FALLS IN PARKINSON'S DISEASE AND HUNTINGTON'S DISEASE

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Falls in Parkinson's disease and Huntington's disease

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Chapter 1

General introduction and aims of the thesis

FALLS

"Some two days after my arrival, I saw a boy staggering through the streets. He fell, stopped and fell again." (Negrette A. Personal communication 2001 to 2003)[1] This was the first encounter in 1952 of Amerigo Negrette, a Venezuelan doctor, with a person with Huntington's disease (HD) (Box 1.1) in Maracaibo, Venezuela. In this region a large population is affected by HD. These large kindred played an important role in unraveling the gene that caused this disease.

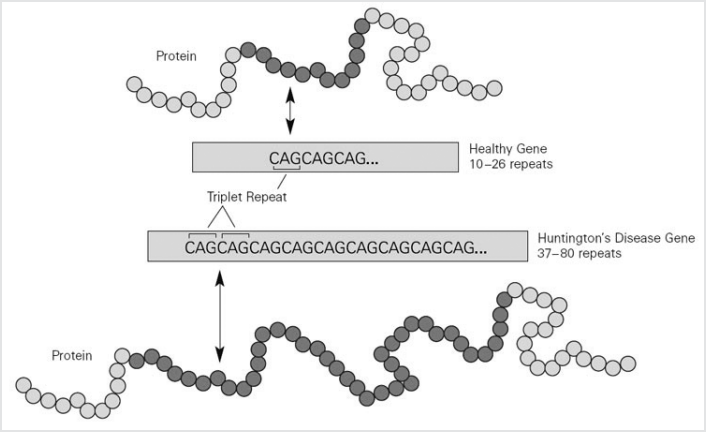
Falls are common in many neurological diseases, including Parkinson's disease (PD) (Box 1.2) and HD.[2,3] These movement disorders share symptoms such as rigidity, bradykinesia, chorea (in HD as part of the disease itself, in PD as a side effect of dopaminergic medication) and postural instability. In both diseases, gait gradually becomes unstable, and postural instability increases as the disease progresses. This almost inevitably leads to falls, frequently with devastating consequences. In the elderly, falls are associated with fractures, hospital admission and nursing home placement.[4,5,6] Next to these sequelae, fallers may also develop an incapacitating fear of renewed falls, and this may in turn lead to a decreased mobility and a lower quality of life.[7]

Box 1.1

Huntington's disease (HD)

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by motor, cognitive, psychiatric, and behavioral disturbances. The prevalence in the United States and Europe is estimated at 5-10 per 100.000 inhabitants and about 5 times as much persons are at risk of developing the disease.[39] Mean age of onset ranges between 43.7 and 55.8 years[40,41] and mean disease duration is approximately 16 years.[38] In 1993 the gene mutation responsible for HD was identified.[42] The 'interesting transcript 15' (IT15) gene on the short arm of chromosome 4 contains an expanded CAG repeat of 36 or more repeats in affected individuals. A repeat of 36-40 is considered as incomplete penetrance, 40 or more repeats invariably lead to symptomatic disease. The length of the CAG repeat plays a role in disease onset leading to an earlier onset for subjects carrying longer repeats.[43,44]

The gene encodes for a protein called huntingtin, and the expanded trinucleotide repeat results in a mutant huntingtin protein containing an expanded polyglutamine tract. Since 1993 research is aimed at the function of huntingtin and the damage that is caused by the mutant huntingtin.



from www.nigms.nih.gov

Despite these devastating consequences, relatively little is known about the epidemiology, circumstances and consequences of falls in patients with PD and HD. There are only few studies that reported the incidence of falls in these disorders. Retrospective studies reported high fall rates, up to 83% in patients with PD[8,9] and 85% in HD.[2] The circumstances and risk factors for falls in these patient groups were not described in detail. Therefore, we prospectively studied the incidence of falls in both diseases, aiming to gain more detailed insight into the potential risk factors and circumstances of these falls (Chapter 3).

The pathophysiology underlying falls is complex and multifactorial, and typically involves combinations of both 'extrinsic' (environmental) factors and 'intrinsic' (patient-related) factors.[10] Examples of extrinsic risk factors include loose rugs or other obstacles on the floor, the presence of stairs in the house, or a cat that wanders about the house. Intrinsic risk factors include, for example, underlying balance impairment, orthostatic hypotension, or violent dyskinesias that may literally perturb the patient beyond the limits of stability. Some of these intrinsic risk factors are specific for PD (e.g. freezing of gait), but patients may also fall due to 'generic' risk factors for falls that would apply to any elderly person. Examples of such generic risk factors include the use of alcohol, visual impairment or the use of sedative medication (in particular benzodiazepines). After mapping all of these intrinsic and extrinsic risk factors, it is possible to develop an individually tailored prevention program that aims to prevent future falls and to reduce the risk of the associated complications (such as fall-related injuries, or a secondary fear of falling).[11]

Box 1.2

Parkinson's disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative disorder. Its cardinal motor features include a resting tremor, rigidity, bradykinesia and postural disturbances. It also encompasses a wide range of non-motor symptoms, such as mood disorders, autonomic dysfunction, olfactory loss and cognitive decline. Some of these non-motor symptoms typically develop in later stages of the disease. Presence of prominent postural instability or severe cognitive disturbances early in the course of the disease is not characteristic for PD and points to the presence of a form of aypical parkinsonism, such as PSP or vascular parkinsonism. The estimated prevalence in Europe is 160 per 100.000 inhabitants.[45] Mean age at onset is approximately 58 years and the prevalence of PD increases with age rising to 360 per 100.000 for those aged 80-84.

The cause of PD remains largely unknown, but genetic and environmental factors are thought to play a role.[46,47] The histological hallmarks of PD are a loss of dopaminergic neurons in the substantia nigra and cytoplasmatic inclusions termed Lewy bodies, that are composed principally of alpha-synuclein. Therapy is mainly focused at correcting the central dopaminergic deficit. Dopaminergic medication improves the main motor symptoms, especially rigidity and bradykinesia. However, not all symptoms improve equally well with dopaminergic therapy. For example, the resting tremor and postural disturbances are typically refractory or respond only partly to dopaminergic therapy. A contribution of non-dopaminergic lesions is supposed to underlie these dopa-resistant symptoms. We hypothesize that a noradrenergic deficit may partially underlie postural disturbances in PD. For this purpose, we review the literature on noradrenergic deficits and the locus coeruleus in PD, and discuss the potential role of this nucleus in postural disturbances in PD (Chapter 2).

ASSESSMENT OF PATIENTS AT RISK OF FALLING

History taking

History taking is the first vital element in assessing fall risk and to screen for the presence of balance disorders. Asking about prior falls is crucial, as these are associated with an increased fall risk in the future in elderly populations.[12,13,14,15] However, recall bias because of cognitive impairment may lead to underreporting of the number of falls.[16,17] It is therefore crucial to interview caregivers to fully elucidate balance problems and to obtain an adequate fall history. Prospectively studying the frequency of falls would avoid such recall problems, and is therefore likely more accurate. For this purpose, falls need to be evaluated on a regular and frequent basis, ideally using a combination of standardized retrospective surveys and prospectively documented falls questionnaires to identify the actual fall circumstances. This method was applied in Chapter 3 and Chapter 4.

Another important element of the assessment is to search for any fear of falling (or its counterpart, balance confidence). Fear of falling may even be present in patients without a history of falls[18], and should always be a part of history taking. In this thesis, we have

studied to what extent fear of falling is associated with falls, and how this may affect the patient's quality of life (Chapter 3 and Chapter 5).

Physical examination

Physical examination should include a generic examination (e.g. blood pressure) and a complete neurological examination. For both PD and HD, specific rating scales have been developed. The Unified Parkinson's Disease Rating Scale (UPDRS) and the Unified Huntington's Disease Rating Scale (UHDRS) include severity ratings of disease-specific symptoms, such as rigidity and tremor for PD, or chorea and dystonia for HD.[19,20] These scales are subdivided into different sections and include not only motor aspects, but also cognitive, behavioral, and functional aspects. Both motor scales include gait and balance evaluations, of which the retropulsion test is probably known best, but this is also the most debated balance test.[21,22,23] The retropulsion test is controversial, because it is difficult to execute and evaluate in a standardized manner. Both the test performance and the rating of the test result are hindered by intrarater and interrater differences.

Therefore, one of the study questions in this thesis was to evaluate the reliability of the retropulsion test in identifying fallers, and its ability to predict future fallers (as documented during prospective follow-up). Furthermore, we wanted to know whether other tests would be more reliable. Several other balance tests have been developed, and we included the most widely used tests in our evaluation (Chapter 3,4 and 5).

Elderly persons commonly encounter difficulties when they have to perform two tasks at the same time (multi-tasking). The 'Stops walking when talking'-test was introduced as a simple test to screen for such difficulties with multitasking.[24] This test examines the ability of subjects to walk and talk at the same time. Difficulty to perform the test adequately turned out to be a good predictor of future falls in the elderly population, at least when patients had some cognitive decline. Specifically, persons who stopped walking as soon as they started a routine conversation were at substantial risk for developing future falls.[23] This is an easy test that can readily be executed in the outpatient clinic, in fact, it can already be carried out when walking the patient to the examination room. We expected this test to have extra good predictive value for patients with PD, because these patients are known to have difficulties performing multiple motor tasks simultaneously or sequentially due to basal ganglia dysfunction.[25] We therefore studied this 'Stops walking when talking'-test in patients with PD, and analyzed its ability to predict future falls in this population (Chapter 6). Dual tasking itself was an important item of the fall questionnaires, and we hypothesized that this would be a difficult task for both PD and HD patients, and also that dual task impairment would be related to an increased fall risk (Chapter 3 and 4).

Quantative measurements

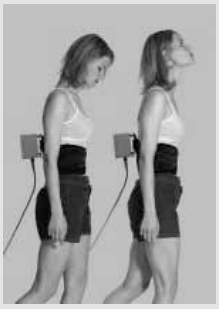
The clinical rating scales described above are all hampered by their subjective nature. Therefore, there is considerable interest in the development of quantitative measurements of gait and balance, hoping that these might offer a more objective perspective on the risk of falls in daily life. Such quantitative studies should investigate both the 'static' and 'dynamic' components of balance. An example of static balance assessment is static posturography, where subjects are quietly standing on a pressure sensitive (but steady) forceplate, which can record spontaneous changes in body sway.[25] An example of dynamic balance assessment is dynamic posturography, where the balance of subjects is actively challenged using either self-inflicted balance perturbations (for example, lifting a weight) or externally induced balance perturbations (for example, the sudden movement after supporting platform upon which subjects are standing).[26] In both cases, the outcome can be objectively recorded using a combination of full body kinematics, surface reactive forces under the feet or surface electromyography. Both techniques have been used quite extensively to evaluate the nature of balance disorders in both PD and HD[21,27,28,29,30,31], although it has thus far proved difficult to correlate these qualitative findings to the problems experienced by patients in daily life.

Next to these qualitative balance studies, several methods have been developed to analyze gait in more detail. This includes comprehensive laboratory-based approaches, where subjects are instructed to walk on a motorized treadmill, and where gait details can be studied in detail using full body kinematics, surface reactive forces under the feet or surface electromyography. Examples of outcome measures include qualitative documentation of step length, step time, walking velocity or the width of the base of support. A specific new development is the use of body-worn accelerometers, that can be used to quantify gait in freely moving subjects.[32,33,34,35] In this thesis, we have used this technique in combination with a pressure sensitive walkway to objective measure several basic gait and balance parameters in freely moving patients with HD (box 1.3) (Chapter 4). Specifically, we wanted to explore the relationship between the documented gait characteristics and the risk of falls in daily life. We expected that studying any differences in gait parameters between fallers (persons who experienced two or more falls in the past year) and non-fallers could identify gait disturbances that were associated with an increased fall risk in HD (Chapter 4).

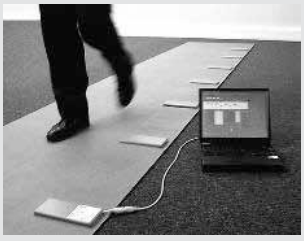
Box 1.3

Accelerometry and electronic walkway.

Assessment of balance control during dynamic tasks can be performed with angular velocity transducers worn on the trunk (Swaystar system, Balance Int. Innovations GmbH, Switzerland).[48] These sensors can measure angular deviations from the centre of mass (COM) in the pitch (anterior-posterior) and roll (lateral) plane during walking without interfering with natural body movements.



Gait disturbances can be quantified using an electronic pressure sensitive walkway that records each footfall as a function of time (GAITRite, CIR Systems, Inc.:Havertown, PA). Outcome measures are spatial and temporal gait parameters such as step length, step time, walking velocity or the base of support. The GAITRite has shown a high validity and reliability in analyzing gait in HD.[49,50]



QUALITY OF LIFE

Do recurrent falls affect the quality of life of patients with movement disorders? In various earlier studies, falls were associated with a lower quality of life in patients with PD.[36,37,38] It is difficult to differentiate between the impact of falls themselves, versus the various factors that are associated with recurrent falls. Disease progression, fear of future falls, injuries or immobilization may all play a role in reducing the patient's quality of life. Therefore, we evaluated the quality of life in PD patients in relation to previous falls and other fall-related factors (Chapter 5).

PREVENTION OF FALLS

The consequences of falls can be devastating for patients with movement disorders. It is therefore crucial to prevent falls in this vulnerable population. As the pathophysiology of falls is multifactorial, any therapeutic approach should include an integrated intervention program aimed at all of the different factors that play a role. A first crucial step is to map all of the intrinsic and extrinsic risk factors that might contribute to the risk of falls for each individual patient. Both generic and disease-specific risk factors should be identified. Only then is it possible to develop an individually tailored prevention program that aims to prevent future falls, and to reduce the risk of the associated complications (such as fall-related injuries, or a secondary fear of falling). The other important goals of such intervention programs should be the preservation of mobility and independence. There is currently no program that describes the development of an individually tailored intervention. We have therefore reviewed all potential risk factors in PD (both generic and disease-specific; and both 'extrinsic' and 'intrinsic'), and propose a multifactorial intervention program to prevent future falls in this population (Chapter 7).

SPECIFIC AIMS OF THE THESIS

This thesis describes the impact of balance disturbances on patients with either PD or HD, and aims to provide better insight into the assessment of risk factors of falls in these two patient groups, as a basis for falls prevention and improvement of the quality of life. The main goals of this study were as follows:

1. To review the neuropathological changes underlying falls in PD, with specific emphasis on the possible role played by the locus coeruleus and the associated changes in noradrenergic neurotransmission (Chapter 2).
2. To prospectively study the epidemiology of falls in PD and HD (Chapter 3 and 4).
3. To gain better insight into the pathophysiology of falls in PD and HD, and to assess potential risk factors of falls (Chapter 3,4 and 6)
4. To evaluate the impact of falls on the quality of life for patients with PD (Chapter 5).
5. To develop a multifaceted prevention program to reduce falls in PD (Chapter 7).

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Chapter 2

Postural instability in Parkinson's disease: the adrenergic hypothesis and the locus coeruleus

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ABSTRACT

Parkinson's disease (PD) is traditionally viewed as a mainly hypodopaminergic syndrome, with symptoms resulting predominantly from loss of dopamine-producing neurons in the substantia nigra. However, while most of the cardinal motor features of PD respond well to dopaminergic therapy, many other features of the disease do not. Balance impairment and the associated risk of falling represent one of the most prominent and potentially disabling features that are typically refractory to dopaminergic treatment. Therefore, it is possible that lesions in non-dopaminergic systems contribute to the pathophysiology of postural instability in PD. Such non-dopaminergic lesions are well recognized, certainly in advanced stages of PD where postural instability and falls dominate the clinical presentation. However, it remains unclear which of the identified non-dopaminergic lesions is specifically responsible for postural instability and balance impairment. In this review, we argue that cell loss in the locus coeruleus and a resultant central norepinephrine deficit are intimately involved in the pathophysiology of postural instability in PD. If proven to be correct, this link between defective noradrenergic neurotransmission and postural instability could have important implications for the future development of new symptomatic treatments aimed to correct postural instability and preventing falls. Studies in the next 5 years could test this hypothesis, using a battery of complementary research techniques, including advanced neuroimaging (structural, functional imaging and nuclear), neurochemical studies of cerebrospinal fluid, post-mortem clinicopathological analyses, and detailed clinical balance evaluations supplemented by posturography studies.

INTRODUCTION

Idiopathic Parkinson's disease (PD) is traditionally said to be characterized by a varying combination of at least two of the following core features: bradykinesia, tremor, rigidity and postural instability, although there is increasing evidence that these features are just a part of a much broader clinical complex.[1] Postural disturbances represent one of the most disabling features of the disease. They are typically a late manifestation of PD[2] and include the distinctive stooped posture, the shuffling gait disorder and progressive balance impairment. Postural instability leads to frequent falls, often with devastating consequences, such as fractures or long-term hospitalization.[3]

The pathophysiology of postural instability in PD remains insufficiently understood, but is likely complex and multifactorial. It is good to realize that what patients and clinicians perceive as "a poor balance" actually encompasses a fairly broad range of pathophysiological processes, and this makes it difficult to easily correlate any given factor to "balance impairment". Indeed, it is now broadly accepted that deficiencies in many of the afferent and efferent postural systems that normally contribute to balance control[4] can contribute to the complex pathophysiology underlying postural instability in PD.[5] Examples include inadequately organized automatic postural reactions, poor anticipatory postural responses, a slowing of compensatory stepping reactions, inappropriately directed protective arm movements, and a defective somatosensory integration of afferent sensory information. The net result is that patients frequently fall (or nearly so), which is defined as inadvertently landing on any lower surface (the definition usually also states that this should not be caused by an overwhelming external force).

Clinically based studies have underscored the magnitude of the problem and the impact on quality of life, but to date have failed to provide good pathophysiological insights, mainly because bedside balance tests are relative crude and subjective techniques.[5] For example, the widely used retropulsion test of the UPDRS (Unified Parkinson's Disease Rating Scale) provides only a gross measure of overall balance disturbances in PD, but is not designed to unravel the complex underlying pathophysiology. This situation has improved with the advent of posturography, which is an umbrella term for a variety of techniques that entail an objective electrophysiological assessment of human balance. In this review, we will refer to papers that used either static or dynamic posturography.[6] S*tatic* posturography refers to all those techniques that measure quiet standing, with or without an instrumented fixed support surface, and without any physical body perturbation. By contrast, *dynamic* posturography techniques employ physical perturbations of stance, using either an unstable or motorized support surface, or an external force applied to one or more body parts.[7] Technological advances such as these have allowed this field to progress at a relatively rapid pace, helping to clarify fundamental disturbances at

the neurophysiological level when PD patients begin to fall. Thus, researchers using this approach have identified various factors that can each contribute to postural instability, including impairment of automatic postural responses (both reactive and anticipatory), bradykinesia of corrective stepping movements, abnormally directed protective arm movements, and axial stiffness.[8,9,10] These improved neurophysiological insights now need to be backed up by a clear understanding of the underlying neurochemical and neuropathological changes. However, this is where much work remains to be done.

PD: A HYPODOPAMINERGIC SYNDROME?

The cardinal symptoms of PD are generally conceived as the clinical offprint of a central dopamine loss, for several reasons. First, progressive destruction of dopaminergic neurons in the substantia nigra pars compacta is a neuropathological hallmark of PD. Second, both neurochemical analyses of the cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging of the nigrostriatal pathway indicate that nigral cell loss leads to decreased levels of dopamine and its metabolites in the central nervous system (CNS).[11,12] Interestingly, nigral cell loss – as documented with fluorodopa PET scans – shows and excellent correlation with bradykinesia, but much less so with postural instability.[13] Third, symptomatic treatment of PD with dopaminergic drugs (especially levodopa) generally leads to marked alleviation of most cardinal symptoms. Bradykinesia and rigidity usually respond best, particularly in early stages of the disease. (Note that tremor responds less well to dopaminergic treatment, and PET studies have in fact associated tremor with serotonergic lesions[14]). Finally, fairly selective nigrostriatal neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can induce a hypokinetic-rigid syndrome in both humans and animals which shares many clinical, neuropathological and biochemical features of idiopathic PD, including prominent postural instability.[15,16,17,18] Treatment with levodopa also markedly alleviates the symptoms of MPTP-induced parkinsonism.[19] Taken together, these different lines of evidence imply that PD is largely a hypodopaminergic syndrome.

POSTURAL INSTABILITY AND DOPAMINERGIC DEFICITS IN PD

There is reason to believe that not all clinical manifestations of PD result solely from dopamine loss in the nigrostriatal pathway. While this is particularly true of the nonmotor features of this disease, it also applies to some of the motor features, including including balance impairment and freezing of gait – although other signs (such as rigidity or bradykinesia) do continue to improve with dopaminergic treatment within the same patients[20,21] (figure 1). Indeed, once present, postural instability is notoriously refractory

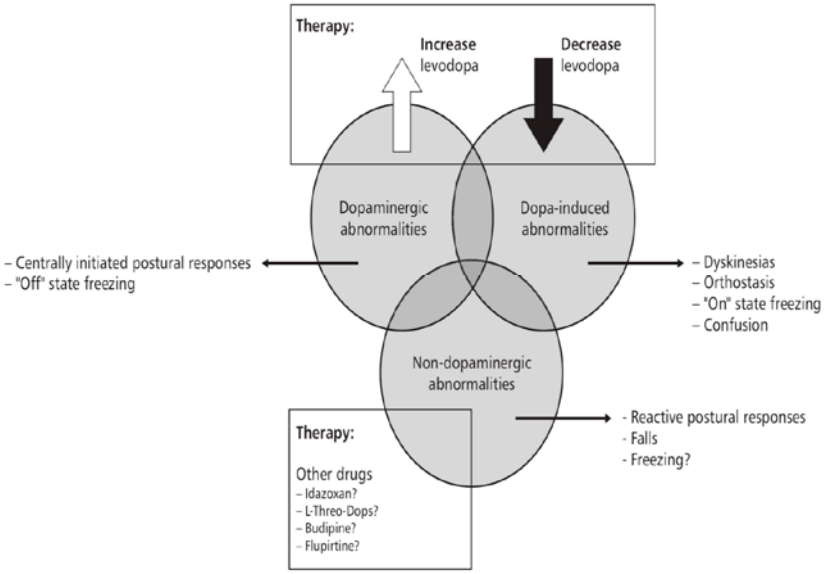

Fig 1 Dopaminergic, nondopaminergic and dopa-induced features in Parkinson's disease, with suggestions for corresponding treatment strategies.
DOPS: Dihydroxyphenylserine
Redrawn with permission from [117] ©John Wiley & Sons.

to treatment with dopaminergic drugs.[20,21,22,23,24] Balance problems are sometimes even aggravated by the adverse effects of dopaminergic drugs, such as dyskinesias (which can be sufficiently violent to throw patients off balance), orthostatic hypotension or confusion.[25]

Studies using dynamic posturography have therefore taken these clinical observations one step further, trying to unravel the contribution of dopaminergic and non-dopaminergic lesions using two different approaches. First, postural responses can be assessed in patients with presumably selective hypodopaminergic syndromes and in patients with PD (where lesions are known to extend beyond the substantia nigra). Responses that are abnormal in both groups might be influenced by supraspinal dopaminergic control (because dopamine loss occurs in both conditions), whereas responses that are merely abnormal in PD could be under non-dopaminergic influence. Following this line of reasoning, automatic postural responses have been assessed in patients with what are presumed to be relatively pure hypodopaminergic syndromes such as neuroleptic-induced parkinsonism[26], MPTP-induced parkinsonism[9] and young-onset PD.[9] Some postural abnormalities that are commonly present in patients with late-onset PD[8,27,28] were found to be absent in these hypodopaminergic syndromes, suggesting that non-dopaminergic lesions probably contributed to their development in PD. However, other

postural abnormalities were present in patients with a selective dopamine deficiency as well as typical late-onset PD, raising the interesting proposition that balance impairment in PD might be related to a combination of both dopaminergic and non-dopaminergic abnormalities. We should note that MPTP-induced parkinsonism is not a perfect model for idiopathic PD, because the onset is subacute and the syndrome does not have the same inevitable process of progressive neurodegeneration. A limitation to studying neuroleptic induced parkinsonism is that postural deficits are often only mild, so this syndrome may not fully reflect the severity of balance impairment in PD.

A second approach to assessing postural responses in patients with PD involves examining patients both before and after administration of dopaminergic drugs.[23,24] Using this approach, some postural abnormalities (for example, the defective voluntary postural corrections) have been found to be responsive to dopaminergic medication, whereas other abnormalities (including the overall instability during dynamic posturography testing, as measured by excursions of the center of mass following a sudden platform movement) persist despite antiparkinson treatment. These observations confirm the results obtained in patients with hypodopaminergic syndromes described and, again, a concept emerged of postural instability as a combined dopaminergic and hypodopaminergic syndrome.

NON-DOPAMINERGIC LESIONS IN PD

It appears that postural instability and other poorly dopa-responsive symptoms are likely to be the clinical results of 'extra-nigral' or 'non-dopaminergic' lesions. Post-mortem studies have clearly identified the presence and extent of these non-dopaminergic lesions, and also shown that these typically develop in elderly patients with long-lasting PD. Affected neurotransmitters include, among others, noradrenaline, serotonin and acetylcholine. For example, cell loss in the noradrenergic locus coeruleus, the cholinergic basal nucleus of Meynert and the mixed cholinergic-glutaminergic pedunculopontine nucleus (PPN) has been demonstrated.[29,30] The latter has recently been studied as a new target for stereotactic surgery, aimed specifically to improve walking and freezing of gait in PD.[31,32,33] Animal studies have shown that the PPN is normally responsible for gait initiation and stepping maintenance, and a recent paper reported a patient with freezing after a bilateral infarction of the PPN, thus suggesting a clinical correlation in humans.[34,35]

POSTURAL INSTABILITY AND THE LOCUS COERULEUS

In the remainder of this review, we propose the hypothesis that postural disturbances in PD are closely related to cell loss in one specific non-dopaminergic nucleus, namely the locus coeruleus and the resultant norepinephrine deficit in the CNS. We realize that evidence supporting a link between balance impairment in PD and the locus coeruleus is only indirect. However, to support our hypothesis, we will carefully address all circumstantial evidence, first by reviewing the normal functions of the locus coeruleus. We then discuss how and when the locus coeruleus is likely to become involved in the pathophysiology of PD, drawing mainly on neuropathological and neurochemical evidence. We conclude by summarizing the available data that therapeutic correction of the central norepinephrine deficit might reduce postural disturbances in neurodegenerative disorders, including PD.

ANATOMY OF THE LOCUS COERULEUS

The locus coeruleus is a small nucleus (the rostrocaudal extent approximates 16 mm) which is situated bilaterally in the pontine tegmentum. Its neurons are pigmented due to presence of neuromelanin in the cell bodies. In the CNS, the locus coeruleus is the main source of norepinephrine[36], an excitatory neurotransmitter which is metabolized mainly to 3-methoxy-4-hydroxy-phenyleneglycol (MHPG). The locus coeruleus also uses various neurotransmitters other than norepinephrine, and this includes among others glutamate, dopamine and GABA.[37] However, these other neurotransmitters and their corresponding pathways are thought to be less important for the functions of the locus coeruleus. In humans, the locus coeruleus has been mapped through immunocytochemical labeling of the biosynthetic enzymes tyrosine hydroxylase (TH) and dopamine-beta-hydroxylase[38,39], as well as by visualizing neuromelanin content.[38,40,41]

Despite its relatively small size, the locus coeruleus innervates widespread areas in the CNS, including the spinal cord, neocortex, hippocampus and cerebellum.[42,43] Retrograde tracer transport studies in rats have identified a topographic arrangement of these projections within the locus coeruleus. The more caudal and ventral part, which consist of densely packed small cells, contain neurons that project to the spinal cord and cerebellum. The more rostral and dorsal part, which are formed by large multipolar cells, project mainly to the neocortex.[42,44] A single neuron originating within the locus coeruleus may branch to widely divergent areas, for example with one fiber to the spinal cord and another to the neocortex.

NORMAL FUNCTIONS OF THE LOCUS COERULEUS

In accordance with these widespread projections, the locus coeruleus and its transmitter, norepinephrine, have rather diverse functions, including the regulation of autonomic responses, cognition and motor control. Interestingly, most functions could be important for normal balance control. First, studies of cats with acute spinal cord lesions suggest that noradrenergic systems are are involved in gait initiation.[45,46] As this may involve the coeruleo-spinal noradrenergic pathway this raises the interesting question whether dysfunction of the locus coeruleus could underlie, at least in part, the freezing of gait phenomenon that, in turn, is one of the leading causes of falls in PD.[47] Second, studies in rats, cats and monkeys found evidence that the locus coeruleus is activated in situations demanding immediate attention and coping responses.[48,49,50] Although the link is only very indirect, this function of the locus coeruleus could be relevant for balance control, because immediate handling of unexpected postural perturbations is of vital importance to prevent falls. The locus coeruleus is known to have various firing patterns: tonic activity is positively correlated with the arousal state, while phasic activity is aroused by sensory stimuli.[48,51] In this respect, one might speculate that the phasic patterns of the locus coeruleus are more task-oriented and related to immediate action, whereas the tonic firing patterns would reflect a more continuous exploration of the environment and thereby help regulate postural control. Third, involvement of the locus coeruleus in autonomic regulation could also be relevant for balance control, because dysfunction could lead to orthostatic hypotension and thereby cause falls. Syncopal falls in PD appear to be relatively rare (perhaps because of inadequate ascertainment), but do occur in more advanced states of PD.[52] Fourth, the coeruleospinal pathway appears to contribute to gain control of vestibulospinal limb reflexes.[53,54,55] For example, work in decerebrate cats subjected to passive neck rotation has shown that activation of coeruleo subcoeruleospinal neurons is opposite to that of the lateral vestibulospinal neurons projecting to the same segments of the spinal cord.[56] Together, this functional coupling could assist in regulating the excitability of limb extensor motoneurons to neck stimulation. A link to human balance may be placed because gain control of vestibulospinal responses is important for regulating upright stance in healthy subjects, particularly when the head is being displaced.[57] Although direct evidence is lacking, it is possible that the influence of coeruleospinal pathways on excitability of limb extensor motoneurons may also affect other automatic balance responses in the legs that are involved in regulation of upright stance in response to externally imposed postural perturbations.[58,59] Gain control of these automatic balance reactions is severely impaired in PD[8,27,60], possibly due to loss of descending coeruleospinal influence.[9] The controlling action of the locus coeruleus on the cerebellum may also be relevant in this respect, because cerebellar output is required to optimally tune postural reflexes.[7,61,62] Finally, given its widespread projections, the locus coeruleus may play a coordinating role in linking different brain functions. As balance

control requires a linkage between many different brain areas and separate functional systems, including both motor and cognitive functions[63], the locus coeruleus could be adequate positioned to serve as "coordinator". Again, dysfunction would lead to postural instability.

