Falls in Parkinson's disease and Huntington's disease

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Chapter 8

Summary, conclusions and future perspectives

A main finding of this dissertation is that falls are common, both in patients with Parkinson's disease (PD) and Huntington's disease (HD). Moreover, falls are already present in early disease stages for both conditions, and the prevalence increases with further disease progression. This dissertation also describes the fall circumstances, risk factors and consequences of falls in PD and HD. In addition, it provides insights into the pathophysiology of postural disturbances and falls in these two neurodegenerative disorders. Finally, this thesis concludes with a proposal for a possible multidisciplinary and multifaceted intervention program to prevent falls in PD.

Postural disturbances are one of the cardinal features of PD. Unfortunately, they generally improve poorly with dopaminergic therapy or with deep brain surgery aimed at the basal ganglia.[1] In **Chapter 2** a 'noradrenergic hypothesis' is proposed to explain this resistance to dopaminergic treatment. Specifically, we propose that lesions in the locus coeruleus and a concomitant central noradrenergic deficit could be responsible for at least part of the postural abnormalities observed in PD. This suggestion was based on observations from several neurochemical and neuropathological studies in PD, which identified significant cell loss in the locus coeruleus (which is the main source of norepinephrine in the central nervous system) as well as a noradrenergic deficit. 2,3,4 The locus coeruleus may well play a role in controlling balance because it projects to many areas in the brain and spinal cord, and as such it is involved in the regulation of e.g. attention and gain control of spinal reflexes, both of which could be important for maintaining balance. Other indirect evidence is generated by drug studies that aimed to restore central norepinephrine transmission in PD. Some of these studies report a beneficial effect on gait and freezing (reviewed in **Chapter 2**), but unfortunately these trials did not focus on balance as primary outcome. This review suggests that further work is justified in this area and that new clinical studies of noradrenaline enhancers should test their specific effect on balance and falls.

In **Chapter 3 and 4** the frequency of falls, fall circumstances and consequences of falls were studied in both PD and HD. A prospective study in 59 PD patients and a meta-analysis of six prospective studies (including a study of our own that was performed in Leiden) showed that falls were common in PD. Specifically, during a six-month follow-up, PD patients had a nine-fold increased risk of sustaining recurrent falls compared to healthy age-matched controls. During this same period, 50% of moderately affected PD patients reported two or more falls. The fall risk increased with disease severity, but at UPDRS values of about 50, the fall risk reached a plateau of around 60% chance of falling in the next 3 months. At even higher disease severity scores there was a slight decline in the risk of falling, perhaps because secondary immobility due to progressive balance impairment reduced the risk of falling.[5] However, the fall risk did not approach zero, as might be expected when patients become fully immobilized. Apparently, patients reduced their overall physical activity levels, but did not become fully bedridden. However, we should be aware that patients admitted in a nursing home were excluded from this study.

In most falls an intrinsic cause, i.e. a patient-related factor, was responsible for the fall. A 'centre of mass' type of fall (involving movements of the trunk) was most common, often occurring while turning around. This suggests that balance disturbances frequently underlie falls in PD. In hindsight, freezing of gait during turning may well have been responsible for some of these falls,[6] but at the time of this study, we did not specifically ask about freezing of gait as a possible cause of falls. We should note that for six falls, subjects indicated that these were related to freezing of gait in our study, although this was not specifically related to turning. More recent work has confirmed the strong relationship between freezing of gait and falls in patients with PD.[7,8]

Most falls occurred during the on-phase, suggesting that dopaminergic therapy was unable to alleviate the intrinsic balance disorder. In fact, most falls occurred when symptoms were well controlled or when patients experienced dyskinesias, suggesting that, if anything, dopaminergic therapy was associated with an increased risk of falls. Several theories may explain this last finding. When symptoms are relatively well controlled, patients could experience an increased mobility, but without an improved balance. Indeed, recent work suggests that the risk of falls can be expressed as a function of distance travelled.[9] Another possibility is the presence of drug-induced dyskinesias, causing an increased postural sway leading to imbalance. A shortcoming of our study was that we did not correlate the severity of dyskinesias to the presence of falls, and this should be the topic of future research.

Most falls happened indoors, and although only a minority of falls had an extrinsic factor, domestic hazards did play an important role in the underlying mechanisms of falls. Importantly, we also found that use of sedative medication increased the risk of falling. Specifically, use of benzodiazepines was associated with a five-fold increase in the risk of recurrent falls, over and above the risk of falling conveyed by PD alone. This finding is consistent with studies in other patient groups[10,11,12,13] and suggests that use of sedative medication should be avoided at all cost in patient groups who are already at risk of falling.

