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Chapter 4

Falls and gait disturbances in Huntington’s disease

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ABSTRACT

Falls are common in patients with Huntington’s disease, but the incidence, falling circumstances and contributing factors have never been examined. We recorded falls in 45 early to midstage Huntington’s disease patients, both retrospectively (12 months) and prospectively (3 months). Fall rates were related to relevant baseline measures, including the Unified Huntington’s Disease Rating Scale (UHDRS) and quantitative measures of balance (using angular velocity sensors) and gait (using a pressure-sensitive walkway). Balance and gait measures were compared between patients and 27 healthy age-matched controls. Twenty-seven patients (60%) reported two or more falls in the previous year and were classified as fallers. During prospective follow-up 40% reported at least one fall. A high proportion of falls (72.5%) caused minor injuries. Compared to non-fallers, fallers showed significantly higher scores for chorea, bradykinesia and aggression, as well as lower cognitive scores. Compared to controls, Huntington patients had a decreased gait velocity (1.15 m/sec versus 1.45 m/sec, p<0.001) and a decreased stride length (1.29 m versus 1.52 m, p<0.001). These abnormalities were all significantly greater in fallers compared to non-fallers. In addition, fallers had an increased stride length variability and a significantly greater trunk sway in medio-lateral direction compared to non-fallers. We conclude that falls are common in Huntington’s disease. Contributing factors include a combination of “motor” deficits (mainly gait bradykinesia, stride variability and chorea, leading to excessive trunk sway), as well as cognitive decline and perhaps behavioral changes. These factors should be considered as future targets for therapies that aim to reduce falls in Huntington’s disease.
INTRODUCTION

Gait may become unstable even in early stages of Huntington’s disease (HD).¹ Falling is another feature of HD, and fall-related complications frequently result in hospitalization or nursing home placement.²,³,⁴ Despite these devastating consequences of falls, little is known about the epidemiology, circumstances and consequences of falls in HD. One small study on falls in HD reported that 11 of 13 patients had experienced several falls in the past, and most patients fell monthly.⁵

Equally little is known about the pathophysiology underlying falls in HD. A complex interaction seems likely and motor symptoms such as chorea or bradykinesia may disturb balance and gait and thereby contribute to falls. Bradykinesia can lead to slowing or inappropriate execution of corrective steps or protective arm movements. Bradykinesia is also associated with a reduced step height, and this increases the risk of tripping over uneven surfaces. Several studies have identified a decreased step length, decreased walking speed and increased stride time compared to healthy controls.⁵,⁶,⁷,⁸,⁹ Increased stride-to-stride variability has also been found, and this may reflect a defective neural gait machinery plus a contribution from excessive choreatic movements.⁵,⁶,¹⁰,¹¹

Second, balance may be compromised by abnormal postural reflexes, leading to inadequate responses to external perturbations and falls. Balance correcting responses in leg muscles of HD patients are inadequately scaled to cope with externally imposed postural perturbations, even when corrected for chorea.¹²,¹³ Third, disturbances in behaviour and cognition, such as “motor recklessness”, inattention or lack of insight can underlie falls in patients with HD.¹ Finally, apart from these “disease-specific” factors (related directly to HD), other “generic” risk factors for falls such as use of sedative medication and alcohol intake may play a role.¹⁴,¹⁵,¹⁶ The relative contribution to falls of these various postulated risk factors remains unclear. The main objective of this study was therefore bifocal. Our first goal was to establish the incidence, circumstances and consequences of falls in a large group of HD patients. Our second goal was to clarify the pathophysiology underlying falls in HD, and to disentangle the relative contributions from bradykinesia, chorea, gait impairment, postural instability and cognitive decline.