THE LOCUS COERULEUS IN PD (AND OTHER NEURODEGENERATIVE DISORDERS)

Neuropathological studies

Post-mortem brain studies of PD patients have identified substantial cell loss in the locus coeruleus, particularly in its caudal part.[64,65] As this caudal part projects mainly to the spinal cord and cerebellum, it could well be related to balance impairment in PD. This cell loss in PD is likely superimposed upon the normal age-related decline of locus coeruleus cell volume, which relatively spares the caudal part of the locus coeruleus.[30,39] If the locus coeruleus is indeed involved in postural control, the combination of these two processes could explain why postural disturbances are a late manifestation of PD. To support this latter contention, it would be interesting to investigate whether cell loss in the locus coeruleus occurs mainly in advanced PD. Unfortunately, most post-mortem studies did not specifically investigate the influence of duration or severity of the disease. Two studies found no relation between disease duration and total cell loss within the locus coeruleus.[66,67] However, total cell loss is possibly a poor parameter because, as stated earlier, cell loss in PD occurs especially in the caudal part of the locus coeruleus. According to the Braak staging of neuropathology of PD, lesions in the caudal brainstem precede pathology in the mesencephalon.[68] This would argue against a role in producing postural instability, as this is typically a late feature of PD. In fact, this raises the interesting question whether an isolated lesion in the locus coeruleus would suffice to produce postural abnormalities or balance impairment, even in the absence of a concurrent lesion in the substantia nigra. Answering this question would require selective lesioning studies in primates (which is technically possible), followed by careful control of changes in posture and balance, but this has thus far never been done. Finally, it is worth noting that accelerated cell loss in the locus coeruleus also occurs in other neurodegenerative diseases. A disease that bears particular mention in this regard is progressive nuclear palsy (PSP) where early, severe postural instability and high fall rates are a prominent feature.[69] Cell loss in the locus coeruleus of PSP has been reported, but the extent to which cell loss occurs is controversial,and cell counts have not been directly studied in relation to postural instability in these patients.[70]

Neurochemical studies

Consistent with the reported cell loss in the locus coeruleus of PD patients, most CSF analyses and post-mortem studies have shown reduced levels of norepinephrine.[71,72,73,74,75,76] However, a few studies did not find such a reduction, perhaps because of differences in patient material or the techniques that were used.[77,78] Unlike norepinephrine itself, CSF levels of its main metabolite MHPG are not significantly reduced.[12,36,74] However, MHPG does not reflect adrenergic activity accurately because, unlike norepinephrine, MHPG is rapidly exchanged across the blood-brain barrier (BBB).

The post-mortem brain studies rarely reported a clinical correlate of the observed pathological changes. The possible clinical relevance was addressed in several CSF studies, but postural disturbances were only mentioned rarely. However, one study reported a significant correlation between the reduced concentration of norepinephrine and the severity of clinically rated gait and postural disturbances in PD.[72] In another study, levels of norepinephrine were significantly reduced in PD patients with a frozen gait, again linking the locus coeruleus to falling via freezing of gait.[71]

Neuroimaging studies

Nuclear imaging techniques using position emission tomography (PET) or single photon emission computed tomography (SPECT) can assess various neurotransmitter functions. There is increasing attention for specific markers of non-dopaminergic functions, including the noradrenergic system.[79] A PET study that examined the uptake of ^{11}C-RTI 32 (a combined marker for noradrenaline and dopamine transporter binding) showed a lower uptake in the locus coeruleus of depressed patients with PD[80], suggesting an influence of noradrenergic function on mood. Balance was not assessed in this study. Based on the hypothesis put forth in the article, we would argue that attempts to explore the role of noradrenergic dysfunction in PD by developing imaging techniques that could assess the integrity of the locus coeruleus are both needed and fully warranted.

CORRECTION OF THE CENTRAL NOREPINEPHRINE DEFICIT

Another way to demonstrate a role for the locus coeruleus on balance control is to explore the therapeutic effects of pharmacologically replenishing the central norepinephrine deficiency. Noradrenergic drugs have mainly been tested because of their potential to suppress levodopa-induced dyskinesias.[81] However, several investigators have used noradrenergic drugs with the specific aim of improving gait or balance (Table 1).

Table 1 Therapeutic studies examining the effect of nordrenergic compounds on postural disturbances and gait.

Treatment regimen	Patients	Controls	Outcome	CSF	Reference
L-threo-DOPS					
600-900 mg/day 6 weeks	202 PD 24 pure akinesia	Yes, double blind	Retropulsion improved, freezing tended to improve	Not assessed	97
100-900 mg/day Unknown treatment period	6 PD	No	Freezing improved in 3 out of 6 patients	NE concentrations increased (dose related)	94
100-900 mg/day Unknown treatment period	13 PD	No	Freezing improved in 7 out of 13 patients	NE concentrations increased (dose related)	95
D(L)-threo-DOPS					
200-2400 mg single dose	6 PD	Placebo-controlled, crossover	No benefit in freezing	Not assessed	96
750 mg -max? 10 days	4 PD	No	Freezing mildly improved in 3 out of 4 patients	No change in DA, noradrenergic metabolites	88
Idazoxan					
1-40 mg 4 weeks	8 PSP	Placebo-crossover, double blind	Postural stability and gait improved (UPDRS items)		104
Methylphenidate					
20 mg single dose	21 older adults	No, open	Gait speed, timed up and go and stride time variability improved	Not assessed	109
10 mg single dose	5 PD	No, open	Freezing improved	Not assessed	110
1 mg/kg/day 3 months	17 PD, with STN-stimulation	Not controlled, videos blindly assessed	Freezing improved	Not assessed	111
1.2 mg/kg/day 2 weeks	12 PD	Placebo-crossover, double blind	No significant effects on walking time	Not assessed	112

Only studies with sufficient information (e.g. concerning trial design and dose of medication) are included in this table.
CSF: Cerebrospinal fluid; DA: Dopamine; DOPS: Dihydroxyphenylserine; NE: Norepinephrine; PD: Parkinson's disease; PSP: Progressive nuclear palsy; STN: Subthalamic nucleus;UPDRS: Unified Parkinson's disease rating scale.

Dihydroxyphenylserine

There are several possibilities to correct the central norepinephrine deficit. Thus far, the compound dihydroxyphenylserine (DOPS), a synthetic precursor of norepinephrine, has been studied most extensively. DOPS has four different stereoisomers that are termed

L-threo-, D-threo-, L-erythro and D-erythro-DOPS. The L-isomer is converted directly to natural (-)-norepinephrine by aromatic L-amino acid decarboxylase. By contrast, D-threo-DOPS inhibits the decarboxylation of L-threo-DOPS in vitro[82] and is therefore theoretically unsuitable for restoring norepinephrine levels. Nonetheless, both L-threo-DOPS and racemic mixtures of both D- and L-threo-DOPS have been used in therapeutic trials.

(D) L-threo-DOPS can restore depleted norepinephrine levels in plasma of both rats[83] and humans, including patients with postprandial hypotension[84], DßH deficiency[85], multiple system atrophy[86] or PD[87]. (D) L-threo-DOPS can pass across the BBB of PD patients.[88,89,90] However, there is disagreement as to whether (D) L-threo-DOPS can actually increase norepinephrine concentrations in the CSF. Several investigators could not detect an increase in norepinephrine or its metabolites in the CSF after administration of L-threo- or (D) L-threo-DOPS to rats[91,92] and patients with PD.[89,90] Conversely, others have found increased MHPG-levels in the brains of mice after administration of L-threo-DOPS.[93,94] Significantly, Tohgi and colleagues found a dose-dependent increase in norepinephrine concentrations in the CSF after long-term administration of L-threo-DOPS to patients with PD.[95,96]

Several investigators have studied the influence of L-threo-DOPS on various 'non-dopaminergic' manifestations of PD, including freezing, gait impairment, retropulsion and postural disturbances. Quinn et al. found no improvement of freezing of gait in a single-dose, placebo-controlled study of (D) L-threo-DOPS in six PD patients.[97] Narabayashi et al. studied the effect of oral L-threo-DOPS in a prospective, double blind and placebo-controlled study of 226 patients with longstanding PD (Hoehn and Yahr stages 3 and 4) and related disorders.[98] After six weeks of treatment, gait, retropulsion and festination had improved according to the clinical impression of a neurologist. Unfortunately this study did not ascertain balance changes with objective assessments as dynamic posturography. Another study reported that administration of (D) L-threo-DOPS during 10 days improved clinically rated gait impairment in a small group of four patients with longstanding PD in an open uncontrolled study.[89] Tohgi et al. noted a moderate to marked improvement of freezing in three out of six PD patients (Hoehn and Yahr stage 3 and 4) treated with L-threo-DOPS.[71] In a later extended study, freezing improved significantly in 7 out of 13 patients, but again this was not a controlled study.[96] Freezing was assessed in four grades while watching the patient walk 10 meters up and down; an improvement by more than one grade was considered significant. Other Japanese investigators reported improvement of postural control and freezing of gait by L-threo-DOPS in Parkinson patients, but these were open trials and details on the outcome parameters of these studies are difficult to obtain.[99,100]

(D) L-threo-DOPS has also been tested in patients with other neurodegenerative disorders. For example, (D) L-threo-DOPS can reduce orthostatic hypotension in patients with severe autonomic failure[101], and such effects could also be relevant for patients with PD suffering from syncopal falls. Its effect on orthostatic hypotension has never been compared directly with other anti-orthostatic measures. Autonomic failure is particularly problematic in patients with multiple system atrophy (MSA), and one study found an increased upright blood pressure after administration of L-threo-DOPS to four patients with MSA.[86] In a single blind placebo-controlled study of two patients with DßH deficiency, stance ability was prolonged after DL-threo-DOPS administration.[85] Interestingly, (D) L-threo-DOPS may also ameliorate orthostatic hypotension in PD patients. One preliminary report mentioned a significant increase in standing blood pressure in PD patients.[102] In addition, subjective complaints of orthostatic hypotension disappeared in seven out of twelve patients.

One caveat to using L-threo-DOPS needs to be mentioned. While it may elevate norepinephrine levels, (D) L-threo-DOPS may adversely affect dopamine levels. Thus, cerebral dopamine levels were significantly decreased in rats after administration of L-threo-DOPS.[103] It is unclear whether norepinephrine levels were actually increased. Similar mechanisms may exist in humans, as the raised dopamine plasma concentration of a patient with DßH deficiency was reduced during treatment with DL-threo-DOPS.[104] By contrast, norepinephrine concentration in plasma was raised and the patient was free of orthostatic symptoms. However, in another study, dopamine concentrations in the CSF did not change in patients treated with levodopa prior to L-threo-DOPS administration.[71,96] In fact, dopamine levels actually increased in patients who received only L-threo-DOPS. Therefore, the precise effects of L-threo-DOPS on dopamine metabolism remain unresolved. However, the potential inhibition of dopamine by L-threo-DOPS could obviously limit its use in the treatment of PD and could partially explain the thus far disappointing results with this compound.

Idazoxan

Another pharmacological strategy aimed at restoring central norepinephrine deficit is to use the selective alpha-2 adrenoreceptor inhibitor idazoxan. Activation of the presynaptic alpha-2 receptor decreases norepinephrine transmission in the locus coeruleus. Hence, inhibition of this receptor with compounds such as idazoxan should boost norepinephrine neurotransmission. The first relevant experiment with idazoxan involved a double-blind crossover study of nine patients with PSP. Treatment over 4 weeks resulted in significant improvement in the ability to rise from a chair, as well as in gait and postural instability.[105] This improvement was scored by a physician according to, among others, the UPDRS and global assessment by patients on a 4-point scale. Thus far, idazoxan has not been tested in PD with a specific focus on assessing gait and postural instability. A

drawback could be the dose-dependent side-effects, such as hypertension and headache. A study on the effects of idazoxan on levodopa-induced dyskinesias showed a drop-out rate of 50% at a dose of 60 mg/day.[106] Moreover, a large phase III trial that aimed to examine the effects of idazoxan on levodopa-induced dyskinesias was terminated early for unpublished reasons[107], but perhaps this was owing to tolerability problems.

Methylphenidate

Methylphenidate, a drug traditionally used to combat attention-deficit/hyperactivity disorder, has predominantly dopaminergic effects through blocking presynaptic dopamine re-uptake. However, it may also improve noradrenergic neurotransmission by presynaptic inhibition of the norepinephrine transporter.[108] Recent work has shown that methylphenidate can decrease fall risks in community dwelling older adults, either by increasing the availability of central dopamine and norepinephrine or by improving attention.[109] Three further trials have shown that methylphenidate can also improve gait and freezing in patients with PD.[110,111,112] However, another double-blind, randomized placebo-controlled cross-over study in 13 PD patients failed to demonstrate a clinically relevant effect on walking speed[113], but these are very small numbers. Furthermore, postural stability was not specifically tested in any of these studies, so the jury is still undecided with respect to methylphenidate.

COULD OTHER NON-DOPAMINERGIC NEUROTRANSMITTERS BE INVOLVED?

Of course there the possibility remains that loss of other non-dopaminergic neurotransmitters also play a role in the pathophysiology of postural disturbances in PD. Biochemical analyses of CSF and post-mortem neuropathological studies of PD brains have identified various other 'non-dopaminergic' lesions, besides the lesion in the locus coeruleus. We previously mentioned the mixed cholinergic-glutaminergic PPN and its presumed role in gait disturbances. Other examples include serotonin and choline acetyltransferase, whose levels are also reduced in patients with PD.[30,114,115] Serotonin is an interesting candidate player in the pathophysiology of postural instability in PD, because in one study, serotonin levels in the CSF were significantly lower in PD patients with severe postural instability and gait disorders, compared with a control group of PD patients with predominantly hyperkinetic symptoms.[115] However, a 4-week treatment with L-5-hydroxytryptophan, a biosynthetic precursor of serotonin, did not improve balance in a small group of six PD patients in an open label trial.[116] Therefore, at the current time there is no compelling evidence that correction of the serotonergic deficit would be likely to improve postural disturbances in PD. Acetylcholine is the second interesting candidate, mainly because cholinergic deficiencies seem responsible for at least some of the cognitive deficits in PD. This is relevant because gait and balance are now increasingly seen as

a' cognitive disorder', and it has been speculated that cholinesterase inhibitors should be tested as adjunctive treatment for gait and balance deficits in PD.[117] However, at the present time there is no compelling evidence to suggest that cholinesterase inhibitors lead to significant improvements of gait and balance. Once again, this leaves cell loss in the locus coeruleus as the prime suspect.

A COMBINATION OF DOPAMINERGIC AND NON-DOPAMINERGIC LESIONS?

Before concluding, we wish to reiterate that postural disturbances in PD are most likely related to the combined presence of both non-dopaminergic lesions – in particular a central norepinephrine depletion due to cell loss in the locus coeruleus – and a concurrent dopaminergic lesion. This view is supported by our severely affected patients with MPTP-induced parkinsonism, whose gait and balance were markedly compromised, yet they almost certainly had a selective nigrostriatal lesion and a severe hypodopaminergic syndrome.[15] Indeed, CSF studies in these patients confirmed the presence of a selective central dopamine deficiency, possibly even with a compensatory increase in norepinephrine turnover.[118] Gait and balance also improved considerably when these patients first received levodopa, and this is also common clinical experience in early stages of PD, a situation in which gait bradykinesia can improve with dopaminergic therapy. Freezing of gait is typically seen in the 'off' state[47], and most patients with freezing improve with dopaminergic therapy ('on' state freezing is a relatively rare phenomenon). Finally, although balance impairment is usually refractory to dopaminergic treatment, careful analyses using dynamic posturography have shown that some postural abnormalities can be at least partially dopa-responsive. Thus, static sway (in some reports[119], but not all[120]), voluntary weight shifts[121], some automatic postural responses[23], anticipatory postural adjustments[122], voluntary toe rises[123] and compensatory steps[124] improved to some extent in PD patients after levodopa administration, albeit typically not to normal levels. One might even speculate that some of the balance abnormalities in PD are only seemingly refractory to dopaminergic treatment, because by the time postural instability emerges, the central dopamine loss has become so severe that it can no longer be overcome by mounting doses of oral levodopa. Furthermore, in this stage of the disease, the cumbersome side effects of levodopa become an important dose-limiting factor. For practicing clinicians, it is therefore always worth trying to treat postural instability with a judicious trial of levodopa, certainly while we await the advent of efficacious non-dopaminergic drugs.

EXPERT COMMENTARY AND FIVE-YEAR REVIEW

In this review, we have argued for the hypothesis that postural disturbances in advanced PD may well be related to a combination of a severe central dopamine loss, plus a concurrent norepinephrine deficiency caused by cell loss in the locus coeruleus. This adrenergic hypothesis should now be tested directly in prospective, randomized and placebo-controlled trials, designed to investigate the influence of norepinephrine precursors on postural instability in PD. Ideally, such trials should be controlled and include appropriate (relevant and reliable) outcome measures. Evaluation of treatment effects should not just rely on clinically based measures of balance impairment (such as the retropulsion test), because clinical judgments are subjective and difficult to standardize.[5] Additional outcome measures should include a prospective assessment of fall rates during a sufficient time frame (at least six months), standardized balance and gait rating scales, and objective measures of postural instability using dynamic posturography. Quality of life, as a reflection of regained mobility and confidence, should also be an outcome measure. If successful, such studies would provide a much welcome therapeutic approach to a hitherto poorly treatable and incapacitating feature of PD, and one of the leading causes of disability as the disease progresses.

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Chapter 3

Epidemiology of falls in Parkinson's disease

Chapter 3.1

Prospective assessment of falls in Parkinson's disease

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ABSTRACT

We studied prospectively the epidemiology, clinical impact and prediction of falls in 59 moderately affected patients with Parkinson's disease (PD) (mean UPDRS motor score 31.5;mean age 61 years) and 55 controls (mean age 60 years).At baseline, balance and gait were evaluated extensively. The retropulsion test (response to sudden shoulder pull) was executed first unexpectedly and five more times following prior warning. All persons used standardised scoring forms to document their falls during six months.

Thirty patients (50.8%) and eight controls (14.5%) fell at least once (relative risk [RR] 6.1;95% confidence interval [CI] 2.5–15.1,$p < 0.001$).Recurrent (≥2) falls occurred in 15 patients (25.4%), but in only two controls (RR 9.0;95% CI 2.0–41.7;p=0.001). Recurrent falls were more common among persons taking benzodiazepines (RR 5.0;95% CI 1.6–15.5;$p < 0.01$). Sixty-two percent of the falls in patients caused soft tissue injuries, but no fractures occurred. A fear of future falls was common (45.8% of patients) and was accompanied by restriction of daily activities (44.1% of patients). Seventy percent of falls reported by patients were 'intrinsic' (due to patient-related factors), but falls in controls were mainly (50%) 'extrinsic' (due to environmental factors). None of the baseline posture and gait variables predicted falls adequately. The first 'unexpected'retropulsion test was more often abnormal than all subsequent (predictable) tests. Irrespective of its method of execution, the retropulsion test did not predict falls. A combination of asking for prior falls, disease severity and the Romberg test yielded the best overall diaginostc utility (sensitivity 65% and specificity 98%). Recurrent fallers were best predicted by disease severity (RR for Hoehn and Yahr stage 3 was > 100; 95% CI 3.1–585) and asking for prior falls (RR 5.0; 95% CI 1.2–20.9). We conclude that falls are common and disabling, even in relatively early stage PD. Recurrent fallers were best predicted by disease severity and presence of prior falls. Strategies to prevent falls in PD should particularly focus at intrinsic (patient-related) factors, such as minimising the use of benzodiazepines.

INTRODUCTION

Postural instability and falls are among the most incapacitating features of Parkinson's disease (PD).[1,24] The epidemiology of falls in PD remains largely unknown. Furthermore, prediction of falls is difficult. Because history taking is often unreliable[17], clinicians depend upon clinical tests to estimate falling risks. The 'retropulsion test' (also termed 'sternum push' or 'pull test') is commonly used to probe postural instability[26,34], but this test can be criticised for several reasons.[4]

We therefore prospectively investigated falls in PD. Our goal was to clarify the epidemiology, circumstances and clinical impact of falls. We also examined what clinical test (including the retropulsion test) could predict falls in daily life. A more detailed account of the fall circumstances has been presented elsewhere.[44]

METHODS

Subjects

We studied 59 patients with idiopathic PD and 55 age-matched controls (Table 1). Subjects were eligible subjects if they were ambulant community residents (with or without walking aids) and able to follow simple instructions (Mini Mental State Examination [MMSE] ≥ 24). We included only patients who fullfilled the criteria for idiopathic PD as defined by the brain bank of the United Kingdom Parkinson's Disease Society[21] and who sustained a clear and lasting beneficial response to chronic treatment with levodopa and/or a dopamine agonist (see below for details of medication).[14] Exclusion criteria were any other neurological dis-

Table 1. Baseline clinical characteristics. Data are displayed as mean ± standard deviation or as the number of persons, as well as the number of persons for which this information was available (percentage between parentheses).

	Patients (N = 59)	Controls (N = 55)	Significance
Demographics			
Age (years)	60.8 ± 9.7	59.6 ± 8.5	p = 0.51
Women	21/59 (35.6)	37/55 (67.3)	p = 0.001
Living with partner	48/59 (84.2)	50/55 (90.9)	p = 0.39
Stairs within the house	46/59 (78.0)	44/55 (80.0)	p = 0.82
(Partially) dependent for ADL	23/59 (39.0)	0/55 (0.0)	p < 0.001
Alcohol (units/day)	0.8 ± 1.0	1.3 ± 1.4	p = 0.03
Duration of disease (years)	7.1 ± 4.8	—	—
Age (years)	60.8 ± 9.7	59.6 ± 8.5	p = 0.51
Women	21/59 (35.6)	37/55 (67.3)	p = 0.001
Living with partner	48/59 (84.2)	50/55 (90.9)	p = 0.39

Table 1. (continued)

	Patients (N = 59)	Controls (N = 55)	Significance
Stairs within the house	46/59 (78.0)	44/55 (80.0)	p = 0.82
(Partially) dependent for ADL	23/59 (39.0)	0/55 (0.0)	p < 0.001
Fall questionnaire			
Number of prior falls (£ 6 months)	2.1 ± 5.4	0.3 ± 0.5	p = 0.16
Fallers (£ 6 months)	23/59 (39.0)	15/55 (27.3)	p = 0.23
Fear of falling	27/59 (45.8)	4/59 (7.4)	p < 0.001
Restriction of activities	26/59 (44.1)	6/54 (11.1)	p < 0.001
Problems with multiple tasks	31/54 (57.4)	3/48 (6.3)	p < 0.001
Walking aids	13/58 (22.4)	0/55 (0.0)	p < 0.001
Neurological examination			
Hoehn & Yahr stage	2.3 ± 0.7	—	—
UPDRS motor score	31.5 ± 11.0	0.8 ± 1.7	p < 0.001
UPDRS total score	48.3 ± 15.2	1.8 ± 2.1	p < 0.001
MMSE	28.1 ± 2.0	29.2 ± 1.2	p < 0.001
Gait and balance			
Tinetti balance score	3.9 ± 3.0	0.4 ± 0.7	p < 0.001
Tinetti gait score	2.7 ± 2.3	0.1 ± 0.3	p < 0.001
Tinetti total score	6.6 ± 4.8	0.4 ± 0.8	p < 0.001
Romberg test	3/58 (5.2%)	0/55 (0.0%)	p = 0.24
Orthostatic hypotension	7/35 (20.0%)	3/30 (10.0%)	p = 0.32
Tandem stance			
Eyes open	23/59 (39.0%)	2/55 (3.6%)	p < 0.001
Eyes closed	44/59 (74.6%)	23/55 (41.8%)	p = 0.001
Tandem gait	24/56 (42.9%)	5/54 (9.3%)	p < 0.001
Standing up	9/58 (15.5%)	1/55 (1.8%)	p = 0.02
Sitting down	19/53 (32.8%)	0/55 (0.0%)	p < 0.001
Turning around	36/58 (62.1%)	2/55 (3.6%)	p < 0.001
Reaching	1/39 (2.6%)	0/35 (0.0%)	p = 0.53
Picking up object from floor	3/39 (8.3%)	0/35 (0.0%)	p = 0.24
Stops walking when talking	7/58 (12.1%)	0/55 (0.0%)	p = 0.01

orders, and visual or orthopaedic problems that were sufficiently severe to interfere with balance. We asked all eligible patients who visited our outpatient department between May 1998 and July 1999 to participate (Figure 1). Sixty-one patients consented to participate, but two of them were later excluded because they were lost to follow-up shortly after inclusion (one patient died, one patient could no longer be reached). Age and sex of the remaining 59 patients were comparable to the entire outpatient population. Thirty-eight healthy partners of the patients were chosen as controls because their domestic risk factors for falls are identical to those of the patients. This is important because domestic variables such as stairs and slippery floors are important risk factors for falls.[41] For the same reason, domestic variables of the remaining 17 controls (healthy acquaintances of the patients or the investigators) were matched to those of the patients. The exclusion criteria used for the patients also applied to the controls. Medication taken during the study included levodopa (50 patients), dopamine receptor agonists (36 patients), anticholinergics (seven patients), amantadine (30 patients), selegiline (six patients), tolcapone (one patient), atypical neuroleptics (six patients), antidepressants (five patients), benzodi-azepines (16 patients and three controls) and antihypertensive drugs (nine patients and 10 controls). All subjects gave informed consent, as approved by the Ethical Committee of Leiden University Medical Centre.

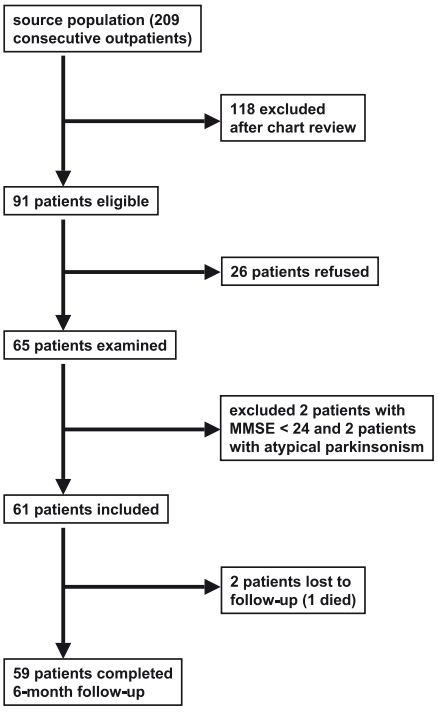

Fig 1 Selection procedure for the patients.

Baseline clinical examination

The same investigator (BRB) examined all subjects (patients approx- imately one hour after intake of their usual medication). Baseline examination included a medical history, detailed evaluation of prior falls (using a standardised questionnaire) and a neurological examination, including the modified Hoehn and Yahr stages, the Unified Parkinson's Disease Rating Scale (UPDRS)[26] and the MMSE. Individual Hoehn & Yahr scores were stage 1 (N=5), stage 1.5 (N=5),stage 2 (N=19),stage 2.5 (N=11),stage 3 (N=18) and stage 4 (N=1).To reduce differences in answers due to e.g. education, the standardised questionnaire about falls was administered in the form of a personal interview. This was always performed in the presence of a partner, other close family member or carer, and these persons were asked to confirm the accuracy of all answers whenever possible. In addition, the standard questions were further clarified if patients misinterpreted our questions or volunteered ambiguities. The standardised interview included a description of living circumstances (alone or with partner / carer; presence of stairs yes/no), dependence (none, partial, or complete) in activities of daily living (ADL), accounts of recent falls (≤6 months),any fear of falling, any restrictions in daily activities because of this fear, and any problems with simultaneous performance of multiple tasks in daily life. Before asking about prior falls, we explained the definition of a fall as 'any unexpected event that caused the person to unintentionally land on any lower surface (object, floor, or ground), regardless of any sustained injury'.[11,25,29] We restricted the account of recent falls to a 6-month period to minimise the risk of recall bias.[17] The question about problems with simultaneous performance of multiple tasks in daily life was illustrated by two standard examples ("We will give you two examples. In the last six months, did you have more difficulty than previously to walk and talk to someone at the same time? Did you have more difficulty than previously to walk and carry something in your hands?"). These two examples were chosen because elderly persons and Parkinson patients are known to have difficulty with these tasks.[6,9,27,28] We also posed an open question about problems with any other simultaneous tasks. Persons were regarded as fallers if they reported at least one previous fall in the preceding six months. Equilibrium and mobility were tested with Tinetti's Mobility Index[40], the normal Romberg test, the sharpened Romberg test (i.e. standing with eyes open and eyes closed, with the feet in tandem stance) [37], tandem gait (walking 10 steps with feet directly in front of each other), reaching for an object (standardised for each subject at a level just above the head) and bending forward to pick up an object from the floor. These additional tests were scored as either normal or abnormal. The 'Stops walking when talking'test[27] was also administered. The results of this test in the first 38 patients and 35 controls are briefly described elsewhere.[5] In 35 patients and 30 controls, blood pressure was measured in a recumbent position and after two minutes of standing. Orthostatic hypotension was defined as a drop in systolic blood pressure of more than 20mm Hg or a drop in diastolic blood pressure of more than 10mm Hg.[32] Specific attention was paid to the retropulsion test, which is commonly used to probe

postural disturbances in PD.[26] Despite widespread clinical use, it remains unclear how the retropulsion test should be executed. The patient can be warned verbally or prepared by practice[26,39,42], but some authors claim that the first and most unexpected test is most informative.[4,34] We therefore assessed several variants of the retropulsion test to identify the best predictive version. The test consisted of a sudden and unexpected shoulder pull, performed by an examiner standing behind the person.[4,26] In all subjects,the test was executed the first time without any warning. Directly thereafter, the retropulsion test was repeated with prior warning. In 39 patients and 35 controls, the test was repeated four additional times with prior warning to study habituation effects.[8] The amount ofretropulsion was scored as described by the Parkinson's Study Group.[26] In addition, we counted the number of backward steps needed to restore balance.

