0.29 (2.48), −8−9</td>
<td>0.28 (1.77), −4−9</td>
<td>0.55</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>
</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>
</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>
</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).

**DISCUSSION**

We showed that carriers reported significantly more complaints about sadness and low self-esteem and marginally about aggression and compulsions. This was not associated with the degree to which they were motor affected. Within the age category 30–49 years, carriers expressed more low self-esteem and aggression compared to non-carriers. When 85% of the participants returned 18 months later for follow up, changes were minimal in both groups but carriers differed significantly now in aggression compared to non-carriers. The decrease of sadness and low self-esteem we found in carriers was not the result of the predominance of complaints among the participants who dropped out of the study, because no differences in behavioural complaints were found between this group and the group who participated in our follow up (results not shown). Our results on aggression and depression are similar to a recently published study by Berrios et al. These authors compared neurologically asymptomatic carriers with non-carriers in a double blind study. The groups did not differ in measures about depression but they did so in inwardly and outwardly directed irritability (that is, the possibility of self-harm and the possibility of angry action, respectively), suggesting that this symptom can occur very early in the course of HD.

In contrast to Decruyenaere et al. and Codori et al, we could not confirm that carriers approaching age of onset are more anxious and manifest a higher post-test depression level. However, the presence of anxiety in younger non-carriers indicates that the impact of the DNA test could still be present in this group. Younger non-carriers could be more actively thinking about the consequence of the test result. Some non-carriers may have expected a different test result and they may have to rethink their plans for their future. Symptoms of depression and anxiety after predictive testing are indeed more likely in those who received a test result contradictory to the expected outcome (Vancouver group in Decruyenaere et al.). 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. This could also explain the positive relationship we found between irritable and aggressive behaviour and the interval since DNA testing in the non-carrier group.

In our study group, female carriers differed marginally from female non-carriers in sadness, low self-esteem, and aggression. The lack of significant differences between male carriers and non-carriers might be because of less power in the subgroups because the number of males was smaller. The fact that no gender differences were found in our study is in line with Codori et al, who suggested that women were just as well adjusted as men, but in contrast to Dudok de Wit et al, who reported that being a woman was one of the factors associated with a higher level of post-test distress.

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 in the subgroup analysis. Another possible explanation would be in line with Berrios et al who reported discrepancies in factor structure of the psychiatric morbidity found in carriers, comprising “personality” (extravertive, dominance, intrapunitive, outward and inward irritability) and non-carriers, comprising “anxiety”. The authors suggest that the psychiatric morbidity affecting carriers 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 intrusiveness, hopelessness, and depressive symptoms disappear after one year. Also, carriers and non-carriers were not as striking as reported by Berrios et al 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.

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, but unfavourable genetic information does not generally produce syndromes of clinical depression. The participants in our study did not present with these characteristics. The highest percentages in our group of carriers were seen in the categories 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, and we do not suggest that phenoconversion has already occurred. In this study, we were interested in 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) may well resolve the lack, so far, of a broader instrument than the UHDRS. This semi-structured interview appears to be more suitable for investigating and describing the prevalence of behavioural symptoms. A review by Naarding et al shows that most published studies on this subject are disappointing because of the lack of diagnostic criteria and adequate rating scales. The investigation of carriers 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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