METHODS

Subjects

Inclusion criteria were early to mid-stage ambulatory HD patients. Exclusion criteria included juvenile HD, concurrent neurological disorders, other causes for balance disorders and severe visual problems. Because cognitive decline may be one of the factors associated with falls, we purposely did not exclude patients with cognitive impairment, but we did exclude patients with marked dementia who were unable to follow instruc-
tions or give informed consent. Eighty-nine patients fulfilled these criteria and were invited to participate. Forty-five patients gave informed consent, while the remaining patients refused or did not respond. There was no difference in gender and age between the participating patients and those who refused. Twenty-seven healthy controls were recruited from hospital personnel, acquaintances of the investigators and spouses of participants. Mean age and gender of patients and controls were comparable (mean age 51.9 ± 10.1 years for patients versus 52.2 ± 8.5 years for controls; 23 (51.1%) women for patients versus 21 (60.0%) women for controls). The Ethical Boards of the participating centres approved the study.

**Baseline clinical assessment**

Medical history, current medication use, living circumstances, alcohol intake and daily activities were recorded at baseline. Fall history, including number of prior falls and fear of falling, was obtained during a personal interview according to a standardized and validated questionnaire. Balance confidence was assessed using the Activities-specific Balance Confidence scale. For all cognitively impaired patients, a caregiver was asked to confirm the accuracy of the answers. We defined patients as “faller” when at least two falls had occurred in the preceding year.

Baseline assessment further consisted of a complete Unified Huntington’s Disease Rating Scale (UHDRS). Functional assessment included the Total Functional Capacity Score (TFC), a score between 0 (maximum disability) and 13 (no disability). The Berg Balance scale was used to clinically rate balance.

**Quantitative gait and balance measurements**

Gait analysis was performed using a pressure sensitive walkway (GaitRite), which can reliably identify gait disturbances in healthy subjects and patients with Parkinson’s disease and HD. Following a test trial, subjects were asked to walk straight ahead at a self-determined and comfortable speed (three trials) and subsequently at a fast speed but without running (three trials). Subjects started walking 2 meters ahead of the carpet and stopped 2 meters after the carpet. Because results were comparable for comfortable and high speed we only report the findings for the comfortable speed condition. Outcome measures included gait velocity, stride length and stride-to-stride variability. During the same gait tasks on the electronic walkway, we also searched for excessive trunk movements due to chorea or postural instability, using two digitally-based angular velocity transducers (SwayStar) worn on the lower back. These velocity transducers measure angular movements of the trunk in the medio-lateral direction (roll plane) and anterior-posterior direction (pitch plane) in freely moving subjects without interfering with natural body movements. Outcome variables included peak-to-peak angular displacements in the roll and pitch directions.
**Prospective follow-up**

Following these baseline examinations, patients recorded all falls using a standardized, validated falls calendar during 3 months. Circumstances and consequences of the first five falls were scored in detail on a standardized fall form, as described previously.17

**Statistical analyses**

Baseline differences between fallers and non-fallers were analyzed using parametric (t-test) or non-parametric tests (Mann-Whitney test, Chi-Square and Fisher exact). We used the Mann-Whitney U test to test for differences between patients and controls in spatial and temporal parameters of gait, as well as measures of angular trunk displacement. To search for associations between motor symptoms and the quantitative gait and balance variables, we calculated Pearson correlation coefficients. Stepwise forward logistic regression was used to evaluate which symptoms were most strongly related to being a faller.

**RESULTS**

**Frequency of falls**

At baseline, 27/45 (60%) of patients reported two or more falls in the preceding year and 34/45 (75.6%) had experienced at least one fall. During the prospective 3-month follow-up these fall rates were respectively 9/45 (20.0%) and 18/45 (40.0%).