Prospective assessment of falls

Both patients and controls were instructed to directly document the circumstances and consequences (injuries or fear) of all falls for six months, using standardised scoring forms. Subjects were asked to describe the fall in their own words, and to tick pre-specified options regarding the environment where the fall occurred (indoors or outdoors), the specific activity at the time of the fall and any complaints that preceded the fall. Subjects were also asked to tick whether they performed multiple tasks simultaneously at the time of the fall. Patients recorded the effect of their antiparkinson medication at the time of the fall, by ticking one o the three following options: (a) insufficient effect, very stiff and slow; (b) good effect, not very stiff and slow; or (c) good effect, but excessive involuntary movements ('dyskinesias'). Persons were carefully instructed to return these scoring forms by mail directly after each fall. In addition, persons were contacted by telephone every two weeks to assure that all falls were documented.

Persons were classified as a 'faller' if they suffered at least one fall, whereas 'recurrent fallers' had at least two falls. 'Injurious fallers' were persons who sustained fractures or soft tissue injuries (including bruises, skin lacerations, haematomas and joint dislocations) after at least one fall. Finally, persons were defined as 'serious fallers' if their falls were recurrent (≥2), injurious, or both. This variable encompasses all clinically relevant falls. Recurrent falls are a better index of chronic disorders than single falls, which are often caused by environmental accidents with a low recurrence rate[33] and therefore have little clinical importance, unless injury occurs. Based upon the answers to the scoring forms, we scored a fall as 'extrinsic' if it was caused by an environmental cause (e.g. collisions), as 'intrinsic' if it was caused by mobility or balance disorders, misperception of the environment or loss of consciousness, and as 'non-bipedal' if it occurred while the person was not in a bipedal stance (e.g. fall from a chair).[25] Falls were also categorised as 'base of support falls' (e.g. trips or slips), 'centre of mass falls', either self-induced (e.g. bending, reaching or turning) or externally applied (e.g .a push or collision), or as falls in which there was no

obvious perturbation (with or without loss of consciousness).[29] The remaining falls were labelled as 'unclassified'.

Statistical analyses

Baseline variables were compared between patients and controls using the unpaired t-test, the chi square test and Fisher's exact test, with a p-value of 0.01 as a Bonferroni-type correction. Duration of the disease was compared between fallers and non-fallers using the unpaired t-test. The recurrent fallers of both groups will be reported as the primary outcome measure. However, very similar results were obtained when single, serious or injurious falls were used as the primary outcome variable, and when patients were analysed separately. The sensitivity and specificity for prediction of recurrent falls were calculated for all baseline variables. In addition, stepwise forward logistic regression analysis was performed to evaluate which combination of variables best predicted recurrent falls. In this model, we successively entered variables from the baseline history (age, sex, alcohol use, dependence in ADL, disease duration), the prior fall history (faller status, fear of falls, restriction of activities, problems with multiple tasks, use of walking aids), the general physical examination (Hoehn and Yahr stages, UPDRS score) and, finally, the balance and gait examination (Tinetti score and the additionally recorded measures).

RESULTS

Baseline assessment (Table 1)

There were more women among controls than among patients (a consequence of our choice for partners, rather than sex-matched persons, as controls). Domestic variables (as exemplified in Table 1 by the proportions of subjects that lived together with a partner, and by the proportions of subjects with stairs within the house) did not differ between patients and controls. Patients were more often dependent for ADL than controls. The MMSE of patients was slightly but significantly lower than in controls, but owing to our inclusion criteria, none of the patients had obvious cognitive impairment. The average number of prior falls and the proportion of self-reported fallers (≥1 fall) during the six previous months were somewhat higher for patients than controls, but these differences were not significant. Almost 50% of patients expressed a fear of falling. A restriction of daily activities because of this fear was also more common among patients than controls. Furthermore, many patients reported difficulties with simultaneous performance of multiple tasks, such as walking and carrying a tray.

Patients performed worse than controls on most tests of balance and gait (Table 1). Tandem stance with eyes closed was most often abnormal in patients, but also in about 42% of the controls. Balance while turning and tandem gait were also sensitive measures of PD, and these tests were rarely abnormal in controls. Several other measures, such

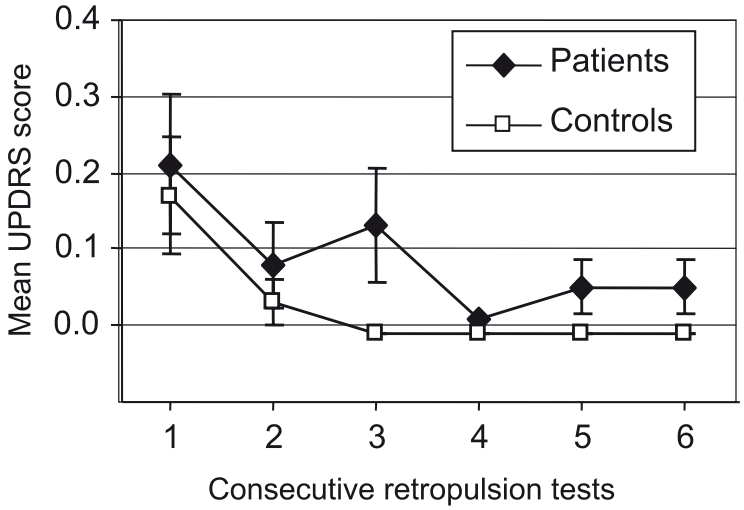

Fig 2 Responses to the six consecutive retropulsion tests for patients and controls. The UPDRS-score is used as outcome measure. Similar results were obtained for the number of corrective steps.

as the Romberg test and orthostatic hypotension, did not differ between patients and controls. The 'Stops walking when talking test' was abnormal in only seven patients, and in none of the controls.

The responses to the six consecutive retropulsion tests are shown in Figure 2. The first retropulsion test (i.e. without prior warning) was abnormal (UPDRS score ≥1) in 10 patients (16.9%) and six controls (10.9%;p = 0.55). Only three patients and one control had to be caught by the examiner (UPDRS score = 2). No person had a spontaneous tendency to fall (UPDRS score = 3). Most corrective steps were taken after the first unexpected shoulder pull by both patients (1.6 ±1.3) and controls (1.6 ±1.2;p = 0.81). Overall, for subjects who received six consecutive retropulsion tests, test abnormality decreased with warning and repetition in patients and controls ($p < 0.001$),both for the UPDRS score and the number of corrective steps taken. These warning and learning effects did not differ between both groups (p = 0.47). The warning and learning effects were largely attributable to the second test, which was performed better than the first test in both groups. No relevant further improvement was noted for the remaining retropulsion tests (no difference between the second and sixth test in both groups; p = 0.30). None of the retropulsion tests discriminated well between patients and controls.

Prospective follow-up (Table 2)

During the six-month follow-up, patients reported 205 falls, whereas controls reported only 10 falls. The period between baseline examination and the first fall was somewhat shorter for patients than controls, but this difference was not significant. However, the mean (±standard deviation) period between baseline examination and the first fall was

significantly shorter for persons who sustained recurrent falls (1.0 ±1.0 month) than for persons with maximally one fall (2.9 ±1.8 month) ($p < 0.005$).Among patients, the proportion of prospectively identified fallers (50.8%) tended to exceed the self-reported estimate during the six previous months (39%;$p = 0.27$).In contrast, fewer controls tended to fall during follow-up (14.5%) than during the previous six months (27.3%; $p = 0.16$). The proportion of persons that reported at least one fall was much higher for patients than controls (relative risk [RR] 6.1;95% confidence interval [CI] 2.5–15.1;$p < 0.001$).The proportion of persons who fell more than once during follow-up was also higher for patients. One quarter of patients had recurrent (≥2) falls, as opposed to only two controls (RR 9.0; 95% CI 2.0–41.7;$p = 0.001$).

Complete documentation about circumstances of falls was available for 150 falls of patients and all 10 falls of controls (Table 2). Information about the falls could not be obtained reliably for 55 falls of the patients (usually due to poorly legible handwriting; a few falls were only detected during the reminding telephone calls, but details of these falls were not included to avoid any recall problems). Patients fell mostly indoors, whereas controls usually fell outdoors. Patients mostly suffered intrinsic falls, whereas environmental hazards (extrinsic falls) caused most falls in controls. 'Centre of mass falls' predominated among patients, whereas controls had more 'base of support falls'. Centre of mass falls among patients occurred most commonly while turning around (24% of the 150 falls), standing up (15%) and bending forward (16%). About one third of falls occurred when patients rated their symptoms as poorly controlled. About two-thirds of all falls by patients occurred when they rated their symptoms as well controlled, although concurrent dyskinesias were present in half of them. Six falls were related to sudden freezing, all when symptoms were poorly controlled. Only one fall was preceded by sudden loss of consciousness.

The proportion of injurious fallers tended to be highest among patients, but the proportion of injurious falls did not differ between both groups (Table 2). Among those persons who fell at least once, the proportion of injurious fallers tended to be even higher for controls (six out of eight fallers or 75%) than for patients (15 out of 30 fallers or 50%; $p = 0.26$). Serious fallers (recurrent, injurious, or both) were more common among patients than controls. No fractures or life-threatening complications occurred, but soft tissue injuries were very common. An inability to get up after a fall occurred in both patients and controls, and several patients lay on the floor for hours. In addition, falls often induced or aggravated a fear of future falls that led patients to further restrict their activities.

Prediction of falls (Table 3)

Of the questionnaire items, asking for earlier falls attained the best sensitivity (76.5%) with a comparable specificity (74.2%) in identifying recurrent fallers. Asking for problems with multiple tasks also had a reasonable sensitivity and specificity. Overall, the proportion of women did not differ between recurrent fallers (9/17; 52.9%) and persons with

Table 2. Fall rates, circumstances and consequences of falls.

	Patients (N = 59)	Controls (N = 55)	Significance
Fall rates			
Time to first fall (months)	1.7 ± 1.7	2.5 ± 2.0	p = 0.35
Fallers (≥1 fall)	30 (50.8%)	8 (14.5%)	p < 0.001
Recurrent fallers (≥2 fall)	15 (25.4%)	2 (3.6%)	p = 0.001
Characteristics [a]			
Falls indoors	124 (82.7%)	2 (20.0%)	p < 0.001
Lach classification (25)			
Intrinsic falls	105 (70.0%)	4 (40.0%)	
Extrinsic falls	20 (13.3%)	5 (50.0%)	p = 0.02
Non-bipedal falls	2 (1.3%)	0 (0.0%)	
Non-classifiable falls	23 (15.3%)	1 (10.0%)	
Maki classification (29)			
Base of support falls	21 (14.0%)	5 (50.0%)	
Center of mass falls	108 (72.0%)	4 (40.0%)	p = 0.02
No obvious perturbation falls	8 (5.3%)	0 (0.0%)	
Non-classifiable falls	13 (8.7%)	1 (10.0%)	
Clinical condition			
Poorly controlled	44 (29.3%)	—	—
Well controlled (no dyskinesias)	54 (36.0%)	—	—
Well controlled (with dyskinesias)	52 (34.7%)	—	—
Consequences			
Injurious fallers	15 (25.4%)	6 (10.9%)	p = 0.06
Serious fallers [b]	21 (35.6%)	6 (10.9%)	p < 0.005
Number of falls with: [a]			
Injury	93 (62.0%)	7 (70.0%)	p = 0.74
Inability to get up	37 (24.7%)	3 (30.0%)	p = 0.71
(More) fear of future falls	63 (42.0%)	1 (10.0%)	p = 0.05

Data are displayed as mean ± standard deviation or as individual counts (percentage between parentheses) with an abnormal test result. [a] Complete documentation available for 150 falls of patients and all 10 falls of controls; b persons with recurrent falls, injurious falls, or both.

maximally one fall (49/97; 50.5%). However, all eight fallers among our controls were women, whereas men (n=8) and women (n=7) were equally distributed among the recurrent fallers in the patient group. Recurrent falls were more common in more severely affected patients and persons with higher scores on the Tinetti Mobility Index. Among patients, fallers had a somewhat longer duration of the disease than non-fallers, but this difference was not significant. For example, disease duration was 8.5 ±4.6 years among patients with recurrent falls, compared with 6.6 ±4.8 years among patients without recurrent falls ($p = 0.18$). The MMSE was only slightly lower among recurrent fallers, but this difference was not significant. Benzodiazepines were used more often by patients (n = 16; 27.1%) than by controls (n =3; 5.5%) (Fisher's exact test, $p < 0.005$). Recurrent falls were reported by 36.8% (7/19) of persons using benzodiazepines, and by 10.5% (10/95) of persons not using benzodiazepines (RR 5.0;95% CI 1.6–15.5;$p < 0.01$).

Most balance and gait tests predicted falls insufficiently. This included the retropulsion test (irrespective of how it was executed or scored), which had a good specificity, but a very low sensitivity. The area under the receiver-operating curve (calculated for the average of all six retropulsion tests) was 0.62 (standard error 0.07), reflecting an insufficient sensitivity and specificity to predict falls. Tandem stance with eyes closed, turning around and tandem gait had a moderate to good sensitivity, but the specificity was only acceptable for tandem gait (79.8%) and turning around (72.9%). The proportion of persons with orthostatic hypotension did not differ significantly between recurrent fallers (23.1%) and non-fallers (13.5%; $p = 0.41$). The 'Stops walking when talking'test was rarely abnormal in recurrent fallers.

The logistic regression analysis has to be interpreted with some caution given the relatively small sample size. When all variables were entered into the logistic regression model simultaneously, the combination of asking for prior falls, disease severity and the Romberg test yielded the best overall diagnostic utility (sensitivity 65% and specificity 98%). However, the added benefit of the Romberg test was limited for practical purposes because this test was impaired in only three recurrent fallers (and in none of the remaining subjects). In contrast, disease severity (as indexed by the Hoehn and Yahr scores) was helpful in identifying subjects at risk for recurrent falls. Thus, the RR of recurrent falls was 13.4 (95% CI 0.4–27) for patients with Hoehn and Yahr stage 1 to 2.5, and > 100 (95% CI 3.1–585) for the most severely affected patients (who were all but one in Hoehn and Yahr stage 3). Asking for prior falls in the previous 6 months was also helpful in identifying subjects at risk for recurrent falls (RR 5.0, 95% CI 1.2–20.9). Identical results were obtained when the prediction model was applied to patients only, and when patients and controls were pooled (where controls were given a Hoehn and Yahr score of 0 and disease duration of 0 years).

Table 3. Prediction of recurrent fallers (pooled results of patients and controls). Non-fallers included persons without any falls or a single fall. Data are displayed as mean ± standard deviation or as individual counts (the percentage shown between parentheses for fallers denotes the sensitivity; the percentage shown for non-fallers is equivalent to 100% minus the specificity). Abnormal retropulsion tests shown here include all UPDRS scores $^{3}1$, but statistical analyses were performed using the actual scores. Only variables that differed ($p < 0.01$) between recurrent fallers and non-fallers are displayed, plus several pertinent variables that did not discriminate well between both groups.

	Recurrent fallers (N = 17)	Non-recurrent fallers (N = 97)	Significance
Fall questionnaire			
Fallers (£ 6 months)	13 (76.5)	25 (25.8)	$p < 0.001$
Fear of falling [a]	9 (52.9)	22 (22.9)	$p = 0.02$
Problems with multiple tasks [b]	11 (73.3)	23 (26.4)	$p = 0.001$
Use of walking aids [a]	6 (35.3)	7 (7.3)	$p < 0.005$
Neurological examination			
Hoehn & Yahr stage	2.8 ± 0.6	2.1 ± 0.6	$p < 0.001$
UPDRS motor score	34.8 ± 12.5	17.1 ± 16.6	$p < 0.001$
UPDRS total score	52.8 ± 17.9	26.5 ± 24.7	$p < 0.001$
MMSE	27.8 ± 2.2	28.7 ± 1.6	$p = 0.13$
Gait and balance			
Tinetti balance score	5.1 ± 2.8	1.7 ± 2.5	$p < 0.001$
Tinetti gait score	3.8 ± 2.4	1.0 ± 1.8	$p < 0.001$
Tinetti total score	8.9 ± 4.6	2.7 ± 4.0	$p < 0.001$
Retropulsion tests			
First	5 (29.4)	11 (11.3)	$p = 0.07$
Second	1 (5.9)	2 (2.1)	$p = 0.05$
Tandem stance			
Eyes open	9 (52.9)	16 (16.5)	$p < 0.005$
Eyes closed	15 (88.2)	52 (53.6)	$p < 0.01$
Romberg test [a]	3 (17.6)	0 (0.0)	$p < 0.005$
Sitting down [a]	8 (47.1)	11 (11.5)	$p = 0.001$
Turning around [a]	12 (70.6)	26 (27.1)	$p = 0.001$
Tandem gait [c]	10 (62.5)	19 (20.2)	$p = 0.001$
Stops walking when talking	2 (12.5)	5 (5.2)	$p = 0.26$

[a] Data were unavailable for one non-faller,
[b] two fallers and 10 non-fallers,
[c] one faller and three non-fallers.

DISCUSSION

The first important conclusion is that falls are very common, even relatively early in the course of PD. More than 200 falls occurred in 59 patients during six months, 50% of the patients fell at least once, and about 35% suffered recurrent or injurious falls. Comparable fall rates emerged from an uncontrolled study where 59% of Parkinson patients fell at least once during three months.[19] In contrast to the latter study, we also investigated falls in healthy controls, which permitted us to estimate relative risks for falls. Thus, Parkinson patients had a nine-fold increased risk of sustaining recurrent falls. These prospectively determined fall rates exceed those of retrospective studies[23,31,35,36] (and the retrospective estimate in this study), perhaps because merely asking for falls underestimates the true incidence.[17] An 'amnesia for falls' may well occur in PD patients who are often cognitively impaired.[18,30] Indeed, patients had a lower MMSE than controls, and elaborate tests might have unveiled more cognitive decline. Another possibility is that concurrent disease progression during the study explained why the prospectively obtained fall rate in our patients exceeded their own retrospective estimate.

The fall rates for patients well exceeded those of controls, despite the female preponderance in controls. This sex difference was a consequence of our choice for partners as controls, which we considered important because domestic variables such as stairs and slippery floors are important risk factors for falls.[41] This advantage outweighed the resultant sex difference between patients and controls. In fact, the actual difference between patients and controls is perhaps even greater than in this study because women fall more often than men.[41] Indeed, all eight fallers among our controls were women.

Our analysis of fall circumstances is the second important result, as this could form the basis for potential preventive measures. PD patients usually fell indoors, suggesting that reduction of domestic hazards could be fruitful. However, this approach may eliminate only a minority of falls, because patients often fell unrelated to environmental hazards (they had a high proportion of 'intrinsic' falls). Indeed, patients commonly had centre of mass falls (most often while turning around), which again suggests that the underlying balance disorder caused most falls. Apparently, antiparkinson medication did not reduce these balance problems, because two- thirds of falls occurred when patients considered their symptoms to be well controlled. Other studies also suggest that postural instability in PD is resistant to conventional pharmacotherapy.[3,10,22,23] In fact, treatment may paradoxically aggravate falls because amelioration of other symptoms improves mobility (and thus increases the risk of falling)[38], without improving balance. Furthermore, our results suggest that drug-induced dyskinesias may contribute to some of the falls.[35] However, more detailed research is needed here because we did not quantify the severity and daytime duration of dyskinesias. Certainly, development of improved therapeutic strategies to reduce postural instability is needed. One important measure that could already be taken is reduction of benzodiazepines, which were commonly used by our patients.

Similar to other studies[13,16], we found that use of benzodiazepines was associated with a five-fold increase in the risk of recurrent falls. A third important finding was the high rate of adverse consequences of falls. No fractures occurred, but soft tissue injuries were very common. The proportion of injurious fallers was slightly higher in controls than in patients, possibly because patients fell mostly indoors where soft carpets may have absorbed the impact of their falls. In addition, patients may suffer more 'low-energy' falls because they walk more slowly or fall from a low height, for example while reaching for objects on the floor. This differs from healthy persons who rarely fall, but if they do, it is usually due to overwhelming external causes that often induce injuries.

A commonly overlooked, yet incapacitating consequence of falls is a fear of future falls, which was common among patients. This fear of falls forced patients to restrict their physical activities and sometimes led to social isolation. This restriction of activities perhaps explains the high proportion of indoor falls in our patients. The immobilisation and reduced ability to participate in social life are as important as falling itself in reducing the quality of life for PD patients.[7] Immobilisation also underlies the complex relation between falls and disease duration, which only tended to be longer in fallers compared to non-fallers. We suspect that falls are most common in relatively early stage PD (as was the case in our patients), when postural instability develops and patients are sufficiently mobile to be actually at risk for falls.[7] Indeed, in our study, fall risks were highest for patients with Hoehn and Yahr stage 3 PD. As the disease progresses further, both postural instability and the fear of falls worsen, causing patients to become increasingly immobilised. In effect, this 'prevents' additional falls and obscures the relation between falls and disease duration.[7]

The fourth aspect of our study related to prediction of falls. Recurrent fallers were best predicted by a combination of asking for prior falls, disease severity and the Romberg test. Although the specificity of this combination was excellent (98%), the overall diagnostic utility was somewhat limited by the moderate sensitivity (65%), indicating that a substantial proportion of recurrent fallers would be misclassified as non-fallers. Because of the grave consequences of falls and the emerging possibilities for therapeutic intervention[7,12,15], a test with a higher sensitivity (perhaps at the cost of a lower specificity) would be preferable. Presently, the best predictors of falls were disease severity and asking for prior falls. For example, the risk of recurrent falls was increased five-fold in persons with earlier falls. The moderate sensitivity is perhaps explained by the amnesia for falls mentioned previously.

Interestingly, none of the commonly used clinical tests of balance and gait could predict falls adequately. This included the retropulsion test which is commonly used to document balance impairment in PD. The retropulsion test has several theoretical shortcomings, and how this test should be executed is debated.[4,7] The response to the first shoulder pull is presumably most informative (certainly when given without prior notice) because this best resembles the unexpected falls that occur in daily life.

Because patients adapt to the test[34] learning effects (that are not operative in daily life) could confound subsequent shoulder pulls. The first retropulsion test is also preferable because PD patients cannot cope with unexpected external perturbations.[37] Indeed, the first and unexpected shoulder pull yielded different results (more corrective steps and a higher UPDRS-score) than all subsequent tests, which produced largely similar results. Both the prior warning signal and learning effects may explain the better performance for the second to sixth retropulsion tests. However, none of the six retropulsion tests discriminated well between patients and controls, and all tests predicted falls poorly. This predictive capability was perhaps insufficient because our patients were relatively mildly affected (even the first and unexpected retropulsion test was normal in most patients). Yet,this moderately affected group is interesting because the added benefit of a screening test for falls would be greatest. We therefore conclude that the retropulsion test is not suitable for early detection of fallers. Perhaps the test is more useful in later stages of PD to rate the severity of balance impairment.

Assessment after overnight withdrawal of levodopa might predict falls better than the present scores. However, major differences are unlikely because most falls occurred when symptoms were well controlled. Furthermore, scores for postural instability usually change little with dopaminergic medication.[3,10,22,23]

A potential shortcoming of our study was created by the inclusion of outpatients attending a university hospital with an interest in movement disorders. This selection bias might preclude extrapolation of our findings to the more general population of patients with PD, for example because relatively severely affected patients are more likely to visit specialised outpatient clinics. However, this possible selection bias by disease severity appeared negligible in our study because we excluded patients with severe signs (inability to walk without assistance, MMSE < 24). Indeed, the average UPDRS motor score of our patients was 31.5 and none of them had a Hoehn and Yahr score of 4. Such patients are also commonly seen in outpatient clinics outside specialised university centres. We also reduced the risk of including patients with atypical hypokinetic-rigid syndromes (who fall more frequently and earlier in the course of the disease[43] by using the inclusion criteria for idiopathic PD as defined by the brain bank of the United Kingdom Parkinson's Disease Society.[21] In addition, all patients responded well to chronic treatment with antiparkinson medication, which always included levodopa and/or a dopamine agonist.[14]

We cannot entirely exclude that our study was underpowered to detect variables with a modest ability to detect falls. However, most comparisons between prospectively determined fallers and non-fallers were highly significant, which generally does not suggest insufficient power. Although the number of subjects was relatively small, the incidence of falls was very high. Furthermore, the observed sensitivities were consistently low to moderate. A larger sample size may have helped to reduce the uncertainty surrounding these sensitivities and attain statistical significance, but it is unlikely that very different sensitivities would have been obtained. Certainly, further studies in larger patient groups

remain necessary. Such studies should also include tests with a 'multiple task' design (simultaneous assessment of different aspects of postural control) as these may predict falls better than simple tests of isolated postural components.[27] This may be particularly true in PD where the pathophysiology of postural instability is multifactorial.[2,3,20] Indeed, during the standardised interview, 57% of our patients reported difficulties with executing simultaneous tasks, such as carrying a tray or talking while walking. Although these answers may be subject to interindividual variability (e.g. due to differences in education) and recall bias[17], it was interesting that very comparable results emerged from the more reliable prospective survey where multiple-task performance played a role in about 50% of the falls (see reference (44) for details). In the present study, we also corroborated our earlier report[5] in a smaller patient group that simple dual-task performance, such as the 'Stops walking when talking' test[27], is rarely abnormal in PD, perhaps because this test is only abnormal in cognitively impaired patients.[5] However, preliminary results suggest that simultaneous or sequential performance of truly multiple (up to eight) tasks can discriminate much better between PD patients and controls, even in relatively early stages of the disease.[6] We are now prospectively investigating whether this 'Multiple Task Test' can also predict actual falls in daily life.

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Chapter 3.2

A meta-analysis of six prospective studies of falling in Parkinson's disease

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ABSTRACT

Recurrent falls are a disabling feature of Parkinson's disease (PD). We have estimated the incidence of falling over a prospective 3 month follow-up from a large sample size identified predictors for falling for PD patients, repeated this analysis for patients without prior falls, and examined the risk of falling with increasing disease severity. We pooled six prospective studies of falling in PD (n = 473), and examined the predictive power of variables that were common to most studies.The 3-month fall rate was 46% (95% confidence interval: 38% to 54%). Interestingly, even among subjects without prior falls, this fall rate was 21% (12% to 35%). The best predictor of falling was two or more falls in the previous year (sensitivity 68%; specificity 81%). The risk of falling rose as UPDRS increased, to about 60% chance of falling for UPDRS values 25-35, but remained at this level thereafter with a tendency to taper off towards later disease stages. These results confirm the high frequency of falling in PD, as almost 50% of patients fell during a short period of only 3 months. The strongest predictor of falling was prior falls in the preceding year, but even subjects without any prior falls had a considerable risk of sustaining future falls. Disease severity was not a good predictor of falls, possibly due to the complex U-shaped relation with falls. Early identification of the very first fall therefore remains difficult, and new prediction methods must be developed.

Recurrent falls are an important and disabling feature of idiopathic Parkinson's disease (PD).[1,2,3,4] Fall-related injuries such as hip fractures or head traumas are among the most recognizable consequences of falls.[5,6] However, falls have many other sequelae that may be less obvious clinically, but which have a significant negative impact on the patients' quality of life. For example, PD patients who have sustained prior falls often develop a fear of renewed falls[7,8] and this may cause or aggravate a concurrent loss of mobility. In turn, this reduced mobility is associated with a host of negative consequences, including a loss of independence, development of weakness, promotion of osteoporosis and, eventually, a deterioration of overall fitness, leading to cardiovascular disease and reduced survival.[9,10] Furthermore, postural instability and falls are associated with increased risk of admission to hospitals[11] or nursing homes.[12]

In light of these consequences of falls, it would be helpful to identify which persons are most at risk of sustaining a fall in the near future. Postural instability and falls are generally difficult to treat pharmacologically, but a host of additional therapeutic measures may help to alleviate falls in individual patients.[13,14] Because asking about previous falls is often unreliable, falls are best studied using a prospective design where patients are asked to document the occurrence of falls shortly after they have occurred. In the past few years, six prospective studies have examined fall rates and consequences of falls in PD.[7,15,16,17,18,19] These studies emphasised the high incidence of falls in PD: depending on the duration of follow-up (which ranged from 3 to 12 months), the percentage of patients with at least one fall amounted to almost 70% for those who were followed for a full year.[19] However, they produced inconsistent findings in their search for a clinically useful risk factor for falls in PD. Ashburn et al[15] concluded that a reported history of two or more falls in the previous year was the best predictor of future falls, and a previous review including all six studies indicated that the presence of prior falls was the only consistently present predictor of future falls.[20]

However, presence of prior falls as a predictor is suboptimal because ideally intervention should occur before the first fall has occurred. Indeed, no previous study has attempted to predict future falls in PD patients who are not currently falling. Moreover, previous studies were based on relatively small numbers, with no study including substantially more than 100 subjects. Here, we report a meta-analysis of individual data from 473 patients in all six previous prospective studies. Our specific aims were: to estimate the incidence of falling from larger numbers; to examine predictors of falling, not only among the group as a whole, but also among patients who had not fallen in the previous year; and to examine the relationship between increasing severity of disease – as measured by the Unified Parkinson Disease Rating Scale motor examination (UPDRS) – and falling.

MATERIALS AND METHODS

The six studies were identified from a PubMed search using the following search terms: "Parkinson's disease" AND "accidental falls" AND ("prospective studies" OR "longitudinal studies"), and this yielded four studies that had been published as full papers.[7,15,17,19] This was supplemented with information available to the authors from international conferences, and this yielded two further studies that have thus far appeared only in abstract form.[18,21] The studies were performed among community-dwelling patients with PD living in Ottawa Canada[17], Leiden the Netherlands[7], Brisbane Australia[18], and three centres in the United Kingdom: Southampton[15], North Tyneside[19] and London.[21] The London study was originally designed as a study focused on progressive supranuclear palsy, but this study was included because the PD patients – that served as controls in this study – were followed in the same way as in the other five PD studies.[21]

There was some heterogeneity across the six identified studies, but the methods were sufficiently similar to allow for a pooling of the data (Table 1). The duration of follow-up ranged from a minimum of 3 months to a maximum of 12 months. The prospective follow-up data were therefore recalculated for a comparable 3-month interval for all studies, which was possible because all studies included in this meta-analysis provided actual number of falls over the first three months, so ascertainment of falls was identical for all studies. Methods used to ascertain falls during the follow-up period also varied somewhat across studies, but were all deemed of sufficient quality to reliably ascertain faller status (single or recurrent faller). There was also a discrepancy in the time interval over which previous falls and near falls were reported (Table 1). To accommodate this, we only used the three studies in analyses incorporating prior faller status or number of falls. Some patients had large numbers of previous falls, the extreme being 500 falls. To reduce the impact of outliers, numbers of falls above 25 were replaced with the value 25, though sensitivity analyses with different numbers or using the original variable showed little difference.