The high risk of falls was associated with a high rate of soft tissue injuries, and with a fear for future falls. This fear of falling could play an important role in restricting physical activities, possible even more so than the physical injuries. Major injuries such as hip fractures were relatively rare, but perhaps our follow-up was too short to adequately document the risk of hip fractures. Other work has underscored that hip fractures are in fact common in patients with PD[14,15] and this risk is compounded by the concurrent osteoporosis which is also common in patients with PD.[16,17]

Another goal of this thesis was to identify possible predictors of future falls in PD (**Chapter 3)**. The best predictor of falls in the near future turned out to be the presence of two or more falls during the preceding year. However, the sensitivity (68%) and specificity (81%) were not high, and importantly, prior falls are by definition unable to predict the very first fall. Asking for fear of falling might be able to identify these new-onset fallers, but its sensitivity and specificity were only moderate. Interestingly, none of the commonly used clinical tests of balance and gait could predict falls adequately. This included the widely used retropulsion test, which could not discriminate between future fallers and non-fallers. As the execution of the retropulsion test is under debate it was executed six times consecutively in our study, the first time without any prior warning. This yielded different results (underscoring the importance of test standardisation), but none of the six tests could predict future falls properly. Taken together, it currently proves difficult to reliably identify future fallers in PD, and commonly used balance tests are insufficient predictors of falling in PD. These observations highlight the need for development of alternative predictors, such as electrophysiological measures of gait, freezing or balance.

We also studied the epidemiology of falls in patients with HD **(Chapter 4).** This study represented the first detailed examination of fall rates and fall circumstances in HD. Our results showed high retrospective fall rates. Specifically, 60% of patients reported two or more falls in the past year. Prospectively documented fall rates (assessed over a period of three months) were lower (20% of patients reported two or more falls, and 40% one or more falls), but the prospective follow-up period was relatively short. Similar high retrospective fall rates were found in a later study in HD patients.[18] As in PD, most falls occurred indoors and resulted in a high rate of minor injuries. A surprising finding was that, unlike PD, only few subjects were afraid of falling. They did show a low balance confidence, suggesting that they were aware of the high risk for falling. A possible explanation could be the low rate of serious injuries. Another explanation may be behavioural or cognitive disturbances, leading to a general indifference to the possible consequences of a fall.

Similar to what was observed in PD, commonly used clinical balance tests could not adequately discriminate fallers from non-fallers in the HD group. A more recent retrospective study reports reasonable predictive values of the Tinetti Mobility Test in predicting falls in HD (sensitivity of 74% and a specificity of 60%).[19] Another study found significant differences in Berg Balance Scores and Timed Up and Go test between fallers and non-fallers, but this was only an explorative study in a small group of patients.[18]

To further identify tests that can predict future falls we added quantitative measurements of balance and gait, using highly sensitive accelerometers that were attached to the lower trunk (see Box 1.3 in **Chapter 1**). Increased medio-lateral trunk sway, as measured with these velocity transducers, was significantly higher in fallers, and this correlated with clinical chorea scores. Analysis of gait parameters showed a decreased walking velocity with a decreased stride length, and this was significantly associated with falls. These findings provide a first step towards development of an objective test algorithm that might be able to reliably predict future falls, either alone or in combination with clinical parameters.

Chapter 5 addresses the impact of falls, fear of falling and balance disturbances on quality of life in PD. Quality of life in PD is associated with many different aspects of the disease, including disease severity, motor disturbances and behavioural symptoms.[20,21] We found that experiencing falls, fear of falling and balance disturbances were all associated with lower quality of life scores in PD. In a multivariable analysis only fear of falling and disease severity were significantly related to the quality of life. Fear of falling was a stronger predictor of reduced quality of life scores than experiencing actual falls or objective clinical measures of balance impairment. This significant impact of fear of falling was also found in an earlier study in PD, which found that fear of falling was a stronger determinant of quality of life than falls or gait related disorders.[22] These findings indicate that fear of falling should be an important target in future strategies to improve the quality of life for patients with PD.