<table>
<thead>
<tr>
<th>Table 1. Fall characteristics from 40 falls, as ascertained during the prospective follow-up period with completed fall sheets returned immediately after each fall.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fall characteristics</strong></td>
</tr>
<tr>
<td>Site of the fall (more than 1 option possible):</td>
</tr>
<tr>
<td>Familiar environment</td>
</tr>
<tr>
<td>Indoors</td>
</tr>
<tr>
<td>Self-reported cause (most reported):</td>
</tr>
<tr>
<td>Obstacle on the floor</td>
</tr>
<tr>
<td>Slippery or uneven surface</td>
</tr>
<tr>
<td>Preceding dizziness</td>
</tr>
<tr>
<td>Specific fall circumstance (most reported):</td>
</tr>
<tr>
<td>Multitasking</td>
</tr>
<tr>
<td>Climbing stairs</td>
</tr>
<tr>
<td>Consequences of falls:</td>
</tr>
<tr>
<td>No consequences</td>
</tr>
<tr>
<td>Minor injuries</td>
</tr>
<tr>
<td>Major injuries</td>
</tr>
</tbody>
</table>
Forty completed fall forms were returned and were used to analyse fall circumstances in detail (Table 1). A high proportion of falls (72.5%) during this 3-month follow-up caused minor injuries, mainly bruises and abrasions. There were no serious injuries (fractures, joint dislocations or head trauma). One third of falls occurred while the patients were performing multiple tasks simultaneously. Additional factors that commonly led to falling included obstacles on the floor and climbing stairs.

Characteristics of fallers and non-fallers

Age and disease duration did not differ from those of non-fallers (table 2). Total functional capacity (TFC) score, as a marker for disease severity, tended to be lower in non-fallers. Medication did not differ between fallers and non-fallers. Fallers were significantly less confident about their balance than non-fallers. However, only a small proportion of fallers was afraid of falling, and this did not differ from non-fallers.

The UHDRS items for gait, total chorea (sum of all chorea scores) and body bradykinesia (item 10 of UHDRS) were significantly higher in fallers, indicating a worse performance among fallers (Table 2). After correction for disease severity (using TFC), these differences remained significant (p<0.01 for gait; p=0.03 for total chorea; and p=0.05 for body bradykinesia). The association between total chorea and body bradykinesia was weak (r=0.23; p = 0.13). Balance measures, indexed by the retropulsion test and the Berg balance scale, were worse in fallers compared to non-fallers. However, after correction for disease severity, the retropulsion test scores were no longer significantly different between fallers and non-fallers.

Total behaviour score was not significantly different between fallers and non-fallers. Of all behaviour items, we only found significantly higher scores in fallers for the aggression frequency (p=0.01) and the aggression severity (p=0.02).

Use of psychotropic drugs and cardiac medication tended to be higher among fallers, but differences from non-fallers were not significant.

All cognitive scores were significantly lower among fallers, suggesting an association between cognitive decline and falling (Table 2). The Symbol Digit Modalities test was most significantly associated with falling (18.6 among fallers versus 29.6 among non-fallers; p<0.01). MMSE scores did not differ between fallers and non-fallers.

Finally, we performed a multivariate analysis including TFC, body bradykinesia, chorea, Berg balance test, total cognitive score and aggression, and with multiple faller status as the dependent variable. In this analysis, cognitive performance (p=0.01) and aggression (p=0.01) were most strongly associated with falling in HD.
Falls and gait disturbances in Huntington's disease

Gait analysis

The various quantitative gait variables will be described separately for fallers and non-fallers, as compared with controls. Patients walked significantly slower than controls (decreased gait velocity) and had a decreased stride length. This was particularly evident among patients with falls (Figure 1A&B). Interestingly, increased stride length variability, was only observed in fallers but did not differ in nonfallers compared to controls (fallers vs nonfallers; 0.060 vs 0.036, p<0.01, Figure 1C).

Trunk movements

Angular trunk displacement, as measured by the range of motion in the roll and pitch directions, was significantly greater in patients than in controls (Figure 2 A&B). This increased trunk sway was more pronounced in fallers compared to nonfallers, but this difference was only significant for medio-lateral angular motion of the trunk (Figure

Table 2. Clinical details of fallers and non-fallers (defined by presence of historical falls). Data reflect either means and standard deviation, or numbers and percentage.