Table 2 shows the number of patients with PD in each study, totalling 473 across all six studies. Whether or not a patient fell in a 3-month prospective follow-up period was available from all the studies. The following potentially predictive variables were common to all (or most) of the studies: age, gender, Hoehn and Yahr stage, UPDRS, previous falls, and fear of falling. The distribution of these variables was broadly similar across studies (Table 2).The UPDRS motor examination score was not recorded using the same version in all studies. The majority recorded the full version in which key symptoms are rated specifically for different areas of the body, making 27 items in total.[22] Two studies (Southampton and North Tyneside) used a reduced version in which only an overall rating of symptoms across body areas was obtained from each patient, resulting in 14

Table 1. Characteristics of the six contributing studies.

	Ottawa (17)	Leiden (7)	Southampton (15)	North Tyneside (19)	London (21)	Brisbane (18)
Inclusion criteria	Idiopathic PD	UK Brain Bank criteria, clear response to medication	UK Brain Bank criteria, independently mobile, live in the community	UK Brain Bank criteria	UK Brain Bank criteria, clear response to medication	UK Brain Bank criteria, clear response to medication
Exclusion criteria	Unable to walk, other causes for falls	Unable to walk, other causes for falls	Other causes for falls, cognitive impairment	Totally bedfast, severe medical instability	Unable to walk, other causes for falls	Unable to walk, other causes for falls
Duration follow-up	3 months	6 months	3 months	12 months	3 months	6 months
Fall ascertainment	Fall diaries, returned at 1-, 4- and 8-week intervals; follow-up phone calls at 2- and 4-week intervals; final study visit to review fall descriptions	Fall diaries, returned immediately after each fall; phone call every 2 weeks	Telephone call at 3 months using 10 question interview	Weekly postcards, followed by phone call when fall was reported	Fall diaries, returned immediately after each fall; phone call every 2 weeks	Monthly falls calendar postcards with follow-up phone calls
Prior faller status	Previous 3 months	Previous 12 months	Previous 12 months	Previous 12 months	Since diagnosis	Previous 6 months

items. To produce a score that was compatible across studies, we assumed that singly rated symptoms in the reduced version were the average of values that would have been obtained had symptoms been rated separately for specific body parts, and weighted the symptom by the number of parts rated in the full version of the UPDRS score. One could justly argue that this "scaling up" of these values to calculate the full UPDRS is a flawed assumption with subsequent overestimation of the full UPDRS scores. Therefore, in a separate approach, we also repeated our analyses when the available full scores were scaled down to the reduced version - using the single maximum score for each item instead. The results were very similar according to these alternative analyses. We prefer the first approach because the majority of cases came from studies where 27 UPDRS items were checked, so only the minority had to be scaled up to become consistent with the 27 item version. Hence only the analyses using the "scaled up" UPDRS scores will be reported here.

Confidence intervals (CIs) around risks of falling were obtained from logistic regression with study included as a random effect, fitted in Stata 9. We examined the potential of age, gender, Hoehn and Yahr stage, UPDRS and reported number of falls in the previ-

Table 2. Summary statistics and numbers missing in each study and combined. Figures are number (%) unless stated otherwise.

VARIABLE		Ottawa (n=118)	Leiden (n=59)	Southampton (n=63)	North Tyneside (n=109)	Brisbane (n=56)	London (n=68)	Overall (n=473)
Subsequent faller in 3 month	yes	70 (59%)	21 (36%)	22 (38%)	49 (46%)	23 (44%)	28 (41%)	213 (46%)
	no	48 (41%)	38 (64%)	35 (61%)	58 (54%)	29 (56%)	40 (59%)	248 (54%)
	missing			6	2	4		12
Subsequent injurious faller in 3 months	yes	(92 falls amongst the 118)	14 (24%)				18 (27%)	
	no		45 (76%)				50 (74%)	
	missing			63	109	56		
Age in years	mean(SD)	71 (10)	61 (10)	71 (8)	75 (8)	65 (9)	64 (9)	69 (10)
	min to max	43 to 90	39 to 80	46 to 87	54 to 92	46 to 84	35 to 81	35 to 92
	missing	2						2
Sex	male	73 (62%)	38 (64%)	33 (52%)	52 (48%)	35 (63%)	42 (62%)	273 (58%)
	female	45 (38%)	21 (36%)	30 (48%)	57 (52%)	21 (38%)	26 (38%)	200 (42%)
Hoehn and Yahr stage	mean(median)	2.6 (2.5)	2.3 (2.5)	2.8 (3.0)	2.0 (2.0)	2.7 (3.0)	2.5 (2.5)	2.4 (2.5)
	min to max	1 to 4	1 to 4	1 to 4	1 to 4	1.5 to 4	1 to 5	1 to 5
	missing					12	1	13
UPDRS	mean(median)	33.3 (33.0)	31.9 (30.5)	38.4 (38.0)	29.3 (29.0)	20.1 (20.0)	23.8 (21.5)	30.1 (29.0)
	min to max	2.5 to 64	7 to 64	4 to 74	6 to 58	8 to 41.5	2 to 69	2 to 74
	missing	12	1	3		13	4	33
Reported number of falls in previous year	mean(median)		1.3 (0)	2.8 (1)	11.0 (1)			6.3 (1)
	min to max		0 to 20	0 to 20	0 to 500			0 to 500
	missing	118				56	68	231
Reported falls in the previous year	yes		23 (39%)	40 (64%)	68 (62%)			131 (57%)
	no		36 (61%)	23 (36%)	41 (38%)			100 (43%)
	missing	118				56	68	242
Reported repeat falls in the previous year	yes		11 (19%)	29 (46%)	53 (49%)			93 (40%)
	no		48 (81%)	34 (54%)	56 (51%)			138 (60%)
	missing	118				56	68	242

Reported near falls in the previous year	yes			47 (75%)			50 (74%)	97 (131%)
	no			16 (25%)			18 (26%)	34 (26%)
	missing	118	59		109	56		342
Fear of falling	yes		27 (46%)	23 (36%)			39 (58%)	89 (47%)
	no		32 (54%)	40 (64%)			28 (42%)	100 (53%)
	missing	118			109	56	1	284

ous year, as predictors of falling in the three month follow-up period in uncontrolled logistic regression models, and models controlled for all the other variables. Because these models were based on only three studies (number of falls in the previous year only being available in Leiden, Southampton and North Tyneside), study was included as a fixed rather than random effect taking account of possible differences in falling between studies. The possibility of non-linear dependency of risk of falling and UPDRS score was examined by additionally including as a regressor UPDRS squared: if the risk of falling were to decrease at higher values of UPDRS the squared term would be needed in the model. Estimated risks from the logistic models are reported as odds ratios with their associated 95% CIs, and likelihood ratio tests are reported. A similar set of logistic models examined the predictive power of items within the UPDRS in relation to risk of subsequent falling. For studies that reported the full version of the UPDRS, symptoms rated over different body parts were averaged and included as a single regressor in the model. Number of previous falls, UPDRS and Hoehn and Yahr stage were also examined as predictors of falling in ROC curves; and the area under the curve (AUC) statistics are reported, along with sensitivity and specificity at selected cut points. Lowess smoothed curves of the relationship between increasing severity of disease (as measured by the UPDRS motor examination score) and risk of falling were produced in Stata. The default bandwidth of 80% was used.

RESULTS

Table 2 shows the baseline characteristics of all contributing studies, as well as the findings on prior and prospectively documented falls. The rate of falling in the 3-month follow-up period amongst all subjects was 213/461 (46%; CI 38%- 54%). Amongst subjects who reported not having fallen in the previous year the rate was 21/99 (21%; CI 12% - 35%), while among those reporting falling once or more the rate was 71/124 (57%; CI 53% - 61%). Observations on injuries falls were only available for three studies (Table 2). Two of these studies reported the proportions of subjects with injurious falls, and the findings were remarkably comparable (24% in the Leiden study, and 27% in the London study). The third study (Ottawa) merely reported the number of falls that was associated with injuries, and this proportion was very high (78%).

The single most important predictor of subsequent falling was the reported number of falls in the previous year (Table 3). Number of previous falls was also the only variable to provide independent predictive power (P=0.000) that was not explained by the two disease severity measures (Hoehn and Yahr stage and UPDRS).

Table 3. Odds ratios (OR) of falling in three months for study, age, Hoehn and Yahr, UPDRS and number of falls reported in the previous year (n=219).

		UNCONTROLLED		CONTROLLED*	
Variable		**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Study					
Leiden		1.00	0.303	1.00	0.188
Southampton		1.12 (0.52, 2.42)		0.70 (0.25, 1.95)	
North Tyneside		1.61 (0.88, 3.11)		1.63 (0.63, 4.22)	
Age (years)	per unit increase	1.00 (0.98, 1.03)	0.781	0.98 (.94, 1.01)	0.183
Sex	Female/male	1.03 (0.60, 1.77)	0.921	0.78 (0.40, 1.51)	0.452
Hoehn and Yahr	per unit increase	2.05 (1.41, 2.98)	0.000	1.72 (0.99, 2.97)	0.051
UPDRS27	per unit increase	1.10 (1.00, 1.21)	0.023[a]	1.05 (0.94, 1.17)	0.661[b]
UPDRS27[a]		1.00 (1.00, 1.00)	0.223[a]	1.00 (0.98, 1.00)	
Number of falls in the previous year	per unit increase	1.54 (1.32, 1.81)	0.002	1.49 (1.25, 1.78)	0.000

* Controlled for the other predictor variables in the table.

[a] P values for uncontrolled UPDRS27 are based on likelihood ratio tests for the linear term on its own, and the quadratic term in the presence of the linear term.

[b] P value for controlled UPDRS27 is based on likelihood ratio test for the linear and quadratic terms removed together, df =2.

Of the two severity measures, the Hoehn and Yahr stage contributed most to predicting falling in the 3-month follow-up. Hoehn and Yahr stage was associated with large increases in risk in the uncontrolled model which were reduced to borderline non-significance (P=0.051) in the presence of the other variables. The UPDRS was significant in the uncontrolled models, but its explanatory power was largely explained by the other variables. Age and gender had little predictive value, in controlled or uncontrolled models.

Figure 1a-c show the ROC curves for reported number of falls in the previous year, the UPDRS, and the Hoehn and Yahr stage. The curves agree with the results of the logistic regression in showing the superiority of number of previous falls in predicting future falls, both in terms of the area under the curve, and the closeness of the curve to the top left corner of the plot (indicating perfect prediction). The point closest to the top left corner of Figure 1a indicates a sensitivity of 68% and specificity of 81% from predicting future falling based on two or more previous reported falls. The point to the right with increased sensitivity of 77% was obtained by predicting patients to fall if they had one or more previous falls, but this was only achieved at the cost of increasing 1-specificity to 40%. Figure 1d shows the predictive power of a combined score, obtained from logistic regression including the three variables together. The combination was not superior to that from number of previous falls alone, the optimal cut point having sensitivity of 72% and specificity of 79%. Figure 1e shows the ROC curve for UPDRS in the subgroup of patients reporting no falls in the previous year. The curve was close to the diagonal line

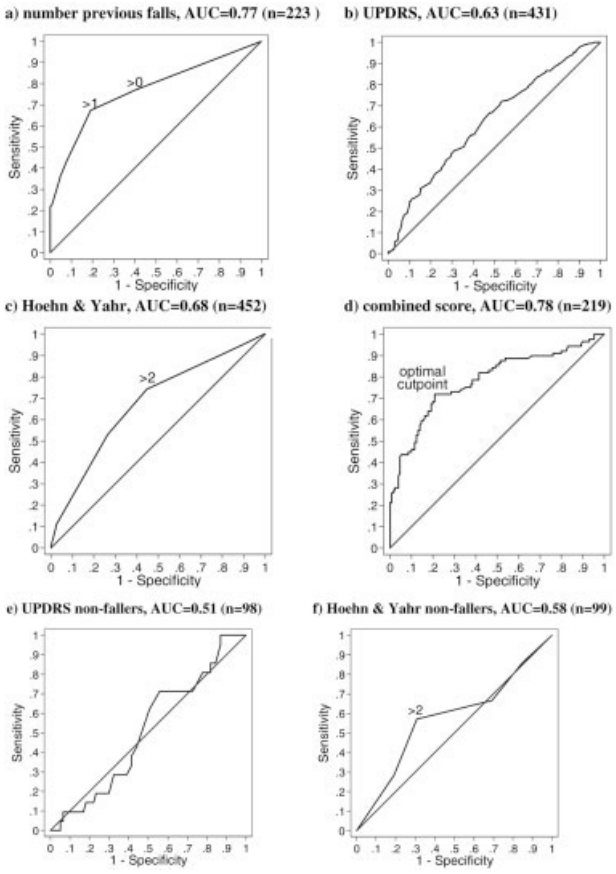

Fig 1 ROC curves for the possible predictors of falling in 3 months: (a-d) all patients; (e-f) patients reporting no falls in the previous year.

of equality (indicating no predictive power) and the AUC statistic was not much greater than 0.50. Finally, Figure 1f shows slightly better predictive power from the Hoehn and Yahr stage in this group.

Table 4 presents the sensitivity and specificity of various potential predictors of subsequent falling. The sensitivity and specificity of previous repeat falling was better in the Southampton study than the others. The accuracy of prediction is acceptable in the North Tyneside study, while in the Leiden study the sensitivity of previous repeat falling is lower. Figures combined over these three studies show only moderately high sensitivity (68%), although specificity was high (81%). Figures from the Ottawa study were based on falling in the previous three months, and higher sensitivity would be anticipated had falls over the previous year been reported. Specificity in the Ottawa study was high (88%), and this would be likely to drop were fall histories over a longer period to be used. A Hoehn and Yahr stage of more than two showed only moderately high sensitivity and

Table 4. Performance of various predictors of falling at 3 months in each study and overall. Figures are number (%).

	Ottawa*		Leiden		Southampton		North Tyneside		Brisbane**		London		Overall	
Predictor	**Sens**	**Spec**	**Sens**	**Spec**	**Sens**	**Spec**	**Sens**	**Spec**	**Sens**	**Spec**	**Sens**	**Spec**	**Sens**	**Spec**
2 or more previous falls	39/70 (56%)	42/48 (88%)	8/21 (38%)	35/38 (92%)	19/22 (86%)	30/35 (86%)	35/49 (71%)	41/58 (72%)	Na	Na	Na	Na	62/92 [a] (68%)	106/131 [a] (81%)
1 or more previous falls	51/70 (73%)	36/48 (75%)	12/21 (57%)	27/38 (71%)	21/22 (95%)	22/35 (63%)	38/49 (78%)	29/58 (50%)	13/23 (57%)	26/29 (90%)	Na	Na	71/92 [a] (77%)	78/131 [a] (60%)
Hoehn and Yahr >2	54/70 (77%)	20/48 (42%)	16/21 (75%)	24/38 (63%)	20/22 (91%)	18/35 (57%)	26/49 (53%)	40/58 (69%)	13/16 (81%)	9/27 (33%)	24/28 (86%)	24/39 (62%)	86/120 (72%)	106/171 (62%)
Optimal cut point for combined score	Na	Na	11/20 (55%)	35/38 (92%)	17/20 (85%)	25/34 (74%)	36/49 (73%)	43/58 (74%)	Na	Na	Na	Na	64/89 (72%)	103/130 (79%)
Fear of falling	Na	Na	14/21 (67%)	25/38 (66%)	12/22 (54%)	28/35 (80%)	Na	Na	Na	Na	22/28 (79%)	22/39 (56%)	48/71 (68%)	75/112 [b] (67%)

* Previous falls and near falls in the Ottawa study over 3 months.

** Previous falls and near falls in the Brisbane study over 6 months, only the presence of falls not the number was available.

[a] Combined over Leiden, Southampton, and North Tyneside.

[b] Combined over Leiden, Southampton and London

specificity. Prediction from the combined score mirrored that from two or more previous falls in the studies separately and combined. Moderately high sensitivity and specificity for fear of falling is also shown.

For the subgroup reporting no falls in the previous year, a reported fear of falling showed only moderate sensitivity (50%) and higher specificity (71%), while sensitivity was somewhat higher (54%) for Hoehn and Yahr stage greater than 2.0, with a specificity of 69%.

Figure 2a shows the relationship between risk of subsequent falling and the UPDRS. The curve starts at low levels of risk for UPDRS close to zero, and then increases to a risk of about 60% chance of falling in 3 months for UPDRS values above 50. The curve shows a tendency for the risk of falling to drop with increasing UPDRS over values of 50, but the observed decrease is slight and is estimated from only few cases. In Table 3 including a quadratic term in UPDRS which would allow the risk of subsequent falling to decrease after an initial rise with UPDRS showed no additional predictive power over the linear

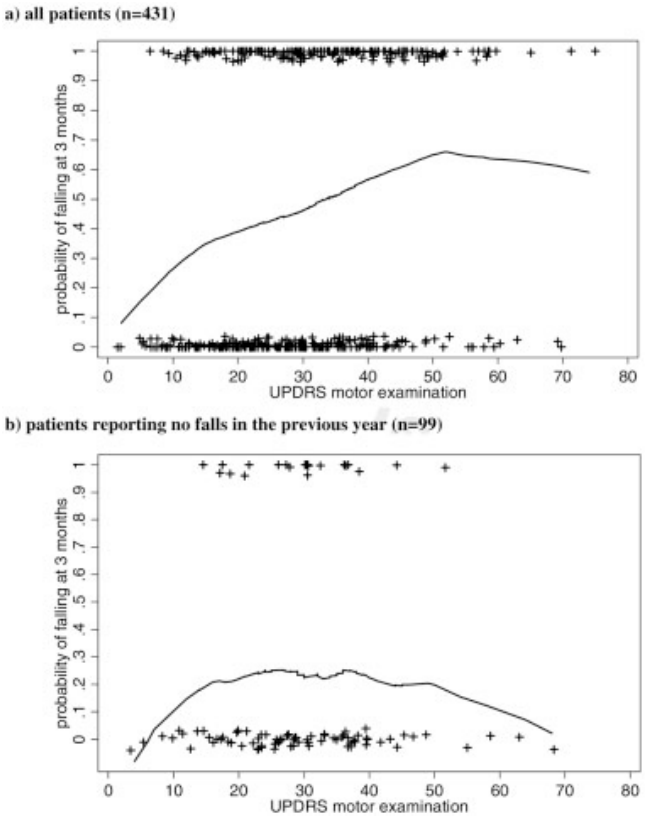

Fig 2 Lowess smoothed curves of risk of faling in 3 months for increasing UPDRS: (a) all patients; (b) patients reporting no falls in the previous year. Points plotted with symbol (+) and subject to jittering.

term (P=0.223) indicating that any decrease at high values of UPDRS is not important in explaining falling. Figure 2b shows the relation between risk of falling and UPDRS for the subgroup reporting no falls in the previous year. The risk of falls is much lower compared to the entire group, and a tendency for risk of falling to decrease with increasing UPDRS over 35 to 40 can be detected.

We also calculated the odds ratios of individual items of the UPDRS as predictors of falling, for the group as a whole (data not shown). Except for resting tremor, all items were associated with risk of falling when controlled only for study. Speech, gait and postural stability were the most important predictors in this analysis, and were the only items that contained independent predictive power after controlling additionally for the other UPDRS items. Within the subgroup of patients reporting no falls in the previous year, none of the items showed significant predictive power (data not shown).

DISCUSSION

The main findings of this meta-analysis were as follows. First, among the total group of patients with PD, we observed a very high rate of falling (46% of subjects) during a relatively brief follow-up of only three months. Injuries were common and occurred in about a quarter of subjects. An interesting new finding was that even subjects reporting no falls in the previous year had a substantial risk of falling during this period (21%). Second, falling was best predicted by the presence of two or more prior falls during the previous year, but even the optimal combination of sensitivity (68%) and specificity (81%) remained less than perfect. Prediction was not improved by the addition of the severity measures UPDRS and Hoehn and Yahr stage. Finally, we identified fear of falling as possible predictors for falls, but this needs to be scrutinized further.

Incidence of falls

Our meta-analysis represents the largest study of falls in PD to date. The observed high rate of falls in the total group confirms the impression gained previously from the contributing individual studies. Fall rates over three months were reasonably consistent across the six studies, despite some methodological differences and possible variation introduced by cultural differences. Injuries were common and occurred in about a quarter of subjects (available from two studies). A third study expressed this differently, and reported that 78% of all individual falls was associated with injuries. A likely explanation is that those persons with injurious falls apparently sustain recurrent injuries. A new and important observation is that even subjects who reported not having fallen in the previous year had a substantial risk of falling during the next three months (21%). Although

this rate is lower than that of the group as a whole, it constitutes an unexpectedly high risk for people reporting not having fallen in the previous year.

Prediction of falls

The best predictor of falls in the next three months was simply asking patients whether they had fallen in the past year. The importance of previous falls in predicting future falling is not unexpected, given earlier observations in elderly persons[23] and in one of the contributing studies in PD.[15] There are a number of issues concerning the practicalities of using reported histories of falls in predicting future falls. First, elderly people tend to forget prior falls[24], or they may have difficulty remembering the timing of previous fall events. It is not unlikely that persons demonstrate inaccuracy in remembering whether events occurred within the specified time window, particularly when these are longer periods of time. But despite these inaccuracies, self-report of prior falls still predicted future falls. We have not attempted to show the predictive power of the "true" number of previous falls, because the accuracy of the reported answer probably depends on how subjects were specifically interviewed. Indeed, methodological differences in ascertaining the fall history may explain some of the observed differences in predictive power across studies included in this meta-analysis.

A second issue is the choice for the cut point. In our meta-analysis, the combined sensitivity and specificity was better using the cut point of two or more falls (sensitivity 68% and specificity 81%) compared to one or more falls (sensitivity 82% and specificity 59%). As expected, when previous falls were ascertained over a shorter period (three months in the Ottawa study[17]), the cut point of two or more falls achieved lower sensitivity. What is judged as the best combination depends on how a test is intended to be used. In order to prevent future falls and potential injuries (assuming there is an effective treatment program), a high sensitivity is required to optimally detect possible candidates for falls. However, this is inevitably achieved at the expense of lower specificity, resulting in higher immediate costs because more persons are falsely identified as fall candidates, so interventions are offered to people who may not fall.

A third important issue is that, by definition, prior falls are unable to predict the very first falls. We repeated the analysis for the subgroup of 100 subjects who reported no falls in the previous year. The results suggested that along with the Hoehn and Yahr stage, asking about fear of falling has some potential to identify these new fallers. Fear of falling had only moderate sensitivity and higher specificity in the reduced group in which the data was available. It may be that "asking is better than measuring", and this may also prove true for other potential predictors, given the lack of validated and reliable clinical tests of balance and gait in PD.[9] Fear of falling can be evaluated using the ABC scale, which has been validated for use in PD[8] and, more recently, also in abbreviated form.[25] One or two of the studies obtained information about prior near-falls, but more work is needed to develop clear definitions and a reliable way of ascertaining near-falls.

Relation with disease severity

Another objective of this meta-analysis was to examine the pattern of increasing risk of falling with disease severity, which in a large retrospective study was related to falls.[26] We addressed this question using the UPDRS motor examination score, because this continuous scale has more potential to show trends than the wider categories of the Hoehn and Yahr scale. In a previous paper[7] the risk was hypothesised to initially increase to a plateau, but to decline thereafter because of compensatory strategies adopted by patients and eventually become effectively zero as severely affected patients became immobilised and therefore no longer at risk of falling. This pattern was not observed as clearly as expected. The risk of falling did indeed increase to a plateau around the 60% chance of falling in three months (for UPDRS values of about 50), but there was only a slight decline in risk of falling observed amongst very few cases thereafter, and inclusion of a quadratic term allowing risk to decline at high severity did not produce significant improvement in the fit of the logistic risk model. The most likely explanation is that the constituent studies recruited patients from the community. Hence, many patients who were "beyond moving" could have moved to a nursing home or other institutional care and were effectively excluded. The drop in risk of falls anticipated at high disease severity might have been observed had institutionalized people been included, or within the context of a long term follow-up study.

We also analyzed the relation between falls and individual items of the UPDRS. Except for tremor, all items were related to falls, the strongest being the scores for gait and speech. In the multiple regression analysis, only speech, and to a marginal level gait and postural stability, had independent predictive power in the presence of the other items. The intuitively more logical items of posture, gait, balance and rising from a chair were not independently associated with falls, possibly because they all act as markers of disease severity and being interrelated did not provide independent predictive power. Another explanation is that current clinical tests for balance and gait are imperfect predictors of falls in everyday life. For example, the retropulsion test is only poorly related to prospectively monitored falls in PD.[7] The relation with speech was unexpected and could well be coincidental, but might also reflect an interdependence between "axial" motor features of PD (which speech and falls both are). Such interdependence has been observed previously, for example in terms of resistance to dopaminergic medication.[27,28]

Shortcomings

This study was not without shortcomings. First, the contributing studies were somewhat heterogeneous in design. We partially accommodated this by restricting the analyses to time frames common to all studies, but this does not deal with differences in fall ascertainment. However, all studies used a reasonable approach to identify faller status. Differences in ascertainment are likely to have introduced a discrepancy in absolute numbers

of reported falls, but we feel confident that all approaches reliably classified subjects as non-faller, single faller or recurrent faller, which was the main outcome measure in this study. Second, baseline assessment included only a limited number of balance tests common to all studies, and it is possible that certain combinations of different gait and balance tests – along with asking for prior falls – may yield a better prediction of future falls.[29] Third, it would have been interesting to look at the influence of polypharmacy. We had to drop this analysis because the methods of recording medications were not consistent across the studies. The issue is also compounded by potential differences in prescribing across countries. Future research should further focus on the effects of drugs, prescribed for either PD or co-morbid conditions, on the risk of falls in PD patients. Finally, it would have been interesting to correlate falls to mental decline (in particular frontal executive dysfunction), given the increasing evidence for links between cognition on the one hand, and gait, balance and falls on the other.[30] However, this analysis was not possible because cognitive status was either not examined or studied using methods that were inconsistent across studies.

CONCLUSION

Our findings suggest that simple clinical measures are insufficient predictors of falling in PD. It proves particularly difficult to identify fallers before they have sustained their very first fall. For these prior nonfallers, asking about fear of falling may have some potential as an early predictor of falling. This will need to be clarified in future large-scale studies among prior non-fallers. Additional work is required to broaden our understanding of the aetiology underlying falling, as this might offer new clues for early detection.

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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 bifold. 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.[17,18,19] Balance confidence was assessed using the Activities-specific Balance Confidence scale.[20] 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. [16,21,22]

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.[23]

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.[9,24,25,26] 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.[27,28] Thesevelocity 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.[17,18,19] 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 symptomswere 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 1. Fall characteristics from 40 falls, as ascertained during the prospective follow-up period with completed fall sheets returned immediately after each fall.

Fall characteristics	Number of falls (percentage)
Site of the fall (more than 1 option possible):	
Familiar environment	37 (92.5 %)
Indoors	23 (57.5 %)
Self-reported cause (most reported):	
Obstacle on the floor	10 (25.0 %)
Slippery or uneven surface	7 (17.5 %)
Preceding dizziness	3 (7.5 %)
Specific fall circumstance (most reported):	
Multitasking	14 (35.0 %)
Climbing stairs	8 (20.0 %)
Consequences of falls:	
No consequences	11 (27.5 %)
Minor injuries	29 (72.5 %)
Major injuries	0 (0 %)

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.

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.

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

†† < 0.01
† < 0.05

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

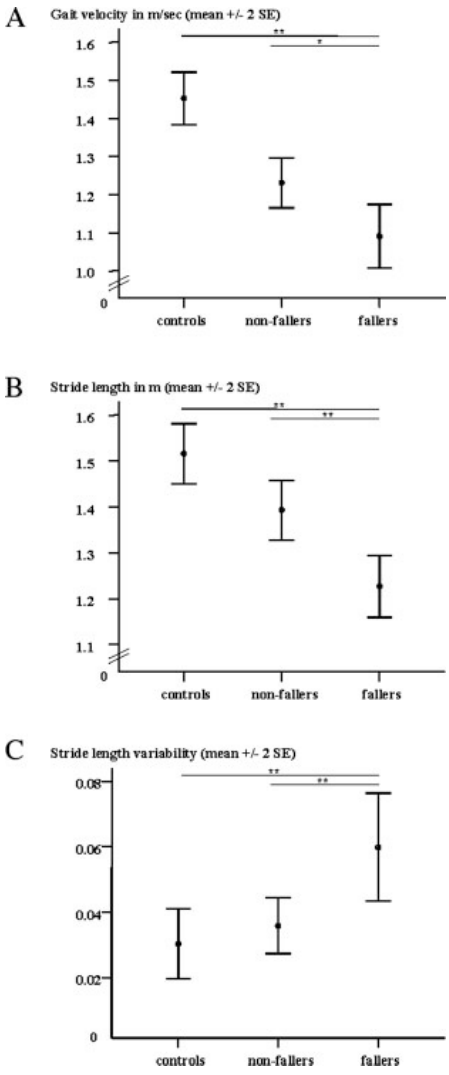

Fig 1 Gait velocity, stride length and stride variability.
*P < 0.05, **P < 0.01.

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.

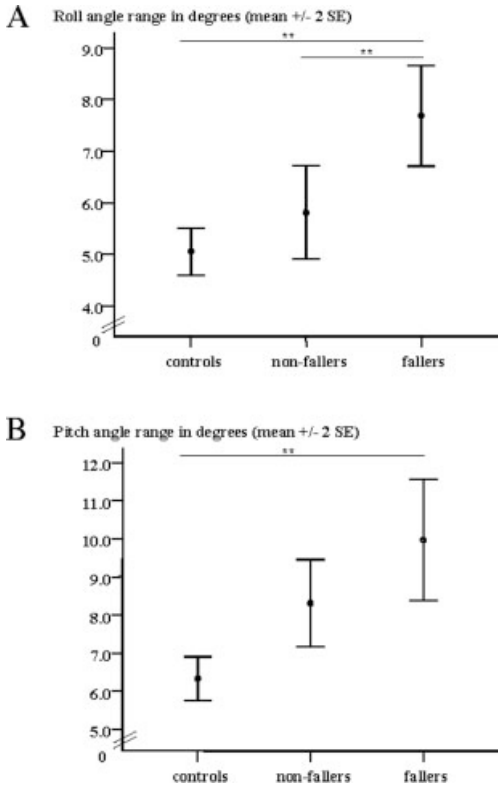

Fig 2 Roll angular range and pitch angular range.
***P <** 0.05, **P < 0.01.