Use of the 'stops walking when talking test' (SWWT), first published by Lundin-Olsson et al[23], introduced a new insight into balance strategies and fall risks in the elderly. An inability to walk and talk at the same time had a good predictive value for the occurrence of falls in the ensuing 6 months, at least in the specific population that was tested (elderly subjects with cognitive decline). The interference between these two tasks apparently induced an inability to walk while subjects engaged in a routine conversation, suggesting that they had a restricted central processing capacity. As this test is easy to perform in an outpatient clinic we also tested it in a PD population. Interestingly we find no difference in performance of the SWWT between fallers and non-fallers in PD **(Chapter 6.2).** In fact, only very few patients with PD stopped walking when they were talking at the same time. A possible explanation for this finding could be the difference in cognitive status of the participants. In the Lundin-Olsson study many subjects had cognitive impairment or were depressed, but in our study subjects with cognitive impairment were excluded. This may suggest that impaired dual task performance is a better marker of falls associated with cognitive impairment than with pure motor impairment.

To further investigate dual task impairment in PD we reviewed studies that described the effect of dual tasking on walking and balance **(Chapter 6.3)**. Although all study designs differed, they consistently showed deterioration of balance and gait when a secondary task was added. This was true for both cognitive tasks (such as mental arithmetic) and for motor tasks (such as carrying a tray). One of these studies reasoned that patients with PD without dementia would still prove to be vulnerable to multitasking if the secondary task load was made sufficiently difficult.[24] For this purpose a 'multiple task test' (MTT) was developed that included, among others, cognitive and motor challenges that could be combined until a very complex situation arose, where subjects had to execute up to eight tasks simultaneously. This study showed a different strategy between controls and PD patients. Specifically, controls favoured execution of motor tasks over execution of a cognitive task, but patients attempted to perform all tasks simultaneously. Patients thus seemed less able than controls to employ a so-called 'posture first' strategy, i.e. a strategy where the safety of maintaining upright balance or gait is prioritised over the execution of any secondary task [Bloem J Neurol Sci 2006]. This inability of PD patients to prioritise their postural safety is an interesting finding that should probably be implemented in future fall prevention programs, for example by instructing patients to avoid secondary tasks during walking or balancing activities, or to postpone a complex secondary task until a safe (e.g. seated) position has been obtained. Interestingly, however, recent work points to an alternative strategy, namely the possibility to train patients to better perform multiple tasks simultaneously.[25].A great advantage to this latter approach is that it closer resembles daily life performance, where multitasking can never be avoided completely. So ideally patients should be trained to better cope with these complex situations, and the latest research results are promising in this respect.

Chapter 6.1 reviews the above findings on the assessment, pathophysiology and treatment of falls, and places these results into perspective with other current literature on falls in PD.

In Chapter 7 a design for a multifactorial falls prevention program for PD is proposed. This program should include PD-specific therapeutic measures, as well as generic strategies (because patients with PD are not exempt from the 'normal' risk factors that are associated with ageing). For this purpose, we reviewed the literature on all previously identified risk factors for falls in PD, we examined existing fall prevention strategies in the literature, and we evaluated published national and international falls prevention guidelines. Based on these sources we developed a menu of therapeutic interventions tailored to each of the possible risk factors, and bundled these into a concept protocol for a Multifactorial Parkinson Falls Prevention strategy. A challenge was to identify therapeutic strategies that would be feasible for PD patients. For example, an accepted strategy to prevent falls from orthostatic hypotension is standing with both legs crossed. This is an unstable posture for PD patients with marked postural instability, and is therefore not a suitable intervention in this patient group.

The suggested intervention program includes one or more of the following approaches (depending on the specific risk profile that is present in each individual patient): optimizing dopaminergic therapy (for example, to reduce off-state freezing of gait); reducing the use of sedative medication; physiotherapy to improve transfers and gait (including freezing of gait); balance and balance confidence training; promoting physical activity; training the use of assistive devices; occupational therapy; and treatment of orthostatic hypotension, urinary incontinence and visual impairment. This concept for a multifaceted falls prevention program is currently being examined and refined by an international panel of experts. Once accepted, this program could serve two purposes: first, it could help clinicians in current clinical practice when they strive to prevent falls in their patients; and second, it could serve as the active intervention arm in future randomised clinical trials that aim to evaluate the merits of a new program for the prevention falls in PD.