<table>
<thead>
<tr>
<th></th>
<th>Fallers (n=27)</th>
<th>Non-fallers (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.1 ± 11.1</td>
<td>51.6 ± 8.8</td>
</tr>
<tr>
<td>Women</td>
<td>15 (55.6 %)</td>
<td>8 (44.4 %)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.9 ± 4.0</td>
<td>7.4 ± 4.8</td>
</tr>
<tr>
<td>Total functional capacity score (TFC) (0-15)</td>
<td>9.4 ± 2.3</td>
<td>10.2 ± 1.7</td>
</tr>
<tr>
<td>Balance confidence (0-100)</td>
<td>64.4 ± 18.8</td>
<td>83.2 ± 13.8 ††</td>
</tr>
<tr>
<td>Fear of falling</td>
<td>4 (14.8 %)</td>
<td>3 (16.7 %)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td>11 (40.7 %)</td>
<td>5 (27.8 %)</td>
</tr>
<tr>
<td>Cardiac medication</td>
<td>5 (18.5 %)</td>
<td>1 (5.6 %)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (25.9 %)</td>
<td>5 (27.8 %)</td>
</tr>
<tr>
<td>Motor score UHDRS (total)</td>
<td>38.7 ± 14.3</td>
<td>27.5 ± 19.5 ††</td>
</tr>
<tr>
<td>Body bradykinesia (item10)</td>
<td>1.7 ± 0.82</td>
<td>1.1 ± 0.10 †</td>
</tr>
<tr>
<td>Chorea (sum of all chorea scores)</td>
<td>13.2 ± 6.1</td>
<td>8.7 ± 6.5 †</td>
</tr>
<tr>
<td>Gait (item 13)</td>
<td>1.2 ± 0.58</td>
<td>0.50 ± 0.62 ††</td>
</tr>
<tr>
<td>Retropulsion test</td>
<td>0.89 ± 0.42</td>
<td>0.56 ± 0.62 †</td>
</tr>
<tr>
<td>Total behaviour score</td>
<td>13.8 ± 10.7</td>
<td>10.8 ± 11.8</td>
</tr>
<tr>
<td>Aggression frequency</td>
<td>2.37 ± 1.18</td>
<td>1.5 ± 0.92 ††</td>
</tr>
<tr>
<td>Aggression severity</td>
<td>1.85 ± 0.95</td>
<td>1.22 ± 0.43 †</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.7 ± 3.7</td>
<td>27.2 ± 3.1</td>
</tr>
<tr>
<td>Total cognitive score</td>
<td>167.5 ± 45.4</td>
<td>217.0 ± 62.1 ††</td>
</tr>
<tr>
<td>Independence scale (0-100)</td>
<td>82.0 ± 10.7</td>
<td>90.0 ± 9.2 †</td>
</tr>
<tr>
<td>Berg balance score (0-56)</td>
<td>54.0 ± 2.4</td>
<td>55.4 ± 1.1 †</td>
</tr>
</tbody>
</table>

††<0.01
†<0.05
A&B). These increases in trunk sway of HD patients in both the medio-lateral and anterior-posterior directions remained significant after correction for gait velocity (linear regression; roll angular range p=0.01 and pitch angular range p<0.01) as compared to controls.

**Fig 1** Gait velocity, stride length and stride variability.
*P < 0.05, **P < 0.01.

2A&B). These increases in trunk sway of HD patients in both the medio-lateral and anterior-posterior directions remained significant after correction for gait velocity (linear regression; roll angular range p=0.01 and pitch angular range p<0.01) as compared to controls.
Correlation with clinical scores

Clinical chorea scores were positively correlated to the range of angular trunk motion in both the medio-lateral direction \( (r=0.59, p<0.001) \) and the anterior-posterior direction \( (r=0.62, p<0.001) \). As expected, we also found a weak but significant negative correlation between body bradykinesia and walking velocity on the electronic walkway \( (r=-0.32, p=0.03) \).

**DISCUSSION**

Falls are common in this group of moderately affected HD patients. We identified that motor deficits (chorea and bradykinesia), cognitive decline and behavioral disturbances (aggression) contributed to falls in HD. Quantitative analyses revealed abnormalities of gait and balance that were more pronounced in HD patients with falls compared to patients without falls.
This is the first detailed examination of fall rates and fall circumstances in HD. The observed fall rates were high. Retrospectively, 60% sustained recurrent falls during the preceding year, and the majority reported weekly or monthly falls. Prospectively ascertained fall rates were also high, albeit lower compared to the retrospective fall rates, presumably because of the relatively brief prospective follow-up (3 months). In addition, underreporting of falls during prospective follow-up due to concomitant behavioral or cognitive disturbances in HD cannot be excluded.