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.[2,5] 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").[29] 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.[17] 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.[5,7] 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.[30,31] 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 ocurred under so-called "multiple task" circumstances. Difficulties handling complex multitask circumstances are particularly prominent among patients with mental decline.[32,33,34,35]

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.[9] Further detailed posturographic or full body kinematic gait analyses remain necessary to fully comprehend the pathophysiology underlying falls in HD.[7,12] 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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Chapter 5

Impact of falls and fear of falling on health-related quality of life in patients with Parkinson's disease

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Submitted

ABSTRACT

Postural instability, recurrent falls and fear of falling are common in advanced Parkinson's disease (PD). We examined the impact of fall frequency, fear of falling, balance confidence and objectively measured balance impairment (using Tinetti's Mobility Index) on health-related quality of life (HrQoL) in PD.

In 74 subjects HrQoL was assessed using the 39-item Parkinson's disease Quality of Life Questionnaire [PDQ-39]. Patients were interviewed using a validated falls questionnaire, addressing fall history, consequences of falls and fear of falling. Neurological examination included Hoehn and Yahr scale, the Unified Parkinson's disease Rating Scale and Tinetti's Mobility Index.

Disease severity, age and gender explained 44% of the differences in HrQoL across patients (R^2=0.44). The combination of these factors and each of the factors fear of falling, balance confidence and falls frequency lead to 55%, 50% and 45% of declared variability, respectively. The standardised regression coefficients of these risk factors were 0.34 (fear of falling), 0.28 (balance confidence) and 0.13 (fall frequency). This suggests that fear of falling is a more important determinant of HrQoL than actual falling. These results emphasise the importance of addressing fear of falling in the clinical management of PD, and the need for development of strategies to reduce fear of falling in intervention programs.

INTRODUCTION

Parkinson's disease (PD) is a progressive and incapacitating disease, affecting many aspects of daily life. As the disease progresses, gait and postural disturbances become more severe and patients start experiencing falls. Postural instability and gait disturbances (PIGD) have been associated with reduced quality of life scores.[1,2] Specifically, freezing of gait has an independent and significant impact on HrQoL in PD patients.[3,4] Freezing also has a negative impact on mobility, is associated with falls and can cause emotional stress in social situations. Falls are associated with injuries, hospital admissions and immobilisation, leading to restrictions of daily activities.[5] Experiencing falls in public can also be embarrassing and lead to social isolation. Not surprisingly, PD patients who experience falls report reduced quality of life scores.[6,7,8,9,10]

Fear of falling is a frequent consequence of previous falls and may lead to further physical inactivity.[11] Furthermore, fear of falling may already develop when patients become more unstable without experiencing actual falls. In elderly women without PD, fear of falling negatively affects HrQoL.[12] A more recent study in PD patients showed that fear of falling plays a significant role in deterioration of HrQoL.[13] However, this study used questionnaires to rate balance and gait and did not assess objective (clinical observed based) measures of balance and gait.

We hypothesised that objective measures of postural instability and gait impairment, fall frequency and fear of falling are all important determinants of HrQoL in PD. To examine this, we investigated the differential impact of falls, fear of falling, balance and gait disturbances on HrQoL in PD.

METHODS

We included consecutive outpatients with PD of Hoehn & Yahr stages II-V. Exclusion criteria were other neurological disorders, psychiatric disorders, disorders which affect balance and severe cognitive impairment (MMSE < 24). Assessment included Hoehn & Yahr staging, UPDRS (motor score), Tinetti's Mobility Index[14], a validated falls questionnaire[11,15,16,17] and the Parkinson's Disease Questionnaire (PDQ-39). Tinetti's Mobility Index is a set of objective tests assessing balance and gait, expressed as a balance and a gait subscore. The balance subscore includes, among others, rising from a chair, balance on standing and on turning. The gait subscore includes, among others, initiation of gait and step symmetry. Maximum scores (indicating worst mobility) are 16 (for the balance subscale) and 12 (for the gait subscale). Tinetti's Mobility index has been validated for use in PD.[18] The standardised falls questionnaire enquired about frequency of falls in the preceding year, fear of falling, circumstances and consequences of previous falls.

Table 1. Characteristics and health-related quality of life scores of the study population.

Clinical characteristics (n=74)	Mean (SD)
Age	64.2 (9.89) (35-81)
Gender (women)	25 (34%)
Disease duration	11.49 (5.4)
H&Y	2.59 (0.94)
UPDRS total score	40.9 (22.7)
Tinetti total score	5.8 (7.6)
Balance subscore	3.5 (4.2)
Gait subscore	2.3 (3.6)
PDQ-39 SI	33.2 (17.3)
Mobility	48.2 (29.1)
ADL	40.5 (29.1)
Emotional well-being	30.0 (20.1)
Stigma	28.1 (23.3)
Social support	11.7 (15.9)
Cognitions	35.9 (24.0)
Communication	31.2 (27.5)
Bodily discomfort	36.3 (19.2)

Falls were defined as 'any unexpected event that caused the person to unintentionally land on any lower surface (object, floor or ground)'.[19] The frequency of falls in the past year was divided into five categories: never; every year or less; every month; every week; wheelchair bound (table 1). The question on fear of falling comprised the answers 'no', 'somewhat' and 'very'. Balance confidence was assessed using the Activities-specific Balance Confidence (ABC) Scale.[20] The PDQ-39[21] comprises 39 questions, subdivided in eight subdimensions (mobility, activities of daily living [ADL], emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort). PDQ-39 summary index (PDQ-SI) and dimensions were calculated according to the scoring algorithm.[21] The maximum score is 100, indicating the worst level of HrQoL.

STATISTICS

First, we carried out univariable linear regression analyses, with dependent variable HrQoL (PDQ-SI). This resulted in standardised regression coefficients for each of potential risk factors fear of falling, balance confidence and fall frequency.

Next we used multivariable linear regression to evaluate to what extent the combination of gender, age, duration of the disease, and UPDRS explained differences in HrQoL between the patients, i.e. we calculated the percentage explained variance (R^2). Additionally, we extended the regression model by including the potential risk factors fear of falling,

balance confidence and fall frequency, both separately and combined. For each analysis, we determined the R^2 and standardized regression coefficients of the risk factors.
Finally, in an additional analysis, we explored the role of Tinetti balance. We repeated the analysis, with the covariables gender, age, duration of the disease and UPDRS, and the potential risk factors Tinetti balance, fear of falling, balance confidence and fall frequency.

RESULTS

Demographics and disease characteristics are shown in Table 1.
In univariable analyses, each of the factors fear of falling, balance confidence and fall frequency were associated with HrQoL (table 2), with standardised coefficients ranging from 0.36 to 0.45 and R^2 ranging from 0.13 to 0.28. However, these associations may (partly) be due to demographic and disease factors. Therefore, we repeated the analyses, adjusted for the variables gender, age, duration of the disease, and UPDRS. First, we investigated to what extent disease factors, on their own, explained differences in HrQoL between the patients and found that a multivariable analysis with the independent variables gender, age, duration of the disease and UPDRS lead to R^2=0.43 Adding the factor fall frequency only marginally increased the R^2 to 0.45, with a standardised coefficient 0.13, indicating that this was not a relevant factor for HrQoL.

Table 2. The relationship between different factors and PDQ39-SI

Model			Standardised coefficients		
Nr.11	Variables in the model	R2	fear of falling	balance confidence	Fall frequency
1	fear of falling	0.21	0.45		
	balance confidence	0.28		0.53	
	fall frequency	0.13			0.36
6	only covariables22	0.43			
7	covariables plus fear of falling	0.55	0.34		
	covariables plus balance confidence	0.50		0.28	
	covariables plus fall frequency	0.45			0.13
8	covariables plus fear of falling and balance confidence	0.56	0.29	0.12	
	covariables plus fear of falling and fall frequency	0.55	0.33		0.05
	covariables plus balance confidencand fall frequency	0.55		0.27	0.10

1 Nr variables in model
2 Gender, age, disease duration, UPDRS

In contrast, a similar analysis with balance confidence and fear of falling as additional factors lead to an R^2 of 0.50 and 0.55, respectively. The standardised coefficients of the two factors were 0.28 and 0.34.

When fall frequency was added to the model that already included fear, the R^2 did not further increase. Hence, fear, and to a less extent balance confidence, seemed to be the major risk factors.

Sex was not a significant factor in any of the above analyses, but age had a p-value below 0.05 in all analyses. Duration of the disease was not significant in the analyses, but it became significant when the factor UPDRS was omitted. UPDRS and duration of the disease were correlated and HrQol seemed more directly related to UPDRS than to disease duration.

In order to explore the contribution of objectively measured balance disturbances the Tinetti balance subscore was separately studied. Adding the Tinetti balance subscore to the co-variables gender, age, disease duration and UPDRS scores lead to R^2=0.44 and a standardized regression coefficient 0.21. The combination of the co-variables and each of the factors. fear of falling, balance confidence and fall frequency resulted in R^2= 0.53, 0.49, 0.43, respectively. These results confirm the earlier finding that fear of falling and balance confidence seem to be the major contributing factors.

DISCUSSION

Frequency of falls, fear of falling, objective (clinically observed) postural impairment and overall disease severity were all associated with reduced HrQoL. However, after accounting for overall disease severity (using the total UPDRS), only fear of falling contributed further to poorer HrQoL, whereas actual falls did not. This confirms the results of an earlier study[13], which also found that fear of falling has a greater impact on HrQoL in PD than the presence of falls or other gait related disorders such as freezing of gait.

Overall disease severity, which includes axial symptoms such as postural instability but also many other aspects of PD, remained the most important determinant of HrQoL. Furthermore, our findings are consistent with previous reports, showing that gender was not significantly associated with worse HrQoL scores.[2,22] However, in contrast to those reports, we found a significant relationship with age and disease duration, although the relation with disease duration lost significance when UPDRS was taken into account and included in the analyses.

We conclude that fear of falling is a significant contributor to low health-related quality of life scores in patients with PD. Fear of falling appears to be a stronger predictor of reduced HrQoL scores than experiencing actual falls or objective clinically based measures of balance impairment. This suggests that in clinical practice, fear of falling should be tackled as a problem in its own right. We therefore recommend that strategies to

improve quality of life in PD should aim not only at the prevention of falling, but also include assessment and treatment to reduce fear of falling, for example using balance training according to evidence-based guidelines.[23]

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Chapter 6

Pathofysiology of falls in Parkinson's disease

Chapter 6.1

Falls in Parkinson's disease

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ABSTRACT

To summarize the latest insights into the clinical significance, assessment, pathophysiology and treatment of falls in Parkinson's disease.

Recent studies have shown that falls are common in Parkinson's disease, even when compared with other fall-prone populations. The clinical impact of falls is considerable, often leading to an incapacitating fear of renewed falls. The associated costs for society are substantial. Clinical assessment often inculdes the retropulsion test, and recent studies have offered practical recommendations regarding the execution and scoring of the test. Insights into the pathophysiology underlying falls are growing and point ot an important role for the loss of inter-segmental flexibility ('stiffness'), which predisposes patients to falls in a backward or medio-lateral direction. New evidence has clarified why Parkinson's disease patients commonly fall during transfers and under 'dual tasking'circumstances. The absence of adequately directed arm movements may explain the relatively high proportion of hip fractures in Parkinson's disease. The importance of freezing of gait as a cause of falls is recognized, and we are beginning to understand the different manifestations of gait freezing. Recent work has defined the contributions of pharmacotherapy, stereotactic neurosurgery,physiotherapy and multidiscliplinary interventions in the treatment of postural instability to prevent falls in Parkinson's disease.

No dramatic breakthroughs have occurred during the review period, but new information in various areas may be useful for practising clinicians. Interesting new questions have been raised theat should fuel studies of pathophysiological meachanisms, which could help in the development of improved treatment strategies to reduce falls in Parkinson's disease.

INTRODUCTION

Recurrent falls have great clinical significance for patients with Parkinson's disease (PD). Proper recognition of falls and knowledge of possible treatment options is important for various reasons. First, falls are common. A review of prospective surveys in PD concluded that almost 70% of patients falls at least once each year.[1] These fall rates are even higher for patients with atypical parkinsonism. Second, falls have an enormous impact on the physical and psychological health of affected individuals, and negatively affect their quality of life.[2,3] Third, the specific nature of falls and the timing of their appearance in the disease process may help clinicians in differentiating PD from atypical parkinsonism. This distinction is clinically relevant, because tailored treatment options are available to reduce falls in different disorders.[4]

This review summarizes progress in the field of falls in PD (Table 1), covering approximately the period between January 2003 and March 2004.For the sake of this review, we will assume a theoretical model in which falls in PD are caused by several independent, albeit often coexistent, mechanisms. These include postural instability (abnormal balance reactions to external perturbations), difficulty with transfers, gait disorders (in

Table 1. Several topics of interest in the recent literature on falls in PD and atypical parkinsonism

Topic of interest
Clinical significance
- Epidemiology
- Fear of falls
- Costs
Pathophysiology
- Posturography
- Proprioceptive deficits
- Freezing of gait
- Transfers
- Dual tasking
- Syncope
Treatment
- Pharmcotherapy
- Stereotactic neurosurgery
- Physiotherapy
- Parkinson nurse
- Multidisciplinary intervention

particular freezing of gait, FOG) and orthostatic syncope. New insights about these different causative factors will be addressed with respect to their assessment, their role in the pathophysiology of falls, and their treatment.

CLINICAL SIGNIFICANCE

The clinical significance of falls for patients with PD is determined by various different factors, including the common occurrence of falls, their association with adverse psychological consequences, and the high costs for society. We will review developments in these areas in the sections below.

Epidemiology

Several prospective studies have clarified the rates and circumstances of falls in PD.[3] The observed fall rates were consistently high and increased with longer duration of follow-up. After one year, about 50% of patients has sustained recurrent (two or more) falls.[5] These fall rates are significantly higher than those observed among community-dwelling elderly individuals.[6] Two recent studies extended these findings and showed that PD is one of the most common neurological disorders leading to recurrent falls.[7,8] One retrospective study documented the causes for falls among inpatients who were newly admitted to a neurological department.[7] In a group of 489 patients, 34 % had sustained falls in the previous year (as verified from self-report). Out of 44 PD patients, 62% had fallen, suggesting that PD was the disorder that was most commonly associated with falls. The other study found that, among individuals with recurrent falls in the previous year, extrapyramidal signs or a diagnosis of PD were risk factors for renewed falls during follow-up.[8] Drawbacks included the short follow-up for some patients (lower limit of only 51 days), the absence of repeated neurological assessments during follow-up (to check for disease progression or appearance of new disorders) and the lack of insight into therapeutic interventions that might have affected the rate of falls.

Fear of falls

An underestimated sequel of falls is a fear of renewed falls. This may lead to self-imposed restriction of daily activities and may therefore cause immobility, which in turn is associated with social isolation, osteoporosis and reduced fitness.[3] Previous studies had merely asked patients whether or not they were afraid to fall; almost 50% answered positively.[6] This issue was further addressed in a survey which reported that PD patients have a significantly reduced balance confidence compared to age-matched controls.[9] Balance confidence – as a surrogate marker for fear of falling – was estimated in detail using the 16-item Activities-specific Balance Confidence (ABC) scale, which had not been used previously in PD. Interestingly, low balance confidence scores correlated with

poorer performance on clinical tests for posture and gait, and also with greater disease severity(assessed using the Unified Parkinson's disease Rating Scale, UPDRS).

Costs

A recent study underscored the impact of falls in PD for the society at large. Analyses of Medicare claims in the United States showed that over a 5-year period, individuals with parkinsonism were 1.3 times more likely to attend a hospital because of injuries than persons without parkinsonism.[10] This study also showed that fall-related injuries, hip fractures in particular, add greatly to the resource use (hospitalisation and skilled nursing facility care) and medical costs in PD.

ASSESSMENT

A proper physical examination is crucial to score the degree of postural instability, to judge the risk of future falls and to rate disease severity. The most widely test documents the postural reactions to an external perturbation, typically a sudden jolt applied to the shoulders (the retropulsion test). Despite its widespread application in everyday practice and in clinical trials, there is no formal agreement regarding the execution and scoring of the retropulsion test. Two recent studies made some practical recommendations. The first evaluated several variants of the retropulsion test with differences in execution and scoring.[11] The most valid test for postural stability in PD was the variant that consists of a single and unexpected shoulder pull (that is, no prior warning or instruction), and where taking two or more corrective steps backwards is abnormal. This variant best discriminated PD patients with and without postural instability. Because there is no gold standard for postural instability, patients were classified as having postural instability if they had two ore more falls or near falls in the previous 6 months, or used walking aids, or used other specific measures to prevent falling. The second study identified several sources of error in executing the retropulsion test.[12] For this purpose, four different raters critically evaluated the videotaped performance of a series of retropulsion tests, delivered by 25 movement disorders specialists. Commonly encountered errors included: tapping or pulling the patient too lightly; not allowing sufficient space to document balance recovery strategies fully; holding the feet too closely together or too widely apart before the perturbation; pulling continuously, rather than suddenly; and allowing patients to brace forward prior to pulling. Unfortunately, judging the videotapes did not permit an analysis of previous instructions given to the patients.

Other common clinical tests in PD include the Functional Reach (ability to reach forward as far as possible, keeping the feet in place) and the Timed Up and Go test. A medication

study of eight patients showed that both tests produced comparable scores on two different days, suggesting good test-retest reliability in this small sample.[13]

Falls in PD occur under a variety of different circumstances, and many different pathophysiological mechanisms contribute to falls. It is therefore unlikely that a single test will be able to predict all fall events. It seems best to use a test battery of different components of posture, balance and gait. Such rating scales are available, but were not specifically developed for use in PD. For example, the Tinetti Mobility Index is used widely in elderly populations, but is not sensitive to changes in gait of patients with PD.[14] A recent study made a welcome attempt to develop a comprehensive clinical gait and balance scale that could be used in PD(although this was not specifically developed for this disorder.[15] The scale included historical information, a physical examination and timed tests. Several items of this scale had moderate interrater reliability and correlated to some extent with quantitative measures of gait (using an electronic walkway that measured spatio-temporal gait parameters) and balance (analysis of weight shifts on a forceplate). However, the scale could be criticized for various reasons: many items had only fair or even poor interrater reliability; the R^2 for the concurrent validity with the quantitative measures was rarely impressive; history taking could be improved, e.g. by using more detailed questionnaires for FOG[16] and by asking about near falls or injuries; the physical examination could be improved, including the retropulsion test; and the inconsistent use of two-point, three-point and four-point scores. Therefore, much work remains necessary to improve this and other rating scales further.

PATHOPHYSIOLOGY

The area in which most progress was reported in recent years was likely the pathophysiology of falls in PD, where new insights were gained with respect to the contribution of (among others) axial stiffness, protective arm movements, central proprioceptive integration deficits and freezing of gait.

Posturography

Clinical observations may generate interesting hypotheses about fall mechanisms, but complementary posturography studies – with standardized postural perturbations and quantitative outcome measures[17], are required to unravel fully the complex pathophysiology underlying falls in PD. This sequence of events is nicely illustrated by recent observations on protective arm movements in PD. For some time, clinicians have had the impression that in PD, wrist fractures may be less common than hip fractures. This suggestion was underscored by the aforementioned study of health costs in PD, which incidentally showed that upper extremity injuries are significantly less common than lower extremity injuries.[10,18] At first sight, this finding is unexpected because pa-

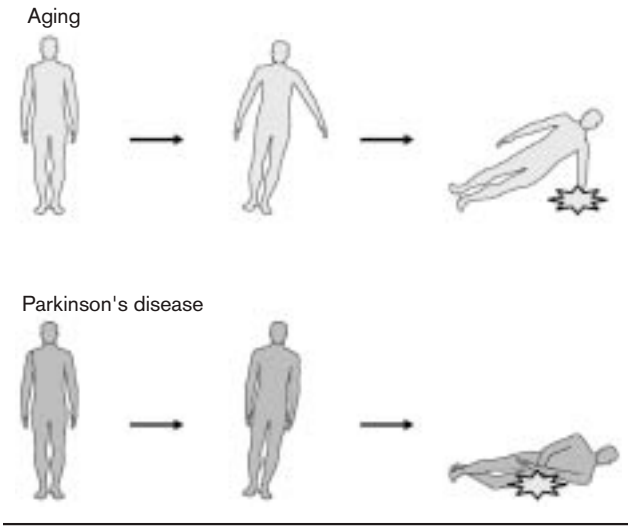


Fig 1 Cartoon illustrating the different fall mechanismes that occur with aging and in Parkinson's disease. (a) Healthy elderly individuals stretch out their arms into the direction of the impending fall [22], and this may contribute to the high incidence of wrist fractures with aging. (b) In contrast, Parkinson's disease patients adduct their arms against the trunk, thereby exposing the unprotected trochanter of the hip.[20] Redrawn from Bloem et al.[18]

tients with PD fall predominantly forwards.[19] Such forward falls are typically associated with wrist factures because individuals land on the outstretched hand. One possible explanation is that arm movements are delayed or abnormally directed in PD. To test this hypothesis, a recent study examined protective arm movements in PD patients who stood on a suddenly rotating platform.[20] Although patients had abnormally early onsets of deltoid muscle responses (documented using surface electromyography), this gave no functional protection because kinematic analyses showed that patients had a decreased arm flexion in the forward-afterward direction, and an increased adduction in the medial-lateral direction. These abnormally directed arm movements kept the patients from grasping for support, and also prevented the arms from performing a "counterbalance" function (keeping the centre of gravity away from the impending fall-direction).[21,22] These abnormally directed arm responses could explain why upper extremity injuries are relatively rare in PD, and could underlie the high incidence of hip fractures because patients fall onto the unprotected trochanter (Figure 1). Absence of adequate arm protection may also explain why fall-related injuries – fractures or soft tissue damage – seem more severe among PD patients compared to other neurological patients.[7]

Three papers described the use of moving platforms that could suddenly move in multiple different directions (multidirectional dynamic posturography) to clarify the pathophysiology of falls in PD. Two of these papers came from a single study that used

horizontal translations in eight directions[23,24]; the other study employed support surface rotations in six directions.[20] Despite differences in nature of the postural perturbations, both studies yielded strikingly similar results. Key findings included: a directional preponderance for falls in a backward and, to a lesser extent, mediolateral direction; presence of co-contraction between agonist and antagonist muscles, both in the legs and trunk; and presence of excessive background muscle activity.

The multidirectional posturography studies also observed a stiffening response in the pelvis, trunk and ankles.[20,23] Another dynamic posturography study found additional evidence for axial stiffness in PD patients who were exposed to relatively slow platform tilts in the sagittal plane.[25] In that study, patients had smaller righting responses of the upper body relative to the lower body, suggesting inter-segmental stiffness. A further study observed trunk stiffness during gait, as reflected by reduced rotation and smaller pitch movements of the trunk.[26] Mechanisms that might contribute to axial stiffness include co-contraction; high background muscle activity; age- or immobility-related changes in elasticity of joints, muscles and ligaments; or fear of falling which may cause active stiffening.[9,24,26] Stiffening has the advantage that fewer degrees of freedom need to be controlled, and that static sway is minimized. However, this "advantage" is offset by the loss of necessary flexible responses that normally dampen external perturbations.[27] This feature has been termed "postural inflexibility" and seems a critical factor in causing falls in PD.

Further evidence for "postural inflexibility" in PD came from a dynamic posturography study where patients were forced to stand with a narrow base of support.[23,24] Compared with controls, patients were less able to increase their balance correcting responses and adapt their reactive postural forces. Interestingly, patients were less unstable when with a wider-than-normal base of support. This observation may offer opportunities for fall prevention using e.g. physiotherapy, because PD patients typically tend to adopt a narrow base of support.

Recent analyses of unperturbed stance ("static posturography") provided additional insights into postural mechanisms in PD. Previous studies of quiet stance had yielded conflicting results, showing either increased or reduced excursions of the centre of foot pressure (CFP) compared with controls. Two studies have now shown that postural tremor is one factor contributing to an increased CFP path.[25,28] Interestingly, antiparkinson treatment further increased the CFP excursions, despite reduced tremor.[25] The presence of dyskinesias offers the simplest explanation for this finding, but a more thought-provoking possibility is that treatment reduced axial stiffness and thus unveiled an underlying problem with regulating quiet stance, perhaps because of a somatosensory integration deficit (discussed in the next paragraph).

Proprioceptive deficits

Postural instability and falls are generally thought to be caused by disturbed motor programming within the basal ganglia. However, this view is increasingly challenged by observations that motor deficits in PD are at least partly caused by proprioceptive disturbances. Afferent information itself is presumably normal, but proprioceptive signals seem abnormally processed within the basal ganglia because of defective higher level integration. So far, such proprioceptive disturbances in PD have mostly been demonstrated for the upper extremities.[29,30] However, proprioceptive disturbances may also contribute to the pathophysiology of postural deficits in PD, in various ways.[31] First, inability to properly process changes in peripheral input could explain the fixed gain of postural responses that underlies the aforementioned postural inflexibility in PD.[20,23] Second, patients might have an abnormally constructed internal map of their stability limits or have lost their normal sense of limb and trunk position. Such "body schema" distortions could explain the difficulties with turning movements and trunk coordination, as mentioned earlier.[20,32,33] Interestingly, the abnormal trunk responses to postural perturbations in PD, as observed in one study[20], resembled the pattern seen in a "deafferented" patient[34], suggesting that PD patients resort to a stiffening strategy to compensate for defective information about body position in space. The mechanisms underlying central proprioceptive integration are unclear, but recent animal work suggested a role for dopaminergic pathways.[35] That study observed that rats with unilateral nigral lesions induced by 6-hydroxydopamine kept their head deviated to the side of the lesion, perhaps due to body orientation problems reminiscent of those seen in PD.

Freezing of gait

Gait impairment and, in particular, FOG episodes are a frequent source of falls in PD.[36] The aforementioned study of falls among neurological inpatients concluded that, within the subgroup of PD, falls were often associated with FOG, and also with turning difficulties.[7] These turning problems are presumably also related to FOG. A recent study confirmed earlier impressions that FOG, at least when present during an "OFF" state – is most commonly elicited by sudden turns.[37] In keeping with this observation, another study showed that PD patients have particular difficulty initiating gait when a step must be directed diagonally, along with turning the trunk into the same direction.[33]

Other studies challenged the belief that FOG is a paroxysmal gait disorder, leading to sudden motor blocks during an otherwise largely preserved gait. Using pressure-sensitive insoles to analyse strides, Hausdorff and colleagues observed that patients with FOG have an increased stride-to-stride variability, even outside episodes with overt FOG.[38,39] This observation fuelled interesting speculations. First, the results suggest that complete motor blocks are only the most extreme form of FOG, and that more subtle disturbances of gait rhythm can be present continuously. In fact, total akinesia is a much

rarer manifestation of FOG than walking with small steps or with the legs trembling in place.[37] Furthermore, the feet oscillate in a fairly organized pattern during FOG episodes with a frequency distinct from normal gait or tremor.[38] This suggests that disruption of one or possibly more central pattern generators is involved in the pathophysiology of FOG. Second, the observations may have clinical relevance, because an increased gait variability is related to historical falls in PD.[40] Whether gait variability also relates to future falls remains to be established.

A preliminary study showed that under everyday circumstances, most PD patients fall predominantly forward.[19] These forward falls might be caused by difficulties with gait termination (sudden cessation of stepping while the trunk still continues to move forward). Attempts of the patients to 'çatch up' with the trunk would then lead to festination or propulsion. Indeed, gait festination was related to historically ascertained falls in one study.[44] Normal gait termination calls for cessation of locomotor activity, as well as activation of braking forces. A study of unexpected gait stops showed that PD patients are able to launch normally shaped stopping strategies, but with undersized muscle responses, leading to weak braking impulses.[42] FOG might also play a role, because this commonly occurs when patients reach a destination.[37]

Transfers

Falls in PD commonly occur when patients make transfers, such as rising from a chair or lying down in bed.[32,43] Better insight is needed to understand why transfers are so problematical in PD. Two studies showed that leg weakness, particularly at the hip, explains at least part of the difficulties experienced by PD patients while attempting to rise from a chair.[44,45] In the light of such findings, one might feel tempted to prescribe strengthening exercises, as these are effective in improvimg balance in PD.[46] However, the efficacy of strength training to improve transfers specifically remains to be demonstrated for PD patients.[47] Alternative strategies to improve transfers are available, including the 'chaining technique': splitting complex movements into a series of simple components that are to be executed sequentially.[48]

Dual tasking

Ever since Lundin-Olsson and colleagues[49] published their seminal paper on the relation between falls and inability to simultaneously walk-and-talk, there has been considerable interest in the nature and clinical relevance of such "dual tasking problems". It was logical to speculate that PD patients would also be vulnerable when one or more tasks have to be performed concurrently with balancing, because the basal ganglia are important for organizing sequential or simultaneous movements. However, cognitively intact PD patients can usually walk and talk at the same time, and inability to do so did not correlate with falls in daily life.[50] A recent study showed that talking while walking also failed to

identify fallers among older persons without overt cognitive impairment.[51] At first sight, this would suggest that dual tasking difficulties are perhaps a better marker for cognitive impairment than for postural instability or falls. Lundin-Olsson et al[49] included mostly individuals with cognitive impairment. However, deleterious effects of secondary tasks on balance could be detected using advanced electrophysiological analysis of postural performance. For example, one study used a static posturography platform to examine the effect of secondary cognitive or motor tasks on reactive forces under the feet.[52] Under dual task conditions, CFP excursions increased disproportionately in PD patients comparedwith controls. Interestingly, this was particularly true for patients with previous falls, suggesting relevance for daily life functioning. Another study showed that gait variability, which is increased in PD and represents a marker for falls in daily life, increases further when PD patients are challenged by a secondary cognitive task.[53]

Syncopal falls

Falls due to a preceding loss of consciousness are deemed rare in PD.[6] When present, such syncopal falls are usually ascribed to the intake of dopaminergic medication, which may cause orthostatic hypotension. Recent work has suggested that orthostatic hypotension can also occur in untreated patients as a result of sympathetic neurocirculatory failure, as reflected by an abnormal blood pressure responses to a Valsalva manoeuvre, by a reduced myocardial dopamine uptake and by reduced plasma norepinephrine levels.[52]. The relation with falls was not investigated, and this should be the subject of future studies. Timely recognition of orthostatic hypotension has clinical relevance, because various therapeutic measures are available to reduce syncopal falls.[55]

TREATMENT

Reducing falls by treating gait and balance impairment is difficult for most PD patients. Recent studies are largely in keeping with this notion, and highlight not only the limited effects of pharmacotherapy and stereotactic neurosurgery, but also point to unexpected effects of alternative treatment strategies such as multidisciplinary teamwork and mobility aids.

Pharmacotherapy

Dopaminergic medication can sometimes reduce falls in PD. A dopa-responsive cause of falling is FOG during "OFF" periods. Levodopa can improve the frequency and duration of FOG episodes during "OFF" periods, and also reduces gait variability.[37,39,40] However, the improvements were partial because stride time variability remained increased in the subgroup of prior fallers.