Future perspectives

Additional work is required to find algorithms that can reliably predict falling in PD and HD, in order to identify subjects at risk for falls, and to determine who are the best candidates for fall intervention programs. Such models should include well studied instruments to measure this risk for future falls, including the use of validated falls questionnaires and the use of prospective diaries to document faller status, as was used in this dissertation. Assessing the presence of fear of falling is important, as this is not only a risk factor for falls, but also an important determinant of quality of life in PD. The questionnaires should also ask about any negative consequences of physical inactivity in PD. Many patients with PD are prone to develop a sedentary lifestyle[26] and fear of falling is among the many reasons why patients start to avoid participating in physical activities, such as walking outdoors for pleasure or to engage in physiotherapy. A crucial challenge that lies ahead of us is to find ways to promote physical activity in PD, considering safety limits. This is now being taken to the test in the ParkFit trial, a large study of exercise for patients with PD, aiming mainly to achieve a behavioural change that will lead to sustained increase in physical activities.[26]

Any prediction model to identify future fallers should also include the best available clinical tests of gait and balance. The current thesis suggests that testing for dual tasking abilities should be part of the test battery, certainly when the second load can be graded to ascertain that the task is also sufficiently challenging for patients without depression or dementia. Our current findings cast doubt on the merits of the traditional retropulsion test, at least as a predictor of falls, although it probably remains a simple test to screen for and score balance abnormalities in clinical practice.

Given the shortcomings of currently available clinical test batteries, we anticipate that objective electrophysiological assessments of gait and balance will play an important role in these fall prediction paradigms. There are now many examples of such devices, including ambulatory equipment that can detect freezing episodes or other basic gait parameters[27,28], transfers[29], or trunk sway measures during a variety of tasks.[30,31]
Recent findings (published after completion of our studies) point to two particularly important developments : (a) the strong relationship between falling and freezing of gait in patients with PD[7,8], suggesting that this should be an important component of the assessment battery, as well as a key target for future therapeutic intervention (optimising dopaminergic treatment; and use of cueing strategies); and (b) the strong relationship between falling and cognitive decline.[32] This latter association is clearly important, both for patients with PD and for patients with HD. It is becoming increasingly clear that gait and balance are not fully automatic and subconscious motor tasks, but in fact represent complex actions that require considerable monitoring and attention. This probably explains why frontal executive deficits are particularly strong related to both gait disability, postural instability and falls in various neurological populations. Whether this association with cognitive decline may also have any therapeutic implications remains unclear. However, cognitive decline has been linked to central cholinergic deficits, and interesting new work is now pointing to the possible therapeutic merits of cholinesterase inhibitors for the prevention of falls;[33,34] We expect that this will be an important area of research in the next few years.

Medication to adequately treat balance disturbances is still not available. Next to levodopa - which can help to improve gait and freezing of gait, but which only partially improves balance - there is a need for development of non-dopaminergic therapies. We already mentioned the ongoing work on cholinesterase inhibitors as important candidates to improve freezing of gait and balance. **Chapter 2** suggests that it is worth trying to improve balance using central noradrenergic enhancers. In addition, non-pharmacological treatments need to be improved as well. Stereotactic deep brain stimulation of the subthalamic nucleus (STN) or the internal globus pallidus does not sufficiently alleviate balance disorders. Recent studies aimed at the pedunculopontine nucleus as a promising new target for gait and balance deficits, by these have shown conflicting results.[35,36] Better physiotherapy programs are currently being developed, and their effectiveness has been documented in a recent evidence-based guideline.[37,38]
Finally, because falling is complex and related to many aspects of the disease, multidisciplinary care is probably needed to optimally treat balance disorders and to reduce fall risks. In **Chapter 7**, we proposed a concept for a multidisciplinary team intervention, but

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such programs now need to be studied further and taken to the test in large randomised clinical trials. The intervention programs should always be tailored to the individual with their specific disease features. For example, relatively few HD patients experience fear of falling, and they may therefore benefit less from interventions addressing fear of falling than patients with PD, where a fear of falling is very common and incapacitating. Simply prescribing walking aids could be hazardous in HD patients, because this carries the risk of tripping over the aid when taking a corrective side step or when patients sway the device around because of their involuntary movements.[39] Patients with PD also often use their walking aids inappropriately, and sometimes this further increases their risk of falling. Such observations underscore the importance of developing intervention programs that contain disease-specific strategies, next to 'generic' fall interventions. In late stages of PD and HD balance may become so severely compromised that it is no longer possible to make safe transfers; in this stage fall prevention strategies may need to focus on wheelchair use and a reduction of unsupervised mobility. Again, the merits of such a multifaceted falls prevention strategy, tailored to individual needs and disease severity, now needs to be examined in future randomised controlled trials.

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