Despite the high proportion of falls with minor injuries (more than 70%), no serious injuries were reported. One explanation may be that patients usually fell indoors, where carpets may have cushioned the impact of the fall. In contrast, major injuries are very common in patients with progressive supranuclear palsy, due to a combination of a severe and rapidly progressive balance deficit, along with a lack of insight (“motor recklessness”). Balance deficits in HD are less prominent and may progress more slowly, thereby allowing for compensatory strategies to develop. Our findings may also indicate that “recklessness” did not contribute much to falls and injuries in HD. Indeed, most behavioral measures were not correlated to falls, except for aggression which was independently associated with falling. However, the UHDRS behavioral assessment does not provide a useful tool to measure recklessness and the available items can only be interpreted indirectly.

Surprisingly, only few patients were afraid of falling, and this differs from other fall-prone patient groups. Among patients with Parkinson’s disease, 53% of fallers expressed a fear of falling, compared to only 15% in the present HD group. Interestingly, fallers with HD did realise that their balance was disturbed, as reflected by their lower balance confidence rating compared to HD patients who were non-fallers. One possible explanation is the low incidence of severe injuries (low “penalty” for falling), but a general indifference to serious consequences (perhaps related to cognitive decline) may also underlie this absence of fear in HD.

We identified several factors that may have contributed to the pathophysiology underlying falls in HD. Excessive choreatic trunk movements are a striking feature in HD that could lead to unstable walking. In this study, the total UHDRS score for chorea was significantly higher in fallers compared to non-fallers, suggesting causative contribution. This assumption was supported by our quantitative assessment of trunk movements during gait (using accelerometers attached to the lower trunk), which showed an increased sway in HD, and more so among fallers than non-fallers. These trunk movements were correlated to clinical chorea scores. We therefore speculate that chorea cause increased postural sway that may at times exceed the limits of stability and thereby cause falls. Bradykinesia could also play a role in falling. First, falls in our patients were commonly related to stumbling over small obstacles on the floor (presumably caused by a reduced step height). Second, clinical scores for body bradykinesia were significantly higher.
among fallers compared to nonfallers. In addition, quantitative gait assessment showed that walking speed was decreased in fallers. Note that body bradykinesia did not correlate to chorea, so perhaps both signs of HD play an independent role in the pathophysiology of falls in HD.

A third “motor factor” that could cause falls is balance impairment. Clinical balance scores (the retropulsion test and Berg Balance scale) were lower in fallers compared to non-fallers, but differences were small. Indeed, most patients had a normal retropulsion test, suggesting a largely preserved balance. Taken together, we suspect that balance abnormalities per se play a relatively minor role in causing falls in HD.

We further observed a strong correlation between falling and cognitive decline, as observed earlier in Alzheimer’s disease and Parkinson’s disease. This could reflect a mere association between balance disorders and cognitive impairment, both becoming more prominent in later stages of the disease but without causal relationship. However, in our patients there was no association between falling and disease duration or disease severity. This would suggest that the observed association is not just a marker of disease progression, but that cognitive disturbances themselves play a causative role in frequent falling. Indeed the majority of falls in HD occurred under so-called “multiple task” circumstances. Difficulties handling complex multitask circumstances are particularly prominent among patients with mental decline.

Our study had several shortcomings. First, our sample size was too small to run a reliable multifactorial analysis, so any claims about factors with a possible independent contribution to falls must be made with caution. However, our study does represent the largest and most comprehensive approach of falling in HD thus far. Second, our quantitative measures were selected based on their reliability, validity and feasibility, but their relative low-tech character implied that this provided only a relative “keyhole” view of gait and balance performance. Further detailed posturographic or full body kinematic gait analyses remain necessary to fully comprehend the pathophysiology underlying falls in HD. Such knowledge, along with the findings of the present study, should form the basis for the development of effective treatment strategies aimed to reduce falls in HD.

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