Most other postural disturbances – including falls – generally do not respond poorly to antiparkinson medication. This notion was corroborated by a small clinical study that examined balance and mobility in moderately affected PD patients before and several times after intake of the first morning dose of antiparkinson medication.[13] There were no fluctuations in gait and balance, which suggests that the underlying pathophysiology involves non-dopaminergic pathways. However, interpretation of this study was complicated by the fact that a manual tapping test, a measure of bradykinesia, also remained unchanged, suggesting that the dose of antiparkinson medication was perhaps insufficient to produce a full "ON" state. Recent posturography studies also underscored that most balance deficits in PD, in particular the postural reactions to support surface perturbations, are largely resistant to dopaminergic therapy.[20,25]

The reasons for the poor effect of dopaminergic medication on balance impairment remain largely unknown, but several explanations are possible. First, postural instability typically appears late in the course of PD. By this time, the dopaminergic deficiency may be so pronounced that pharmacological correction becomes difficult, particularly because adequate dosing is progressively hampered by dose-limiting adverse effects in late-stage PD. Supporting evidence for this explanation was offered by an interesting study of rats with unilateral nigral lesions induced by 6-hydroxy dopamine.[35] The results showed that some postural deficits, including rotational behaviour induced by apomorphine, occurred in animals with moderately severe dopamine loss, but that additional postural deficits only appeared in animals with more severe dopaminergic deficits. This suggests a link between degree of dopamine depletion and balance abnormalities, at least in rodents.

Another explanation is that falls are related to the presence of non-dopaminergic lesions, which typically emerge with advancing disease.[56] One way to 'prove' that non-dopaminergic mechanisms play a role is by showing improvements in postural performance after the administration of drugs that act via non-dopaminergic pathways. This was the topic of two trials. The first was a double-blind and placebo-controlled study of flupirtine, a functional antagonist of N-methyl-D-aspartate (NMDA) with a confirmed influence on automatic postural responses in healthy subjects.[57] A single dose of 50 mg or 100 mg flupirtine failed to improve automatic postural responses to sudden tilts of a supporting platform. Clinical balance scores also remained unchanged, but it is still possible that higher doses or prolonged administration do relieve balance impairment. The second was an open-label study, which showed that intravenous flumazenil, a gamma-aminobutyric acid antagonist, tended to improve the UPDRS scores for posture, balance and gait, and also tended to improve a timed walking test.[58] A placebo effect might have caused the small improvements, and the short half-life makes this drug impractical for

use in clinical practice. The efficacy of non-dopaminergic drugs therefore remains to be demonstrated convincingly.

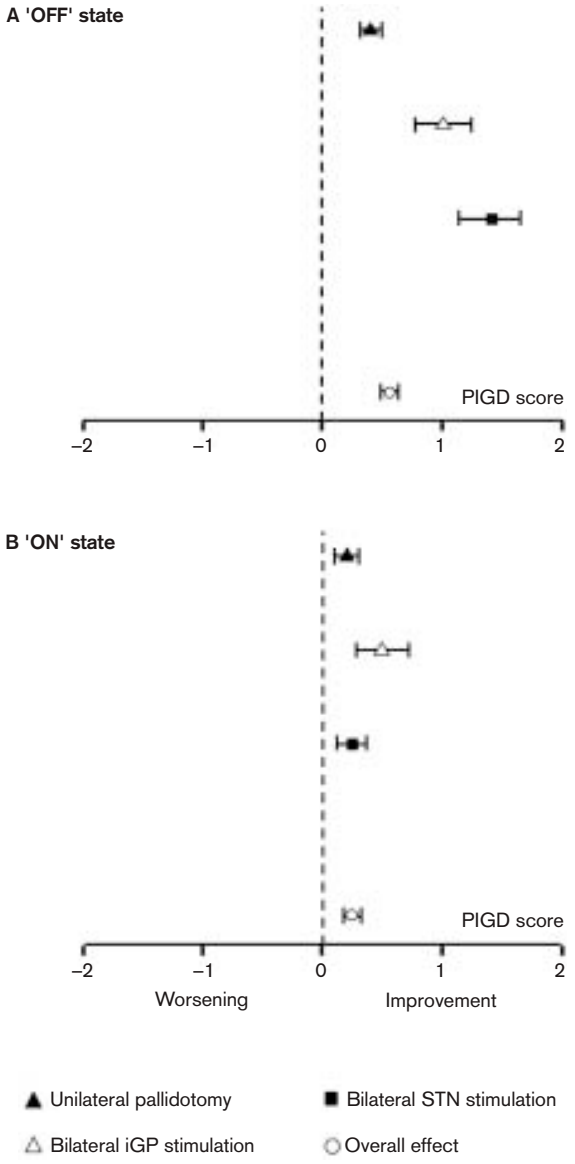
Stereotactic neurosurgery

Stereotactic neurosurgery of the basal ganglia is a therapeutic alternative for patients who respond well to dopaminergic therapy, but suffer from dose-limiting treatment complications. The effects on axial symptoms, including falls, are incompletely understood, except for the fact that thalamic surgery and bilateral pallidotomy (with lesions placed in the internal globus pallidus, GPi) often cause or aggravate balance deficits.[59]

The effects of unilateral pallidotomy were examined in a randomised trial of surgery versus medication.[60] Compared with optimal drug therapy, unilateral pallidotomy significantly improved clinical gait and balance scores after 6 months of follow-up. However, this difference was not sustained after 2 years. Another study showed that unilateral pallidotomy gave no marked improvement of unperturbed stance (measured quantitatively using a static forceplate).[28] A third study showed that unilateral pallidotomy improved the walking speed, but reaching movements, which may be relevant for falls in daily life, responded inconsistently.[61] These results are unimpressive and, along with the contraindication for bilateral surgery (which is presumably required for optimal relief of axial symptoms), suggest that patients with falls are no good candidates for pallidotomy.

Bilateral stimulation of the subthalamic nucleus (STN) may improve gait and elements of postural instability in properly selected patients. A recent paper reported the 5-year follow-up of bilateral STN stimulation in 49 patients.[62] Using the UPDRS as clinical outcome measure, this study showed an improvement of postural stability, gait and FOG during the 'OFF' phase which persisted after 5 years. However, gait and balance during the 'ON' phase deteriorated from the first year onward, perhaps reflecting natural disease progression (but there was no control group without surgery to prove this). Adverse effects on balance and gait were not reported, or could the aggravation of 'ON' state scores be regarded as such? Another comprehensive study, using both static and dynamic posturography, showed that bilateral STN stimulation reduced axial stiffness and postural tremor during unperturbed stance.[25] However, dynamic postural reactions to platform tilts were not improved, and the abnormal response to a moving visual scene improved only partially. Other studies showed that bilateral STN stimulation can improve gait, both clinically (UPDRS scores) and more objectively (kinematics). Improvements were seen for 'traditional' measures such as walking velocity or stride length,[63] and also for abnormal trunk movements during gait.[26] Most studies observed a synergistic effect of STN stimulation with levodopa.[25,26,63] These joint findings are promising, but bilateral STN stimulation remains far from a panacea for all balance problems.

Fig 2 Meta-analysis of published studies, showing the pooled effect and 95% confidence intervals of the Unified Parkinson's disease Rating Scale scores for postural instability and gait disability for three different types of surgery, as well as the overall effect, both in the 'OFF' state and in the 'ON' state (b).



The effect is expressed as the difference score compared with the preoperative state. A positive score indicates improvement; no overlap of the confidence interval with zero indicates a significant effect of surgery. PIGD, Postural instability and gait disability (▲) Unilateral pallidotomy; (■) bilateral nucleus stimulation; Δ bilateral internal globus pallidus stimulation; ○ overall effect.
Redrawn from Bakker et al [59], with permission.

Only few studies have directly compared the different types of deep brain surgery. In a recent randomized trial, bilateral STN stimulation afforded greater symptomatic relief compared to unilateral pallidotomy, but improvements in postural instability or falls were not specified.[59] The incidence of persistent adverse effects on balance appeared roughly equal. Another study compared the effects of bilateral STN stimulation versus bilateral iGP stimulation on unperturbed stance.[64] Significant baseline differences between patients selected for either type of surgery prohibited a detailed face-to-face comparison. Finally, a recent meta-analysis of published trials reviewed the effects of three types of deep brain surgery, unilateral pallidotomy, bilateral iGP stimulation or bilateral STN stimulation, on UPDRS scores for posture, gait, balance and falls.[59] The results showed significant and approximately equal improvements in 'OFF' scores for bilateral stimulation of iGP or STN and, to a lesser extent, for unilateral pallidotomy (Figure 2). Smaller improvements were noted for 'ON' scores.

Physiotherapy

Many PD patients are referred to a physiotherapist for improvement of everyday activities, gait and balance.[65] The effectiveness of physiotherapy was examined in comprehensive meta-analyses.[47,66,67,68] All reviewed studies were hampered by methodological drawbacks, which made it impossible to confirm or deny with certainty whether physiotherapy has therapeutic effects in PD. However, the meta-analyses did note that most reviewed studies showed improvements of gait, everyday activities and quality of life following physiotherapy. Sensory cueing (providing subjects with rhythmic visual, auditory or mental stimuli) seems a promising technique to bypass the defective basal ganglia circuit and thereby reduce FOG in PD.[68] However, such improvements are no guarantee of fewer falls. For example, physiotherapy might render patients more active, thereby increasing their risk of falls. Moreover, it is possible that an increased gait velocity, which is frequently presented as an 'improvement' obtained with physiotherapy, might actually produce a less safe gait pattern. Unfortunately, falls have never been examined as a direct outcome of physiotherapy interventions in PD. As a surrogate outcome measure, a recent studie measured the effect of physiotherapy on balance.[46] Nine patients who completed a balance improvement exercise program were compared with six patients who completed a balance improvement and muscle strengthening programme. Both exercise programs lasted 10 weeks. Balance was examined pre- and post-intervention using a moveable platform. The results demonstrated a significant improvement of balance scores in both groups. However, only the combined intervention group retained the effects after 4 weeks. Regrettably, the number of included patients was low, no control group was examined and the clinical relevance of posturography measures remains questionable. Despite these shortcomings, this study can be regarded as an informative pilot study.

Multidisciplinary team intervention

In general elderly populations, the most consistently successful approach to prevent falls has been multifactorial risk assessment, followed by tailored multidisciplinary interventions to target the identified risk factors.[69,70,71] A similar strategy should be effective in PD, because the multifactorial pathophysiology underlying falls in this disease calls for a multidisciplinary approach. However, the effectiveness of multidisciplinary team intervention in PD remains to be investigated. A large randomized crossover trial recently compared patients and carers who had received multidisciplinary rehabilitation 4 months before assessment with those who had not.[72] The results were striking, showing a trend towards improved mobility (stand-walk-sit test) in treated patients, but this came at the expense of worsened general and mental health, as well as more strain for carers. This unexpected result sends us straight back to the drawing board, where new studies should be designed that focus on the pros and cons of different mulidisciplinary interventions.

Other therapeutic measures

Placing subjects on a rapidly rotating chair might offer a novel approach to treat FOG, and thereby reduce falls.[73] Patients who had been placed on a rotating chair (speed between 4 – 92º/sec) until they felt nauseous showed a more than 50% reduction in FOG in daily life, with a gradual return to baseline over several days. The study had methodological drawbacks (including the open label design), but the time course of the effect seemed real and warrants further studies.

Walking aids are frequently prescribed for unstable patients, but a recent study showed that caution is needed when walkers are given to patients with FOG.[74] Wheeled walkers gave no reduction in FOG, while standard walkers actually increased FOG. The latter are therefore best avoided in patients with FOG.

CONCLUSION

The research that was published in the review period did not produce dramatic breakthroughs in terms of unexpected new insights into the pathophysiology of falls, or a revolutionary treatment strategy that effectively abolished falls. However, useful new information was produced that helped to clarify the epidemiology, clinical significance and pathophysiology of falls in patients with parkinsonism. Existing fall prevention strategies, ranging from pharmacotherapy to individually tailored multidisciplinary programs, have been scrutinized, and the results provide a basis for further refinement of these interventions. Future studies should continue to elucidate fundamental pathophysiological

mechanisms, which could act as starting point for rational development of improved strategies to reduce the debilitating impact of falls in PD.

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Chapter 6.2

"Stops Walking when Talking" Does Not Predict Falls in Parkinson's Disease (letter)

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Ann Neurol. 2000;48: 268 [Letter to the editor]

Evaluating whether persons are unable to walk and talk simultaneously ("stops walking when talking"; SWWT) is a simple test with good predictive value for falls in frail, institutionalized elderly persons.[1] Because it is relevant to know whether this test has similar predictive value in other populations prone to falls, we studied SWWT in Parkinson's disease (PD). Recurrent falls in PD are incapacitating, but their prediction is difficult.[2] Theoretically, SWWT should be sensitive in PD patients who have difficulty performing multiple tasks sequentially or simultaneously.[3] This is also true when walking is one of the tasks.[4]

Thirty-eight patients with idiopathic PD (mean age, 60.1 ±10.8 [SD] years; 34% women; mean Hoehn and Yahr stage, 2.3 ± 0.7 [SD]) and 35 controls (mean age, 58.0 ± 8.9 [SD] years; 74% women) participated. All persons were ambulant community residents without depression or cognitive impairment (MMSE ≥ 24). SWWT consisted of a conversation during a standardized 150-meter walk (positive result if persons stopped walking for ≥ 3 seconds). Because we wanted the conversation to be cognitively challenging, the investigator (Y.A.M.G.) consistently used open (rather than closed) questions regarding details of the medical history and recent changes in medication. Such items are also emotionally important for most persons. Persons were followed up prospectively for 6 months, using standardized scoring forms to document all falls. Persons were also contacted by telephone every 2 weeks to ensure that all falls were documented. Recurrent (two or more) or injurious fallers were used as outcome measure. Fourteen of the PD patients (36.8%) reported 119 falls. Five of the controls (14.3%) reported a total of 7 falls. SWWT was abnormal in only 4 patients and in none of the controls. The reverse (stops talking while walking) never occurred. SWWT was positive in 2 patients that were fallers and in 2 patients who did not fall. Comparing fallers with nonfallers within the PD group, SWWT had a poor sensitivity (14.3%; 2/14), although the specificity was adequate (91.7%; 22/24). Pooling patients and controls improved the specificity (96.3%; 52/54) at the expense of the sensitivity (10.5%; 2/19). SWWT was an unexpectedly poor predictor of falls in PD. In fact, although many patients fell, the test was only rarely abnormal. Hence, even if SWWT had greater discriminative power, most falls would not have been predicted. In contrast, many frail elderly persons cannot walk and talk simultaneously [1], and this inability predicted falls much better than in PD. Differences in test execution are unlikely to underlie the discrepancy, although the nature of the conversation while walking was not specified in the original report of Lundin-Olsson and colleagues.[1] The key difference is that many persons in the earlier study [1] were demented or depressed, whereas we excluded patients with cognitive impairment. This suggests that impaired dual-task performance is a better marker of falls associated with cognitive impairment than (extrapyramidal) motor impairment. In addition, age differences may partially explain our observations (including those in controls), because all persons in our study were considerably younger than those studied by Lundin-Olsson and co-workers (mean age, 80.1 years).[1] We did confirm the high specificity of SWWT. Yet, even a normal test result has little value because SWWT

was normal in 17 subjects who were fallers. Finally, the low sensitivity obviously restricts the ability to identify eligible candidates for therapeutic intervention.
We conclude that SWWT does not predict falls when cognition is preserved. The results of ongoing studies (www. carestudy.com/falls/intro.htm)[5] should further delineate the clinical use of SWWT.

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Chapter 6.3

The 'posture second' strategy: a review of wrong priorities in Parkinson's disease

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ABSTRACT

Falls are common in Parkinson's disease. It remains difficult to predict these falls, presumably because clinical balance tests assess single components of postural control, whereas everyday fall mechanisms are typically more complicated. A substantial proportionof everyday falls appears to occur while Parkinson patients attempt to perform multiple tasks at the same time. Furthermore, little attention is generally paid to the possible contribution of cognitive impairments to falls. The importance of mental dysfunction is supported by the fact that cognitive loading while walking or balancing can lead to marked deteriorations in postural performance, and there is some evidence to suggest that such "dual tasking" is particularly difficult for elderly persons with dementia or depression. We examined what strategies Parkinson patients used when a basic walking task became increasingly challenging by adding additional tasks (both motor and cognitive). Most patients could perform a simple "dual task" test: simultaneously walking and answering simple questions. However, as the walking task became more complex, patients' performance began to deteriorate. Interestingly, this was reflected not only by failure to answer questions, but also by an increasing number of blocks in motor performance (walking and balancing). This behaviour was different from that of both young and elderly controls, who appeared to sacrifice performance on the cognitive task in order to optimise their gait and balance ("posture first" strategy). Preliminary evidence suggest that impaired multiple task performance is associated with a two-fold increased risk of sustaining falls in daily life. We conclude that Parkinson patients are less inclined than healthy persons to maintain a safe gait. Instead, Parkinson patients use a "posture second" strategy and treat all elements of a complex task with equal priority, which in daily life may go at the expense of maintaining balance and lead to falls.

INTRODUCTION

Life is about priority, evident even in mundane tasks such as driving a car and using a mobile phone at the same time. Most people can achieve this during regular driving, but the conversation is likely to cease temporarily when a busy crossing is approaching. This "secondary task" (or dual task, as it is more commonly termed) interference is at play during everyday tasks, including seemingly simple acts such as walking. In the field of balance and gait research, perhaps one of the most influential publications of the last decade was the description of the "stops walking while talking" (SWWT) test by Lundin-Olsson and colleagues[1]: an inability to walk and talk at the same time had a good predictive value for the occurrence of falls in the next six months. This observation was made in a mixed group of elderly persons, may of whom were depressed, had dementia of both. Apparently, the two concurrent tasks of walking and talking competed within the central nervous system. The inference was that those unable to talk while walking had a restricted central processing capacity, permitting them to do only one task at a time to avoid a system overload. The restricted central processing capacity could also explain the association between ' stops walking when talking' and dementia or depression;whether depression or dementia itself is in any way causally related to dual tasking limitations has never been demonstrated. Another consequence of this finding – with a potentially far-reaching implication – was that gait was not a simple automatic task that is governed solely by subcortical structures, but in fact represents a much more complicated job requiring conscious attention and perhaps some ongoing cognitive processing.

The Lundin-Olsson paper left many questions unanswered. For example, it is theoretically possible that some persons purposely stopped walking while talking, simply because they considered this to be unsafe. If so, then such people who stop walking while talking should perhaps have the lowest risk of falling, not the highest, because they opted for a safe behaviour. Clearly, this was not true for the group as a whole, where the overall riskwas increased, but individual, within the group may have chosen different strategies. In other words, dual tasking difficulties may well be solved in different ways by different populations, depending on such factors as age, disease status, or prior experience. This would set limitations to the generalisation of dual tasking problems. Also, some may have stopped walking while talking out of politeness to face the person you are talking to, which in effect deprives the person of visual feedback of the gait trajectory? This by itself may be enough reason for persons who rely heavily upon visual feedback to stop walking. And what about the nature of the secondary task, which was actually poorly defined in the original description as "maintaining a routine conversation"? Might a more complex and more demanding secondary task be able to predict falls even better? Is the dual task interference restricted to "cognitive" secondary tasks, or is a secondary "motor" task also able to jam the system? And, finally, what about dual task problems in patients

with neurodegenerative diseases characterised by cognitive decline, restricted central processing capacities, or frequent falls?

Because of these many unanswered questions and the potentially important implications, the "SWWT principle" was widely followed and extrapolated to a host of other tasks – including balancing and a range of other secondary or even tertiary tasks – and to a range of pathological conditions, including e.g. Alzheimer's disease,[2,3] Parkinson's disease (PD),[4,5,6] stroke,[7] vestibular disorders[8] and peripheral neuropathy.[9] Adverse effects on balance were noted not only for secondary tasks with cognitive loading, but also for types of secondary tasks that either stressed the motor systems or called for attention. For example, difficulty with carrying a glass of water while walking can also predict falls in the elderly.[10] Here, we will briefly review our own work in this field, which mainly concentrated on patients with PD, with some extensions to the ageing processes. The results provided some new insights into the mechanisms underlying "failure" to execute multiple tasks simultaneously – and in particular on the role of priority processes.

PARKINSON'S DISEASE

Background

Falls are very common in patients with PD. Depending on the duration of follow-up and the method of falls ascertainment, prospective studies identified an incidence of persons with at least one fall from 39 to 68%, and from 25 to 50% for recurrent (twice or more) fallers.[11,12,13,14] The impact of these falls is considerable, due not only to the associated injuries, but also because of the secondary immobilisation caused by a fear of renewed falls.[13,15,16] Prevention of these falls is important. Several strategies may be effective.[17,18] To implement prevention programs, fallers must be identified in an early stage, but this remains difficult in PD patients, presumably because most clinical balance tests merely assess single components of postural control, whereas everyday fall mechanisms are typically complicated. Indeed, in daily life, almost half of all falls occur while PD patients attempt to perform multiple tasks at the same time, for example carrying an object while walking.[19] Furthermore, falls in PD patients are probably the net result of a complex and multifactorial pathophysiology, with contributions of multiple "intrinsic" (patient-related) and "extrinsic" (environmental) factors.[20] Very few tests are specifically designed to measure this multifactorial character of postural instability.

In light of the Lundin-Olsson publication, we reasoned that a simultaneous challenge of posture and cognition might predict falls better than tests of isolated components of postural control. Multiple task performance may be particularly informative in PD patients because studies on arm motor control suggest that they cannot execute simultaneous or sequential tasks adequately.[21] In addition, experienced clinicians noted that PD patients

may have difficulty with a second task while walking.[22] Finally, PD patients can improve their motor performance (including balance and gait) by using external cues or by focusing attention on the task at hand, allowing the frontal cortex to compensate for the defective basal ganglia circuitry.[23,24,25] These "conscious" motor strategies could make PD patients vulnerable during performance of secondary tasks that distract their attention.

Dual task impairment

With these ideas in mind, various groups studied the influence of secondary tasks on gait or balance in patients with PD (summarised in Table 1). Although no two studies were the same, the general picture that clearly emerges from this work is that both gait and balance can deteriorate when a secondary task needs to be performed simultaneously. This was true both when the secondary task was cognitively demanding (e.g. mental arithmetic) or when it required a motor skill, such as carrying an empty or a loaded tray. For the "motor" tasks, additional factors may have played a role, including the need to pay attention to the task or – in the case of carrying a tray – visual deprivation of the gait trajectory and the subjects' own feet. As expected, patients appeared to have extra difficulties when the secondary task was more demanding.[4,32] A recent paper drew attention to extra variables that need to be accommodated in the overall equation when interpreting why patients have difficulty performing multiple tasks at the same time.[32] This study not only evaluated the influence of secondary motor and/or cognitive tasks on gait, but also analysed the contribution of common clinical symptoms to the disturbance of gait. The results showed that dual task problems are related not only to cognitive dysfunction and disequilibrium, but also – at least in part – to symptoms such as fatigue and depression.

We also studied the influence of secondary tasks on gait and balance. We initially began with applying the simple "SWWT" test to patients with PD.[27] In that study, we included 38 patients with idiopathic PD and 35 controls who were all ambulant community residents without depression or cognitive impairment (MMSE ^{3}24). SWWT consisted of a conversation during a standardised 150-meter walk, and we arbitrarily scored a positive result if persons stopped walking for ^{3}3 s. Persons were also followed prospectively for six months, using standardised scoring forms to document all falls. To our initial surprise, SWWT occurred in only four patients, and in none of the controls. More importantly, SWWT did not predict falls in PD, as the SWWT was positive in two patients that were fallers and in two patients who did not fall. These results were confirmed when we extended the original group to 59 patients and 55 controls in a subsequent study.[13] What could be the explanation for this striking discrepancy between our findings and those of Lundin-Olsson and colleagues?[1] Setting aside possible small methodological differences, the key difference resided in the degree of cognitive co-morbidity. Indeed, many persons in the Lundin-Olsson study were demented or depressed, whereas we excluded patients with cognitive impairment. This suggests that impaired dual task performance is perhaps a

Table 1. Summary of published research studies that focused on the influence of secondary tasks on gait or balance in patients with Parkinson's disease.

Reference	Subjects	Primary task	Secondary task	Outcome measures	Results in PD patients
Bond 2000 [4]	12 PD patients 12 controls	walking	1. carry empty tray 2. carry loaded tray	force-sensitive insoles	- problems only in condition 2. - decreased walking speed - reduced stride length
Hausdorff 2003 [6]	10 PD patients	walking	serially subtracting 7's	force-sensitive insoles	- increased stride time - increased stride variability
Ashburn 2001 [5]	48 PD patients (29 fallers)	quiet standing	colour judgment of playing cards	postural sway	- increased sway in fallers
Bloem 2000 [27]	38 PD patients (15 fallers) 35 controls	walking	talking (routine conversation)	stops walking (clinical judgement)	- no difference with controls - no prediction of falls
Camicioli 1998 [26]	19 PD patients (10 with freezing) 19 controls	walking	verbal fluency task	clinical judgement of step number	- increased step number, only in patients with freezing
Rochester 2004 [32]	18 PD patients 15 controls	walking	1. carrying loaded tray 2. answering simple questions 3. combination of 1+2	five accelerometers attached to legs and trunk	- problems greatest for condition 2. and 3. - decreased walking speed - reduced step length - relation to cognition, fatigue and depression
O 'Shea 2002 [30]	15 PD patients 15 controls	walking	1. manual dexterity task 2. serially subtracting 3's	force-sensitive insoles	- effect equal for both conditions - decreased walking cadence
Marchese 2003 [31]	24 PD patients (8 fallers) 20 controls	quiet standing	1. serially subtracting 3's 2. manual dexterity task	static forceplate	- effect equal for both conditions - increased sway amplitude
Bloem 2001 [29]	20 PD patients 20 elderly controls 50 young controls	walking	Multiple tasks, among others: 1.avoiding objects 2. carry empty tray 3. carry loaded tray 4. answering questions	clinical judgment of hesitation or block in performance	- more often motor errors - no "posture first" strategy
Morris 2000 [28]	30 PD patients (15 fallers) 15 controls	1.quiet standing (various foot positions) 2.internal perturbations 3.external perturbations	reciting days of the week backwards	clinical judgment of performance	- deterioration under dual-task conditions comparable to controls

The final column summarises the main effect of the secondary task(s) on the primary task (maintaining balance or walking), as observed within the patient group relative to controls. The effects of secondary tasks on performance within the control group are not indicated separately.

better marker of falls associated with cognitive impairment than (extrapyramidal) motor impairment.

Some additional insights into dual task performance came from subsequent efforts. In one study, we administered the original SWWT to 17 institutionalised elderly persons (mean age 86.3 years, range 79 to 93 years).[33] In addition, we asked the subjects to walk two trials of 8 m each. During the first 8 m trial, no question was asked (control trial). During the second 8 m trial, subjects had to answer a simple question ("What is your age?") after 2 m of walking. During both trials, we measured not only the simple trial duration, but we also quantified the amplitude of trunk sway and the angular velocity in the forward-backward (pitch) and side-to-side (roll) directions using a trunk sway measuring device – containing two orthogonally mounted and highly sensitive angular velocity sensors[34,35] – that was strapped firmly to the lower back (Swaystar system). Four of the 17 persons (29%) stopped walking while talking during the SWWT as originallydescribed by Lundin-Olsson (i.e. during a routine conversation while walking in the corridor). This percentage quite similar to the 21% reported by Lundin-Olsson et al.[1] However, when subjects were required to answer a simple question during a short (8 m) walking trajectory, eight persons (47%) stopped walking while answering the question. This may have been caused by the greater "urge" to provide the answer because the short trajectory afforded only little time to respond, unlike the SWWT that was applied during a longer walk (several hundred meters). In addition, we suspect that the brief test may also have caused greater problems because we used a sudden question, unlike the more predictable routine conversation during the SWWT. Elderly persons may well have greater problems with such sudden and unexpected events than with more predictable routines. Unexpected interruption of gait by an abrupt question might mimic an event leading to a fall more effectively than a predictable conversation during a longer walk. These results suggest that a shorter and much simpler version of the SWWT (asking a single question during an 8 m walk) may provide a fast and perhaps more effective method of identifying subjects with impaired dual task performance, classified as "stoppers", with less space requirements.

In the same study[33], we also observed that persons who stopped during the 8 m trial with a question had significantly longer walking durations and, more interestingly, a larger trunk roll angular displacement. This was evident not only during the dual task trial, but also during the control trial without a question. This indicates that the "stoppers" had more lateral instability – perhaps an index of a heightened risk to fall sideways – even at a time when they did not come to a full stop. This was not apparent to the naked clinical eye, but was only unveiled by quantitative measurement of trunk movements using the angular velocity sensors. These results suggest that persons with impaired dual task performance have a poorer dynamic control of trunk roll. Other studies also used more sensitive quantitative outcome measures to document the effects of secondary tasks on the quality of gait or balance (see Table 1). For example, Hausdorff et al.[6] used

pressure-sensitive insoles to quantify strides, and observed an increase in stride variability in patients with PD who were subjected to a cognitively challenging task. Future studies should clarify whether such quantitative electrophysiological measures of gait or trunk movement also have the ability to predict actual falls in daily life.

In another study we determined the predictive value of dual tasking on falls in the general population of oldest old (a cohort of 509 individuals, all aged 85 years).36 There were no selection criteria on health, and about 30% of subjects were demented (MMSE <24), while some 20% were depressed. In this cohort, we measured the walking time over a 12-meter distance as well as verbal fluency to recite names of animals or professions during a 30 seconds period. In the dual task, we assessed performance when participants combined walking with reciting names. The incidence of prior falls was assessed by interviewing the participants and checking their medical history. We found that no less than 45 percent of our participants stopped walking during talking. The results also showed that dual task performance was related to prior falls, but – again to our surprise – it was in fact not a better predictor for incident falls than single task performance (simple walking time). This difference in results with prior studies[1,10,37] can be explained by differences in methods. Instead of a straightforward walk from one place to another, we asked our participants to walk back and forth along a 3-meter line. Consequently, participants had to make three 180-degree turns, what may have added considerable difficulty to the walking task. This could partially explain why so many persons stopped walking while talking in this study. Increased difficulty of the single walking task could also explain why the dual task provided little additional predictive information.

Such findings suggest that the very nature of the primary – and likely also the secondary – tasks may affect the overall predictive ability of the combined test. Indeed, such observations led to speculation that combinations of multiple motor tasks (e.g. walking plus carrying an object) may better probe areas of the central nervous system that are involved in motor or, even better, postural control than secondary mental tasks.[10,13] It may also be possible to further increase the sensitivity of detecting balance difficulties by combining more or other simultaneous tasks to enhance overall task complexity. Indeed, strictly dual task designs do not always distinguish well between patients and controls, over and above any baseline differences between these groups.[27,28] As mentioned earlier, evidence is now beginning to emerge that more demanding secondary tasks (or a more unpractised "primary" postural task) may be needed to fully bring out the balance deficits, not only in elderly subjects[38,39,40], but also in patients with PD.[4,32]

Multiple task impairment

We have explored this concept further in two studies in which we developed a true multiple task design. We speculated that combinations of various motor tasks would be particularly useful for patients without cognitive impairment, because their falls

are not well predicted by combining a single motor task with a mental task.[27] We further reasoned that falls in daily life would be predicted best by tests that represent complex everyday situations.[41] We also argued that falls would be predicted best by tests that truly challenge postural safety. Finally, we wanted to develop a balance test that would potentially be easy to apply in a consulting room by clinicians. To develop this "multiple task test" (MTT), we first identified relevant risk factors for falls (from a literature review) and actual fall circumstances (from a prospective survey of falls in PD).[42] The factors identified from this review were "translated" into functional tests (or postural "components") that resembled everyday situations. We distinguished a "cognitive" component (answering a series of relatively simple questions regarding everyday situations, in order to provide a continuous and verifiable cognitive load) from largely "motor" components (standing up, sitting down, turning around, walking, avoiding obstacles, and touching the floor). Four additional components included carrying an empty or loaded tray, wearing shoes with slippery soles and reduced illumination. These components were combined to yield eight separate tasks of increasing complexity that had to be executed sequentially. The first and simplest task consisted of standing up, undisturbed walking, turning around and sitting down. For each of the next tasks, a new component was added to the previous and otherwise identical task. All components within each task had to be performed simultaneously. The MTT thus contained all desirable ingredients for an optimal multiple task design: perceptual manipulations (reduced illumination), cognitive manipulations (answering the questions), motor manipulations (e.g. turning) and mechanical manipulations (e.g. avoiding obstacles).[41] Unlike some other studies[43], we urged subjects only once (at the beginning of the experiment) to not purposely prioritise any given component. If this instruction is continuously repeated, one might theoretically obscure any tendency to 'disobey' the initial instruction and to lend priority to what subjects perceive as the primary task (e.g. maintaining balance). The study of such priority strategies was a main goal of our study. Impaired multiple task performance can be reflected by slowing[3,10,37] or a complete stop[1,44] in executing one or more components. Therefore, errors in performance for all tasks were scored as follows: rapid performance of all components within the task ("Normal"); obvious slowing in one or more components within the task ("Hesitation"); complete stop or inability to perform one or more components within the task ("Block"). Hesitations and Blocks were analysed separately, and also combined as Errors. The scoring was simply done through clinical inspection, without complex electrophysiological instrumentation. Errors were scored separately for execution of the motor and cognitive components.

The MTT was first administered to 50 young healthy subjects and 13 elderly subjects.[42] All subjects completed the MTT without falling. In both age groups, 62% of subjects performed all eight tasks without any Errors in the motor components (Figure 1A). Among those making Errors, the proportion of subjects that made motor Errors increased significantly as the tasks became more complex. More elderly subjects produced motor

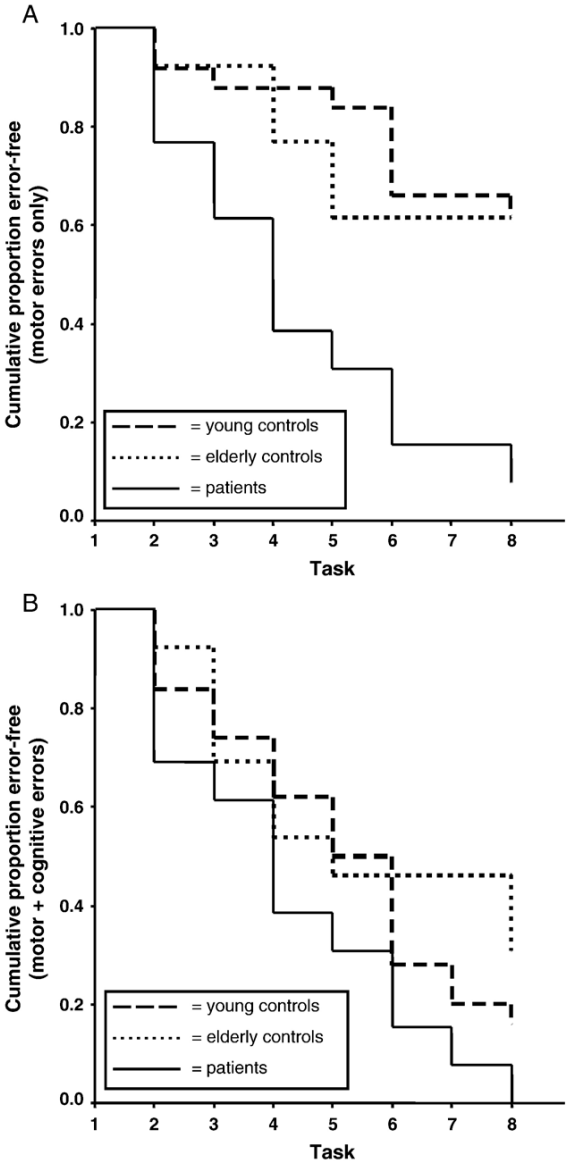

Fig 1 A. Kaplan- Meier curves for the cumulative proportion of subjects with a completely Error-free performance for all motor components within each respective task of the MTT. Subjects who made an Error (Hesitation or Block) for at least one motor component (answering serial questions) were ignored for this analysis. Only 7.7% of the patients had an Error-free performance, as oppposed to 62.0% in both control groups ($p < 0.0001$). B. Kaplan-Meier curves for the cumulative proportion of subjects with a completely Error-free performance for all component (both motor and cognitive) within each respective task of the MTT. Subjects who made an Error for at least one component of any given task were excluded from the following tasks. 16% of the young controls, 30.8% of the elderly controls and none of the patients completed the test without any Errors (no significant difference).

Errors during the most complex tasks. Cognitive Errors increased even more than motor Errors with task complexity. Interestingly, this increase was most pronounced in young subjects, who apparently postponed answering until the motor components had been completed safely. This suggests that for complex postural tasks, healthy subjects favour execution of motor components over execution of a cognitive component. The results thus provided some interesting insights into normal coping strategies with increasingly complex postural tasks. On the one hand, we found evidence that impaired multiple task performance may reflect a limited processing capacity. Indeed, most of our healthy subjects were able to integrate fairly complex postural tasks without errors, although errors inevitably appeared during the most complex tasks. On the other hand, it also seemed that during extremely complex tasks, healthy subjects lent priority to complete certain task components at the expense of others. In other words, their "blockades" should perhaps not necessarily be regarded as a marker of postural instability or pathologically impaired central processing capacity, but rather as a form of "prudent" behaviour intended to optimise the primary task (maintaining balance). This strategy had been observed previously by others and is termed "posture first".[3,39,41,43,45] It is indeed a safe postural strategy to favour maintaining balance (the "primary" task) over execution of e.g. a manual or mental secondary task. Apparently, young subjects are more inclined than elderly subjects to use this "posture first" strategy, and may therefore be better able to avoid falls.

In the second study[29], we studied if performance on the MTT could discriminate between healthy subjects and PD patients. We were particularly interested to study the strategies for increasingly complex postural tasks in PD. Theoretically, patients might reveal various abnormalities. One possibility is that patients use intended "priority processes", much like the young subjects described above. Due to their underlying balance impairment and restricted central processing resources, patients would need to prioritise (and thus make "errors") during less complex tasks than healthy subjects. Patients and controls would thus show a resemblance, albeit at differing task difficulties. This phenomenon indeed occurs in healthy subjects who show Parkinson-like impairments on cognitive tasks if sufficiently distracted by demanding secondary tasks.[46] Alternatively, patients may have lost the ability to lend priority to complete particular components of a complex task. If this were true, performance of the postural task would deteriorate by a challenge to multiple components of postural control. Patients might even be expected to fall, while attempting to continuously perform all components of the task.

We addressed these questions by administering the MTT to 20 non-demented PD patients, and compared their performance to that of the previously tested controls.[29] Significantly more patients produced Errors than young and elderly controls, and only 8% of the patients completed all tasks without any motor Errors (Figure 1A). Patients particularly produced more motor Errors than controls during the most complex tasks. Interestingly, this difference between patients and controls disappeared if the cognitive

component was also scored, because more controls made cognitive Errors during complex tasks than patients (Figure 1B). Patients apparently gave less priority to execution of the motor components. Patients thus seemed less able than controls to employ a "posture first" strategy, but instead attempted to perform all tasks simultaneously. However, due to their balance impairment and restricted processing resources, neither motor nor cognitive components were executed very successfully. This might be interpreted as a form of "risky" behaviour that might lead to falls in daily life. In fact, one patient actually had an imminent fall during the eighth task that was prevented by the examiner. The clinical relevance of our findings is further underscored by the fact that more than half of our patients reported difficulties with simultaneous tasks in daily life, including simultaneous motor tasks, such as carrying a tray while walking. Many patients described falls during situations that resembled the most complex tasks of the MTT.

In a subsequent follow-up study, we examined the predictive value of the MTT by asking the 20 PD patients and 20 matched controls to prospectively monitor their falls in daily life for 6 months using standardised diaries (Bloem & Munneke, unpublished observations). Because of the relatively small sample size, we have pooled the data of patients and controls. At least one motor Error was made by 21 of the 40 subjects. Only three out of the 19 subjects who produced no motor Errors during the MTT fell during the 6-month follow-up, while seven out of the 21 subjects with ≥1 motor Error fell during the same time period (Relative Risk [95 % confidence interval] = 2.1 [0.63 – 7.01]). Although the confidence interval was wide due to the small sample size and limited number of incident falls, these preliminary findings do suggest that impaired performance on the MTT was associated with a two-fold increase in the risk of falling. Furthermore, it is interesting to note that only 10 out of the 21 falls in the Lundin-Olsson study[1] were identified by the SWTT, whereas seven out the 10 falls in our study were identified by the MTT. This may reflect a good sensitivity for the MTT, which could be useful for a screening device to pre-select candidates for more detailed evaluations. Larger studies are now underway to fully examine the predictive abilities of the MTT.

GETTING THE PRIORITIES ENTIRELY WRONG

We have suggested that young healthy subjects are well able to cope with complex situations by adopting "safe" strategies (prioritising balance over other concurrent tasks), and that such behaviour is less often seen in elderly persons and, in particular, in patients with PD. Interestingly, however, even young healthy subjects may occasionally get their priorities wrong. In a nicely designed study, Bhateni et al.[47] suddenly perturbed upright standing young persons who held a cane (or, in some trials, merely a useless top handle portion of a cane) in their hand. Instead of optimally using their arms to grab a nearby

handrail for support, the subjects tended to cling onto the cane, even when it had no stabilizing value (holding a cane during backward falls) or any intrinsic value whatsoever (carrying a canetop). These findings could have important implications for understanding the mechanisms leading to falls in persons using assistive devices.

There may be subgroups of patients who get their priorities wrong altogether. In PD, many patients are afraid to fall[13,15,16], and this fear of falling may well prevent them from engaging in potentially hazardous activities. The flip side of the coin is that patients with excessive fear may suffer from unnecessary immobilisation.[13] Conversely, patients who are overly confident (possibly due to coexistent cognitive deficits and lack of insight) are at increased risk of sustaining falls and injuries. Some preliminary evidence suggests that this may occur in patients with PD[48], and such patients may be particularly at risk of falls due to their hazardous behaviour.

Such apparent lack of insight is encountered more commonly in patients with progressive supranuclear palsy (PSP), characterised by atypical parkinsonism, supranuclear vertical gaze palsy, pseudobulbar palsy and dementia. Development of postural instability and recurrent falls occur early in the course of the disease.[49,59] We recently determined the frequency and characteristics of falls among 117 patients with PSP, using a detailed questionnaire and a 3-month prospective follow-up.[51] At least one fall had occurred since disease onset in 97% of PSP patients, while daily falls were present in 23% of patients who were still mobile. Injuries were also much more common than in PD, not only because postural instability was more severe, but also owing to "motor recklessness": many patients with PSP move abruptly and seem unable to properly judge the risk of their actions. There was no evidence for an overall lack of insight because balance confidence was markedly reduced in PSP patients (mean score of 17.6, on a visual analogue scale of 0-100, with 0 being worst performance). The key problem seems to be impulsiveness, leading patients to respond immediately to external stimuli in a direct "stimulus-response" type behaviour. This impulsiveness or recklessness is presumably related to the pronounced frontal atrophy in PSP.[52] Medical treatment often proves difficult, and strict supervision of activities is typically a mainstay of treatment in this disorder.

Patients with Alzheimer's disease (AD) may be another example of a group who fall because of bad judgement. Their rates of falls and injuries are also high[53,54], despite much less impaired motor function, at least in the early stages of AD. This discrepancy between relatively mild motor problems and frequent falls suggests that falling is possibly related in part to behavioural problems in AD, such as lack of insight or wandering behaviour. A relation with cognitive problems is further suported by studies demonstrating that dual tasking has a profound influence on balance and gait.[2,3,55]

IMPLICATIONS FOR TREATMENT

Recognition of dual tasking limitations and their impact on the risk of falls may have treatment implications. It is conceivable that safer dual tasking strategies can be trained by physiotherapists, for example by instructing patients to avoid secondary tasks during complex walking or balancing activities.[56] Another possibility is the use of cognitive rehabilitation.[57] Such treatment possibilities and their effect on everyday performance have thus far not been investigated, and this could be a fruitful subject for future research.

CONCLUSIONS

Evidence is beginning to accumulate that healthy subjects may correctly perceive the difficulty of multiple task performance, and purposely lend priority to execution of one part of a complex task, at the expense of other elements. Which particular type of strategy is chosen may depend on the preference of individual subjects. Some persons will adapt their behaviour by decreasing the walking speed and thus avoid the risk of a fall. Others may lend priority to the walking task at the expense of the other concurrent tasks, an approach referred to as the "posture first" strategy. This strategy is typically implemented by young persons, but less often by elderly persons. Still others may favour the mental task or entirely fail to lend priority to any particular task, but they could pay the price by an increased instability or even a fall. This latter mechanism seems to play a role in patients with PD, and is seen in an extreme form in patients with PSP whose tendency to fall is aggravated by motor recklessness. The opposing effect of these different "strategies" obscures simple interpretation of dual or multiple task performance, and underscores the importance of accommodating the adopted strategy when using dual tasking as a predictor of falls. Another factor that needs to be taken into account is the nature of the secondary tasks. A simple dual task design with a combination of motor and cognitive tasks is perhaps sufficient to detect abnormalities in patients with mainly *cognitive* decline. For these populations, even measurements of simple walking time may suffice, perhaps supplemented with additional quantitative measures of trunk sway or changes in stride. However, more complex tasks such as the MTT (which consists mainly of multiple motor components plus a cognitive component) may be more informative for subjects with mainly *motor* disabilities, such as PD patients. Finally, preliminary evidence suggests that multiple task performance is perhaps best probed using a sudden and unexpected insertion of a secondary task, rather than a more continuous and predictable dual loading.

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Chapter 7

Gait, postural instability, and freezing

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INTRODUCTION

A chapter on gait and balance impairment is inevitable in this book on non-motor and non-dopaminergic features of Parkinson's disease (PD), for several reasons. First, even though gait impairment and postural instability (jointly referred to in this chapter as "axial motor disability") are traditionally regarded as "motor" features of PD, evidence is accumulating that our ability to walk or maintain balance are, at least in part, also governed by cognitive processes. For example, many PD patients find it difficult to walk and talk at the same time, and when they nevertheless try to combine these two seemingly easily tasks, a fall is often the result.[1] Also, the appearance of axial motor disability typically coincides with cognitive decline, as becomes obvious in patients with the so-called PIGD (postural instability and gait disability) subtype of PD.[2,3,4] This co-occurrence could be a chance finding, simply reflecting the more widespread disease pathology in this subtype of PD. But an interesting alternative explanation is that patients may only begin to fall when they fail to consciously compensate for their axial motor deficits. In its most striking form, this is seen in patients with progressive supranuclear palsy (PSP) who have an unusually high risk of falling, not only because their balance is so poor, but also because they fail to adjust their behaviour due to lack of insight – a feature sometimes referred to as "motor recklessness".[5] Taken together, these observations suggest that difficulties with gait or balance are perhaps more "non-motor" than one might have initially thought.

Second, axial disability can rightly be included among the non-dopaminergic features of PD. Gait impairment and postural instability are typically "late" features of PD, appearing at a time when the disease extends well beyond the dopaminergic substantia nigra.[6,7] Several observations support a non-dopaminergic basis for axial motor disability in PD. Axial motor features are typicaly indequately controlled with dopaminergic medication.[8,9,10] This is particularly the case for postural instability and, to a lesser extent, also for gait abnormalities. Indeed, most falls in PD occur when patients are in their ON state.[11] Such clinical observations have been tested with dynamic posturography: evaluating balance quantitatively while upright standing subjects are perturbed by sudden movements of a support surface.[12] The results suggest that several balance problems (mainly the reactive automatic postural responses) in PD are not primarily dopamine-dependent.[10,13,14,15] In fact, dopaminergic medication can paradoxically increase the frequency of falls by inducing ON period freezing, or orthostatic hypotension leading to syncopal falls, or violent dyskinesias that can literally throw the patients off their feet.[16,17,18,19]

Third, neuropathological and biochemical studies suggest that non-dopaminergic lesions emerge at about the same time when gait and balance problems develop.[20] Specifically, post-mortem brain studies in patients with gait and balance impairment demonstrate substantial cell loss within the locus coeruleus, particularly the caudal part

that projects mainly to the spinal cord and cerebellum.[21,22] Consistent with this cell loss in the locus coeruleus, CSF analyses and post-mortem brain studies have shown reduced norepinephrine levels in PD. Further, there is a relation between the reduced concentration of norepinephrine and the severity of gait and postural disturbances, and levels of norepinephrine are significantly reduced in PD patients with freezing of gait.[23] Gait impairment, especially freezing (and possibly also balance abnormalities) may further be linked to dysfunction of the mixed cholinergic-glutamatergic pedunculopontine nucleus (PPN) in the dorsal brainstem.[24,25,26] The PPN normally governs step initiation and step maintenance. PPN dysfunction is caused partially by excessive inhibition from the internal globus pallidus and substantia nigra pars reticulata. In addition, cell loss occurs within the cholinergic portion of the PPN, and this neurodegeneration likely further aggravates the gait problems.[26]

Observations in patients with atypical parkinsonism provide a final argument to support a non-dopaminergic basis for axial motor disability in PD. Generally, gait and balance problems emerge earlier and are more prominent in patients with atypical parkinsonism; this includes patients with progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), dementia with Lewy bodies (DLB) and vascular parkinsonism.[5,27,28] These atypical parkinsonian syndromes are all typically characterised by more widespread pathology compared to PD, including abundant extranigral and non-dopaminergic lesions.

This is not to say, of course, that gait and balance problems can be ascribed entirely to the presence of non-dopaminergic lesions. For many patients, dopamine replacement therapy can provide a partial benefit, particularly in early stages of the disease, and more so for gait than posture or balance. The bradykinetic gait in early disease stages – characterized by a reduced walking velocity and small, shuffling steps – usually improves with dopaminergic treatment. And freezing of gait – which usually appears later in the course of the disease – will also improve in most patients when dopaminergic therapy is started or augmented.[17,29] Freezing may become more resistant in later stages of the disease, but the issue here may be related to inadequate dosing: because of adverse effects of treatment such as response fluctuations or hallucinations. Indeed, it has been our clinical impression that the threshold to obtain a therapeutic response may be higher for freezing compared to other motor signs (Figure 1) This could partially explain the presence of ON period freezing of gait: at certain doses most motor signs will have improved, but freezing persists, falsely creating the impression that medication actually induced the freezing symptoms. A link to dopaminergic lesions was recently made in a large prospective aging study, were during post-mortem examination of brains of 50 subjects without PD detected an association between cell loss in the dorsolateral quadrant of the substantia nigra and UPDRS scores for postural instability, stooped posture and gait disturbances.[30]

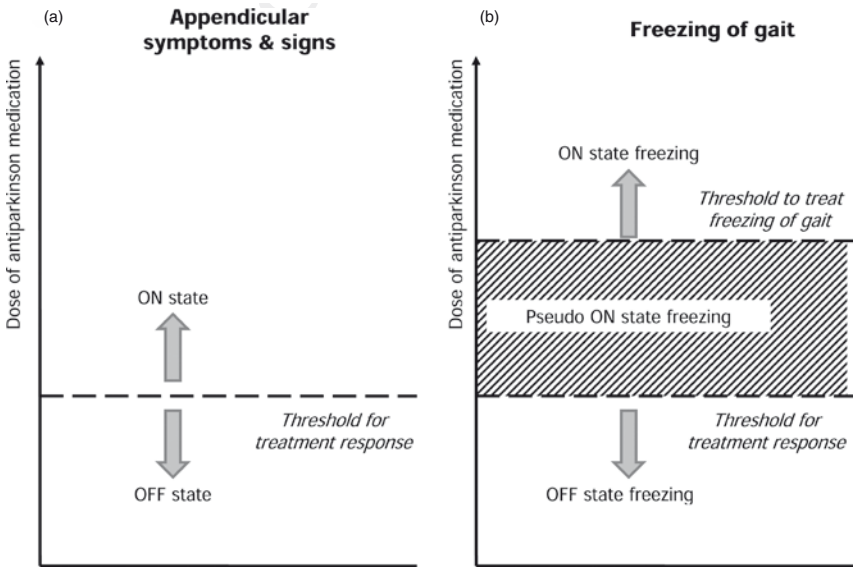

Fig 1 Treatment of freezing of gait, in relation to other motor symptoms and signs. The threshold for symptoms and signs to improve may be lower for appendicular manifestations of PD (a), compared with the threshold for freezing of gait to improve (b). This creates an intermediate level, occurring at doses where patients generally appear to respond well to medication, but nevertheless experience freezing of gait. Although counterintuitive, we recommend first increasing the dose of anti-parkinson medication in these patients, provided that they do not experience dose-limiting side effects. If freezing improves, the patient actually has "pseudo ON" freezing. If freezing worsens, the patient has true ON period freezing, and the dose should be reduced.

The most devastating consequence of gait and balance impairment is falling. In this chapter, we summarize the dominant clinical features of axial motor disability in PD, provide a pathophysiological framework for falls in PD, and consider how to develop an individually tailored and multifactorial falls prevention program. We propose a battery of measures that are based on published observations in PD, personal experience and knowledge obtained with falls prevention in the elderly. The protocol proposed here may serve both as a guide for current clinical use, and also as a basis for future formal evaluation in adequately designed randomised clinical trials.

CLINICAL ASSESSMENT OF BALANCE AND GAIT

Importance

Careful recognition of gait and balance abnormalities is crucial, for several reasons (Table 1). First, axial features can often assist clinicians in refining their differential diagnosis in patients presenting with a hypokinetic-rigid syndrome. It is not rare for the specific gait or balance features to provide the clue to the diagnosis. Examples include the occurrence

of seemingly spontaneous backward falls in the first year of the disease – suggesting a diagnosis of PSP – or the presence of dominant lower-body parkinsonism with early and levodopa-resistant freezing of gait – suggesting a diagnosis of vascular parkinsonism.

Second, as indicated earlier, careful clinical assessment provides the basis for subsequent treatment, aimed at improving gait and balance, reducing or preventing falls, and minimizing their consequences. Indeed, falls in PD often have devastating consequences, leading to a poor overall prognosis. Hip fractures appear in about 25% of patients within 10 years after the diagnosis[31] and are associated with high morbidity, admission to nursing home, and mortality.[32,33,34] Fractures of the wrist seem less common, perhaps because the hands are not stretched out fast enough after a fall.[35] "Minor" injuries such as bruises

Table 1 Importance of gait and balance assessment in clinical practice

Importance of gait and balance assessment in clinical practice
Support for the differential diagnosis
Basis for individually tailored treatment
Prevention of complications
– Falls
– Injuries
– Constipation
– Pressure sores
– Insomnia
– Osteoporosis
– Physical inactivity
– Loss of independence
– Social isolation
– Fear of falling
– Reduced quality-of-life
– Caregiver stress
Marker of poor prognosis/greater disease severity and associated symptoms
– Depression
– Anxiety
– Rapid disease progression
– Urinary incontinence
– Cognitive decline
– Nursing home admission
– Reduced survival
Marker for underlying abnormalities
– Frontal executive deficits
– Underlying cerebrovascular disease
Socio-economic impact
– Loss of productivity
– Costs related to injuries

or lacerations are even more common than fractures. Furthermore, reduced mobility is associated with other incapacitating complications, including constipation, pressure sores, insomnia and osteoporosis, which in turn increases the fracture risk. Immobility also deprives patients of their independence and social contacts. These problems are aggravated by a commonly present and incapacitating fear of renewed falls.[11] When this fear of falling becomes excessive, patients become unnecessarily immobilized, with great consequences for their social interactions as well as their physical fitness.

Third, the presence of gait and balance abnormalities can serve as a marker for other signs that are perhaps less obvious during routine clinical examination, such as frontal executive deficits[36,37,38,39] or underlying cerebrovascular disease.[40] This will be discussed in more detail in the section on clinical manifestations.

Fourth, gait and balance abnormalities have considerable prognostic importance. In a large group of 362 patients who were originally enrolled as part of the DATATOP study and who were carefully followed for disease progression, the level of gait dysfunction did not predict future changes in health-related quality of life.[41] However, worsening gait and balance over time were accompanied by worsening mental as well as physical health-related quality of life, underscoring the need to preserve balance in order to prevent a worsening of health-related quality of life. Furthermore, a prior fall remains the best predictor of future falls[42] , and postural instability and falls are associated with a reduced survival.[27,43,44] This increased mortality is explained by the occurrence of lethal falls and by secondary immobilization, which reduces general fitness and increases the risk of cardiovascular disease. Importantly, the disease also progresses at a faster rate once falls are present.[28]

And finally, gait and balance abnormalities have implications for society at large. Falls and fall-related injuries are extremely costly and contribute to the overall costs of PD.[45,46] Falls are also a major reason for caregiver stress[47,48] , and health care costs rise considerably when the caregiver support collapses.

In the light of these considerations, it should be appreciated that the clinical examination of parkinsonian patients is incomplete without a proper gait and balance assessment. Whenever possible, patients should be examined during both the OFF state (preferably following withdrawal of antiparkinson medication for at least 12 hours) and the subjective "best ON" state. It is recommended to have a sufficiently large examination room, or else to take the patients to the corridor to examine their gait. At the same time, gait and balance need to be challenged using a series of specific tests, in order to bring about the full range of abnormalities. Note that performance is usually much better in the hospital, where lighting is optimal and gait is rarely complicated by obstacles in the pathway. Hospital examination is also obscured by a phenomenon termed "kinesia paradoxica", namely the ability of poorly mobile patients with advanced disease to move unexpectedly well under emotional circumstances sometimes (which a doctor's visit). In contrast, at home patients are more at ease, and they need to walk in crowded living rooms (forc-

ing them to make narrow turns), with poor lighting or loose rugs on the floor. Some of these domestic factors can be copied in the examination room, for example by forcing patients to turn around in tight quarters to provoke freezing.[49] Nevertheless it is often very informative when a physiotherapist or occupational therapist pays a home visit and to witness the patients' performance in their own habitat.

Gait

For most patients, walking already changes can already be detected in early stages of the disease, and can even be the presenting symptom, for example an asymmetrically reduced or absent arm swing.[50] Other early features include difficulties turning around in a standing or recumbent position. As the disease progresses, gait becomes slower and the typical parkinsonian gait emerges with shuffling and short steps, a bilaterally reduced arm swing and slow turns which are executed *en bloc*. In contrast to most other gait disorders, gait is typically not wide-based.[51] Presence of a broad-based gait generally suggests presence of atypical parkinsonism. A simple test is asking patients to take 10 consecutive tandem steps; patients with idiopathic PD can usually perform this without dfficulty, even when moderately severely affected.[52] Hence, taking even a single corrective side step is suggestive for atypical parkinsonism, particularly in early stages of the disease. Note that patients may compensate for their "automatic" gait problems by paying conscious attention to the act of walking. Distraction or asking the patient to perform a double or secondary task (answering questions, carrying an object) interferes with this compensatory strategy and often aggravates the gait disorder, causing patients to slow down or completely stop walking.

Freezing of gait

The features described above represent a form of "continuous" gait abnormality: they are more or less consistently present. In addition, PD patients can also experience "episodic" gait disorders, that is, walking problems that are only irregularly present, intermingled with periods when gait is much better.[53] The prime example of these episodic gait disorders is freezing of gait, when patients experience sudden and usually brief moments where the feet subjectively become "glued to the floor".[17] For practical purposes, freezing of gait was recently defined as "a brief episode during which patients find it impossible to generate effective forward stepping movements, in the absence of another cause than parkinsonism or higher cortical deficits".[54] The prevalence of freezing increases with disease duration and progression of disease severity, although it can be present in early stages of PD, and occasionally even at disease onset. However, early freezing episodes should generally alert the clinician to the presence of a form of atypical parkinsonism, or a disorder called primary progressive freezing of gait.[55] In patients with PD, freezing is more common after prolonged dopaminergic treatment, but this does not necessarily implicate that the drugs are causally related to freezing (because more severe symptoms

also require more medication). Indeed, freezing can occur in drug-naïve patients, and most forms of freezing in PD improve with dopaminergic medication. Note that freezing is also common in other parkisnonian disorders (e.g. PSP, MSA, vascular parkinsonism and normal pressure hydrocephalus).[56,57] However, freezing is rare in drug-induced parkinsonism.

Freezing most commonly appears while patients are making turns, in particular narrow turns in tight quarters. Other circumstances that commonly provoke freezing include negotiating a narrow passage such as a door, trying to initiate gait ("start hesitation"), executing a double task (such as talking while walking) or upon reaching a target. It is less common for freezing to occur during straight, undisturbed walking. Although the name perhaps suggest otherwise, freezing is usually not a complete "immobile" blockade of walking movements (complete akinesia), but is a much more dynamic phenomenon. The most common presentation is with shuffling small steps, or a characteristic "trembling" of the legs, with the frozen foot in plantar flexion and the forefoot stuck to the floor.[58] Freezing of just one leg may occur, particularly while turning. Most freezing episodes are brief, usually lasting only several seconds or less, although in more advanced stages of the disease freezing may persist for minutes. Freezing episodes are also much briefer during the ON phase, compared to the OFF phase.

Detection of freezing often depends on a careful history taking, with detailed enquiry about the feeling of being glued, and attention to the provoking circumstances. It can be difficult to assess freezing reliably during physical examination, because the anxiety associated with the doctor's visit may suppress the phenomenon. A freezing of gait questionnaire has been developed for this purpose. There is now an updated version where patients and their immediate carers are shown video clips of characteristic freezing events, in order to facilitate recognition of the phenomenon.[59] This updated questionnaire also addresses the impact of freezing on daily life, for example fear of falling.

Physical examination should include a dedicated "freezing of gait trajectory" that features specific triggers to elicit freezing: gait initiation; undisturbed walking in an open space; and walking under challenging situations (crossing a door or other narrow space, turning around, negotiating obstacles and performing a dual task) (Figure 2). Interestingly, many patients only experience freezing during full turns (360 to 540º) and not during partial turns (180º), so a standardized gait trajectory should include full turns (in both directions, because freezing often shows a directional sensitivity, being much worse and sometimes even exclusively present for turns in one direction). In addition to such attempts to *provoke* freezing, it is also useful to evaluate the response to external cues. This may have diagnostic importance, because freezing will improve in PD patients, but generally not in patients with higher-level gait disorders.[53] Evaluating the effect of cues may also help to determine possible therapeutic interventions. Finally, various quantitative gait assessments have been proposed, but these methods do not yet have a proven value for clinical practice.

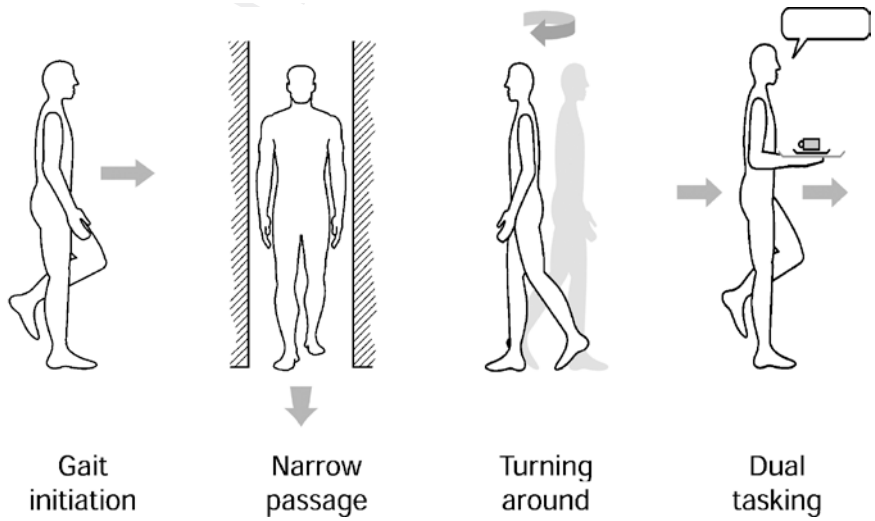

Fig 2 Essential elements of a dedicated "freezing of gait trajectory". Reproduced from Snijders et al[49] with permission from John Wiley & Sons, Inc.

Postural abnormalities

Changes in posture can provide important diagnostic information. A gently stooped posture can be seen in early stages of PD, and this becomes more pronounced in later stages of the disease, usually with some lateral leaning of the trunk. However, severe and persistent lateroflexion – the so-called "Pisa syndrome" or pleurothotonus – often (but not always) suggests neuroleptic-induced dystonia, MSA or post-encephalitic parkinsonism.[60,61,62] Camptocormia refers to a marked anteflexion of the thoracolumbar spine between 30 to 90 degrees, but without forward flexion of the neck.[63] This can occur in both PD (where it may occasionally improve with dopaminergic medication or deep brain surgery) and forms of atypical parkinsonism. Camptocormia is apparent on standing, worsens while walking, but decreases while sitting and even disappears when patients are lying down. This latter feature separates camptocormia from the fixed kyphoscoliosis seen in patients with degenerative changes of the spine. An extreme degree of antecollis relative to other body parts, with the neck held in a relatively fixed and severely flexed position, or when the chin touches the chest, is unusual and suggests a diagnosis of MSA.[64,65] Antecollis develops in about half of pathologically proven MSA patients, usually in the middle or late stages of the disease.[65] In contrast, retroflexion of the neck (retrocollis) suggests a diagnosis of PSP, but this is usually not an early feature.[66] In PSP axial rigidity of the neck is higher than in the trunk, whereas the opposite pattern occurs in PD.[67]

Balance impairment

Postural stability is preserved early in the course of PD, and falls never occur at onset or within the first two years of the disease in pathologically confirmed cases of idiopathic PD.[28] Balance impairment gradually develops as the disease progresses[68], appearing later (and in less prominent form) in patients with the tremor-dominant type of PD. Being unable to stand on one leg, for example while getting dressed, is often one of the earliest signs of postural instability.

A battery of clinical tests is needed to capture the complex nature of balance problems in patients with basal ganglia disorders. Functional "everyday" tests should be performed whenever possible. These include rising from a chair, sitting down and getting in and out of a bed. It is particularly important to test the so-called defensive balance reactions, which are evoked by imminent falls. Examples include the ability to take corrective steps or to make protective arm movements (to grasp for support, or to cushion the impact of an impending fall). Evaluation of these defensive reactions is often difficult in a clinical setting because patients must be brought close to (or even beyond) their limits of stability. Quantified assessment following standardized balance perturbations – using dynamic posturography – is perhaps more suited for this purpose, although the clinical utility for the management of individual patients remains unclear.[69] In clinical practice, the retropulsion test is typically used to test defensive reactions, but this test is not without problems. There is great variability in test performance across clinicians (depending on subjective preferences, but also on height or weight of both the patient and investigator), scoring of the response is subjective, and its interpretation is not straightforward. For example, it is unclear how many corrective steps can still be regarded as "normal". Interestingly, taking more steps is usually equated with greater balance impairment, but this may not be correct because corrective steps are important defensive reactions. Indeed, the most abnormal reaction is not taking any corrective step at all, leading to a fall "like a pushed toy soldier" (note that freezing can be a "confounder" here, interfering with the ability to step backward and leading to a fall "like a log" into the arms of the investigator, even when balance itself is otherwise preserved). We recommend taking the speed and quality of balance reactions into account (rather than merely counting the number of corrective steps), and to regard a slow response as abnormal even if only one or two steps are taken. A particular problem is the inconsistency in the strength of the shoulder pull, within and between raters (depending on experience or physical strength), as well as within and between patients who may have different degrees of instability. Consequently, the retropulsion test has an only moderate intra- and inter-rater consistency, correlates poorly to objective measures of postural instability (as quantitatively ascertained in a balance laboratory) and is a poor predictor of actual falls in daily life.[70] We usually deliver one shoulder pull without specific prior warning, as this may best mimic daily life circumstances where falls are usually unexpected events. We then repeat the test several times and regard failure to "habituate" to the test as another sign of bal-

ance impairment. As such, the retropulsion test indexes the degree of postural instability. However, the test fails to predict falls, at least in PD, [11] probably because falling is the net result of a complex interplay between gait, balance and protective mechanisms.

The "Push and Release" test was recently proposed as a more consistent and apparently also more sensitive alternative to the pull test (or retropulsion test).[71] The essence is to eliminate the inconsistency of the stimulus by instructing subjects to actively push backward against the palms of the examiner's hands (placed on the subject's scapulae), allowing the trunk to move backward while the examiner supports the subject's weight. Balance is then perturbed when the examiner suddenly removes the external support, forcing the patient to take a backward step to regain balance. The first experience showed that the "Push and Release" test correlated better with self-reported prior falls, when compared with the retropulsion test, and that it could be used in both the ON and the OFF states.[71,72] A drawback of this Push and Release test is that patients may have difficulties following the instructions, and some are hesitant to adequately push back into the examiner's hands due to lack of confidence.

Falls

Falls are a devastating consequence of postural and gait disturbances. Prospective surveys in PD note high rates of falls that exceed those of community-dwelling elderly subjects.[42] The incidence of falls is even higher when near-falls are included[73], and these near-falls typically precede the onset of actual falling.[74] The risk of falling is highest when patients reach Hoehn and Yahr stage 2.5 to 3, when balance becomes impaired but patients are still sufficiently mobile to be at risk of falling. In these moderately affected PD patients, the risk of sustaining a single fall was six times higher than in healthy age-matched peers, and the risk of sustaining recurrent falls was nine times higher. The falling rate may level off in later stages of the disease due to disease progression and increasing immobility.[42] Indeed, patients in Hoehn and Yahr stage 5 are bound to their bed or wheelchair are for this reason unlikely to fall. Furthermore, patients may compensate for their worsening balance by moving slower and purposely restricting their activities.

It is important to realize that most falls occur when patients are in their ON state, possibly reflecting their increased mobility. This observation also underscores that dopaminergic medication usually provides little or no improvement of postural instability. In fact, dopaminergic medication can cause dyskinesias that may perturb patients and increase falls. In addition, medication may cause or aggravate cognitive dysfunction, for example by causing delirium and risky wandering behaviour, leading to more falls.Most falls involve movements of the trunk, in particular sudden turning movements, presumably because this provokes freezing. Changes in posture ("transfers"), such as rising from a chair, are also commonly responsible. Orthostatic hypotension has been mentioned as an independent risk factor for falls in PD.[75] However, falls due to preceding loss of consciousness

are rare, and when this occurs clinicians should consider MSA, where syncope due to autonomic dysfunction is common.[76]

Cognitive deficits

PD patients with gait and balance problems should always receive a cognitive examination, especially testing the frontal executive functions and attention. This may seem unnecessary, because gait and balance control are traditionally considered to be a largely automatic process, governed mainly at a subconscious level by spinal and perhaps some brain stem neural structures. However, recent studies have shown that neuropsychological processes such as attention are necessary for adequate balance maintenance. Walking is an even more complex process than standing, involving a range of cognitive systems.[77] This role of cognition is obvious during many activities of daily living, when people need to perform multiple actions simultaneously or quickly shift attention and control from one task to another. To perform such actions, cognitive abilities are needed to effectively monitor the environment, choose flexible response patterns to appearing threats and to make appropriate motor responses necessary for completing goals - and this is precisely where patients with PD experience great difficulties, perhaps explaining why gait and balance deficits are such prominent features of PD. Indeed, cognitive dysfunction is particularly prominent in patients with the PIGD subtype of PD.[2,3,78] And it may also explain why falls seem to be particularly prominent in disorders that are characterized by a combination of both motor deficits (gait impairment, postural instability) plus a concurrent decline in cognitive functions. PD itself is one good example, but there are many other such disorders, including various forms of atypical parkinsonism (PSP, Lewy body dementia, vascular parkinsonism), and Alzheimer's disease.[79] Patients with PD have difficulty executing two different motor tasks simultaneously, such as walking and carrying an object[80,81,82,83,84,85,86,87,88] , and these dual task problems are associated with the risk of falling.[1] Various studies have shown that frontal executive dysfunction is related to gait impairment in PD patients[89] and is associated with an increased risk of falls.[90] Moreover, frontal executive dysfunction and freezing frequently co-occur, but there is as yet no proof of a direct causal interrelationship.[36] Recklessness, decreased ability to learn cues and an increased sensitivity to cognitive overload (for example when dual tasking) may explain why patients with frontal executive dysfunction are more prone to falls. Moreover, the presence of frontal executive dysfunction may give a clue to the underlying aetiology, as it is more prominent in atypical parkinsonism than in idiopathic PD. A clear example is provided by patients with PSP, where "motor recklessness" combined with progressive balance deficits are jointly responsible for the high rates of falls.[5] Finally, other mental functions should also be examined. Depression is associated with falls[91] , and possibly increased freezing,[58] and freezing is also associated with anxiety and panic attacks.[92]

TREATMENT

A multifactorial falls prevention program

Adequate treatment of gait and balance impairment is crucial in view of their potentially devastating consequences. The key goals should be prevention, preservation of a safe mobility and independence. We have recently reviewed the specific medical and non-medical treatment options of specific gait and balance problems in PD.[93] Rather than reiterating these treatment recommendations, we focus on a newly developed protocol for a multidisciplinary falls prevention program. To achieve this, it is particularly important to consider the pathophysiology of falls, as this offers a rationale for preventive strategies. Falls in PD patients are usually not just caused by a single factor – such as a reduced step height – but are typically the net result of a complex and multifactorial pathophysiology. This pathophysiology includes both "extrinsic" or environmental factors (e.g. loose rugs on the floor) and "intrinsic" or patient-related factors (including balance impairment and gait disability, in particular freezing of gait). Many of these factors are specific for PD, but patients may also fall due to generic risk factors for falls that apply to any elderly person ('generic risk factors').

It is therefore unlikely that, just by themselves, single interventions will be able to prevent patients from falling. Instead, we anticipate that a multifactorial falls prevention program will be needed, including PD-specific therapeutic measures plus a set of generic strategies. The merits of such a comprehensive falls prevention program have never been evaluated in PD, and in fact, there is no accepted menu of the most effective interventions. Here we will propose such a program, based on (*a*) determination of previosly identified risk factors for fals in PD and (*b*) determination of those factors that are potentially amenable to therapeutic intervention. We subsequently tailored a menu of therapeutic interventions to address risk factors, including not only disease-specific strategies, but also a selection of "generic" falls prevention strategies derived from the literature and from published national and international falls prevention guidelines (Table 2). A challenge here was to identify therapeutic strategies that would be both relevant and feasible for PD patients. For example, standing with both legs crossed is an accepted intervention to reduce falls caused by orthostatic hypotension, but is unlikely to be an acceptable treatment for PD patients given their postural instability. Also, each falls prevention strategy needs to strike a balance between being both comprehensive (covering every single potential risk factor) and tolerable (in being not too demanding for PD patients, given their fatigue and at times limited learning abilities). Based on these considerations, we have constructed a concept for a Multifactorial Parkinson Falls Prevention Strategy that accomodates all of the above factors. This protocol is summarized in Table 2. We will briefly discuss a few elements of the multifactorial strategy.

Table 2 Selected generic and disease-specific risk factors for falls, and tailored interventions.

Risk factor for falls	Tailored intervention
PD-specific	
Gait impairment (e.g. reduced step height)	· Increase antiparkinson medication · Physiotherapy (cueing strategies) (94;95)
Freezing of gait	· Optimize antiparkinson medication - ON phase freezing: decrease levodopa - OFF increase freezing: increase levodopa; MAO-blocker · Physiotherapy (cueing strategies) (94;95) · Eliminate domestic hazards (96)
Postural instability	· Optimize antiparkinson medication (usually ineffective) · Physiotherapy (balance training) (94) · Lower limb strength training (97)
Bradykinesia (e.g. slow protective arm movements)	· Increase dopaminergic medication
Dyskinesias	· Optimize antiparkinson medication
Inability to handle dual tasks	· Avoiding dual tasks (physiotherapy, occupational therapy) (1;89) · Cognitive movement strategies (chaining) (94)
Transfers	· Increase antiparkinson medication · Cognitive movement strategies (94)
Generic	
Polypharmacy	· Reduction of medication (consult a geriatrician)
Sedative drugs (benzodiazepines)	· Stop when possible
Daily use of alcohol	· Minimize alcohol intake
Fear of falling	· Increase balance confidence (94)
Impaired ADL	· Occupational therapist (96)
Physical inactivity	· Physiotherapy: improve physical capacity, muscle power, mobility, muscle length (94)
Improper use of assistive device	· Train use of assistive devices (physical therapist; occupational therapist)
Visual impairment	· Consult eye specialist · Restrict use of multifocal glasses · Cataract surgery (98)
Cognitive impairment	· Medication (no evidence for PD to reduce falls) - Cholinesterase inhibitor · Physiotherapy - Avoid multitasking - Minimize hazardous behaviour
Behavioural disturbances	· Atypical neuroleptics · Restriction of activities (only if all other measures fail)
Muscle weakness	· Muscle strength training (94;97;99)

Table 2 Selected generic and disease-specific risk factors for falls, and tailored interventions. (continued)

Risk factor for falls	Tailored intervention
Postural hypotension	· Decrease antiparkinson medication · Decrease other hypotensive medication (100) · Increase dietary salt and fluid intake · Anti-orthostatic manoeuvres (if balance is good) · Pressure stockings · Small meals · Raising cranial end of the bed · Symptomatic medication: - Fludrocortisone - Midrodine
Urinary incontinence and nocturia	· Reduce coffee and alcohol in the evening · Adequate night-time lighting · Incontinence materials
Environmental risk factors	· Occupational therapy at home

Medication

As outlined at the outset of this chapter, dopaminergic medication has mixed effects on gait, balance and falls. On the one hand, some axial motor features can improve following treatment with dopaminergic medication. For example, freezing is usually seen during the OFF state, and such OFF state freezing of gait may improve when dopaminergic medication is increased. However, other gait and balance problems are more resistant to treatment[8,9,10] or are even aggravated by dopaminergic medication.[16,17,18,19] It is therefore fimportant to review carefully the relation between falls and the timing of intake of dopaminergic medication. When freezing appears to occur during the ON state[101,102] – which is the case in only a small proportion of PD patients – the first step is to nevertheless further increase the dose of dopaminergic therapy, as some patients actually have "pseudo-ON freezing" (see Figure 1). In a few patients, freezing will worsen further, suggesting it is a true ON period sign, and this necessitates a dose reduction. Benzodiazepines and other sedative medication also need to be avoided whenever possible, as this may further increase the risk of falling.[11]

Pharmacotherapy of gait and balance problems should ideally aim at correction of both dopaminergic and non-dopaminergic deficits. Attention is now shifting towards development of 'non-dopaminergic' drugs directed at other neurotransmitter systems.[20,103] Unfortunately, such drugs are not yet available for treatment of axial disability.

Physiotherapy

There is increasing evidence to support the use of physiotherapy as part of a comprehensive falls prevention program.[94,104,105,106,107,108] Patients who have difficulties with initiating or maintaining gait often report that simple tricks can promote walking; these include clues that are environmental (e.g. stepping over an object on the floor) or generated (e.g. counting). This technique of using internal or external cueing can be exploited by physiotherapists, who can train patients to use auditory cues (such as listening to rhythmic

sounds of a metronome), visual cues (such as stepping over lines pasted onto the floor), tactile cues (such as tapping on the leg) or mental cues (such as simple arithmetic, or generating a mental image of the appropriate step length). Physiotherapists can also teach patients how to handle their freezing episodes. The risk of falling appears highest in patients who actively try to "overcome" their gait blockade, so patients should be instructed to simply wait for the freezing to disappear. Physiotherapists can also address the cognitive aspects of falling, for example by teaching patients to avoid multitasking in daily life, and to split complex tasks into several less complex sub-movements (a technique called "chaining"). Such cognitive movement strategies have been shown to improve transfers or rolling over in bed in PD patients.[94] Another approach is to restore balance confidence and diminish the fear of falling. This may help to restore mobility and promote independence. There is no specific evidence for PD, but studies in the elderly suggest that group treatment using a behavioural-cognitive approach to change attitudes, as well as training with a physiotherapist, can help.[109] The use of an assistive device and gait training can enlarge self-confidence. Instructions on how to stand up after a fall may also decrease fear of falling. An entirely different approach is required for cognitively impaired patients who can be overly confident and inappropriately 'over-rate' their own balance, resulting in risky behavior and falls. For them, restriction of hazardous activities might be the best solution to prevent recurrent falls. It is also important to inform the caregiver about activities that should be avoided.

Prevention of complications

Despite all efforts, most patients will continue to sustain at least occasional falls, and for patients with advanced PD the problem may become treatment-resistant. For this latter group, attention should increasingly be focused on preventing the complications of falls. For example, patients with PD can have a coexisting osteoporosis (caused by immobilization and perhaps endocrine disorders)[110] , that increase the risk of fracture. In PD patients presenting with a fracture, one should consider performing DEXA bone densitometry to establish whether osteoporosis is present. Treatment of osteoporosis may then reduce the risk of new fractures.

Who should be candidates?

It isnecessary to identify patients who are most at risk of falling. Various factors are related to falling, but many are interrelated. Prior falls, disease severity (Hoehn and Yahr stage 3) and disease duration appear to be the most consistent predictors of falls. In a meta-analysis, the only independent predictor of falling was asking for earlier falls[42], and this is not a satisfactory predictor because patients have already begun falling. Less robust, but potentially interesting, predictors of falls were fear of falling, avoiding activities because of this fear, and presence of prior near-falls. This may offer a way to identify eligible candidates for fall prevention, even before the very first real fall has occurred.

One size fits all?

For clinicians, this is a familiar problem in clinical practice. The good part of the falls prevention approach, as described above, is its comprehensive character: this minimizes the risk of "missing" relevant risk factors, and theoretically provides the most aggressive and complete "gunshot" approach of the falling problem. But there are also less attractive sides of the coin. Being comprehensive, the entire program is costly, and importantly, it may be excessive for patients where a single factor is obviously responsible for the falling problem. For example, when patients exclusively fall while tripping over one particular rug in the living room, simply removing this rug may treat the problem and obviate the need for the remainder of the comprehensive falls prevention program. Alternatively, when patients fall because of syncope, is it necessary to pay a home visit and eliminate domestic risk factors for tripping? There is no evidence to support any particular strategy, but a practical compromise may be the following. When patients consistently display a

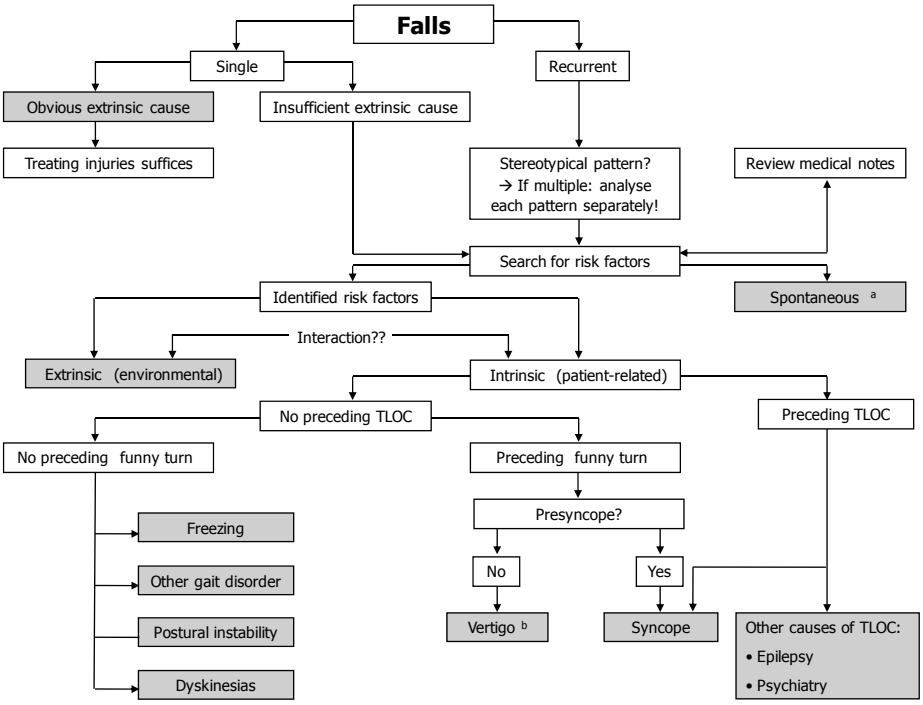

Fig 3 Diagnostic algorithm to classify the main types of falls in patients with a hypokinetic–rigid syndrome, modified after Voermans et al[111]. The main categories of falls are shown in gray boxes. TLOC =transient loss of consciousness. [a] When patients claim to fall spontaneously, this is usually caused by either freezing of gait (that is not recognized as such by the patient), or transient loss of consciousness (which is often incorrectly denied by elderly patients). b Although there is only little supportive literature[112], it has been our impression that vertigo – in particular that caused by benign position-dependent vertigo – is not rare in patients with PD, perhaps because their relative immobility promotes development of debris in the semicircular canals.

specific type of falls, where one obvious risk factor is consistently responsible for the falls, then simply tackling this single factor may suffice. Figure 3 shows the most common fall types, as well as a pragmatic approach to ascertain which specific type of falls is present. In other patients a comprehensive multifactorial approach is recommended.

CONCLUSION

This chapter underscores that gait disability, postural instability and falls are common and frequently devastating features of PD. We have reviewed the clinical features, mainly to provide a rational basis for a multifactorial falls prevention program. This approach includes identifying both generic and PD-specific risk factors, in order to define a multidisciplinary and multifactorial intervention program that is tailored to each individual patient. This program includes: optimizing dopaminergic medication; reducing the use of sedative drugs; physiotherapy to improve transfers, gait (including freezing), balance and balance confidence, physical activity and the use of assistive devices; occupational therapy (home visits to eliminate domestic hazards); and treatment of orthostatic hypotension, urinary incontinence and visual impairments. More research is needed to underpin the merits of the proposed multidisciplinary falls prevention program, and to evaluate its cost-effectiveness. We also need to develop better ways of finding those patients who are most at risk for falling.

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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 re-

duced 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

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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Samenvatting

SAMENVATTING

De belangrijkste bevinding van dit proefschrift is dat vallen frequent voorkomt bij de ziekte van Parkinson (ZvP) en de ziekte van Huntington (ZvH). Al vroeg in het beloop kan vallen optreden en naarmate de ziekte vordert, neemt de prevalentie toe. Het onderzoek in dit proefschrift beschrijft bij beide aandoeningen de risicofactoren en consequenties van vallen en de omstandigheden waarin zij optreden. Verder wordt de pathofysiologie van houdingsstoornissen en vallen nader bestudeerd. Het proefschrift sluit af met een voorstel voor een multidisciplinair interventie programma ter voorkoming van vallen bij de ziekte van Parkinson.

Houdingsinstabiliteit is een van de hoofdsymptomen van de ziekte van Parkinson. Het reageert echter minder goed op dopaminerge therapie dan andere symptomen zoals bradykinesie en rigiditeit.[1] Ook chirurgische therapie gericht op de basale ganglia biedt tot nu toe minder resultaat op de houdingsstoornissen. In **Hoofdstuk 2** wordt een verklaring gezocht voor deze slechte reactie op dopaminerge therapie en wordt de hypothese geopperd dat een noradrenerg tekort medeverantwoordelijk is voor de posturele stoornissen bij de ZvP. Meerdere neuropathologische studies vonden een celverlies in de locus coeruleus (de belangrijkste bron van noradrenaline in het centraal zenuwstelsel) en een daarmee gepaard gaand tekort aan noradrenaline.[2,3,4] De locus coeruleus heeft verbindingen met vele gebieden in de hersenen en het ruggenmerg en is daardoor bijvoorbeeld betrokken bij de controle van de spinale reflexen. Hierdoor zou deze kern een rol kunnen spelen bij het onderhouden van een goede balans. Indirecte aanwijzingen volgen uit studies waarin noradrenaline wordt gesuppleerd bij de ZvP (zie hiervoor **Hoofdstuk 2**). Enkele van deze studies vinden een gunstig effect op lopen en bevriezen, maar hebben helaas niet het verdere effect op balans onderzocht.

In **Hoofdstuk 3 en 4** worden de frequentie, de omstandigheden en de consequenties van vallen bij de ZvP en de ZvH besproken. Dat vallen frequent voorkomt blijkt uit een prospective studie van 59 patiënten met de ZvP en een later gepubliceerde meta-analyse van zes prospectieve studies. Parkinson-patiënten hadden een negen maal verhoogd risico op herhaaldelijk vallen vergeleken met gezonde leeftijdgenoten, gedurende een prospectieve onderzoeksperiode van zes maanden. Vijftig procent van de matig aangedane parkinson-patiënten viel gedurende deze zes maanden twee of meer keer. Het risico op vallen nam toe met de ziekteduur maar bereikte een plateaufase bij een Unified Parkinson's Disease Rating Scale (UPDRS) score van 50. Hierna bleef het risico steken op een kans van ongeveer 60% op een nieuwe val in de komende drie maanden. Bij nog hogere UPDRS scores nam het risico zelfs weer wat af, mogelijk door de inmiddels ontstane immobiliteit als gevolg van de balansstoornissen.[5] Het risico daalde echter

niet naar nul, wat erop duidt dat patiënten niet volledig geïmmobiliseerd waren. Dit was echter ook inherent aan de studie, waaraan geen verpleeghuispatiënten deelnamen.

De meeste vallen hadden een 'intrinsieke' oorzaak. Dat wil zeggen dat de oorzaak gelegen was in patiënt gerelateerde factoren. De meeste vallen traden op als gevolg van verplaatsingen van het zwaartepunt van het lichaam, veroorzaakt door rompbewegingen. Dit gebeurde met name tijdens omdraaien. Dit onderschrijft het idee dat balansstoornissen ten grondslag liggen aan het vallen bij de ZvP. Achteraf bezien zou bevriezen tijdens draaien ook een belangrijke rol kunnen hebben gespeeld[6], maar in het kader van deze studie hebben we daar niet specifiek naar gevraagd. Wel waren zes gerapporteerde vallen gerelateerd aan bevriezen tijdens lopen en dit is in latere studies ook een grote risicofactor voor vallen gebleken.[7,8]

Tijdens de 'on'-fase werden de meeste vallen gerapporteerd. Dit suggereert dat dopaminerge therapie onvoldoende de intrinsieke balansstoornis verbetert of mogelijk zelfs vallen kan veroorzaken. Hiervoor zijn verschillende verklaringen theorieën mogelijk. Tijdens de 'on'-fase zijn patiënten mobieler omdat de rigiditeit en bradykinesie verbetert. Maar indien de balansstoornis minder goed reageert op dopaminerge therapie kan dit juist tot vallen leiden. Een recente studie beschreef het risico op vallen als functie van de afgelegde loopafstand.[9]
Een andere verklaring zou kunnen zijn gelegen in het optreden van dyskinesieën. Een toename van de rompzwaai kan de patiënt daarbij uit evenwicht brengen. In onze studie hebben we de relatie tussen dyskinesieën en vallen niet bestudeerd. Dit zou in een volgende studie moeten worden onderzocht.

Verder vonden de meeste vallen binnenshuis plaats en hoewel de minderheid een 'extrinsieke' oorzaak had, speelden huisgerelateerde gevaren (zoals kleedjes) een belangrijke rol in het veroorzaken van vallen.
In overeenstemming met studies bij andere patiëntgroepen was het gebruik van sedativa geassocieerd met een verhoogd valrisico.[10,11,12,13] Het gebruik van benzodiazepinen veroorzaakte binnen onze patiëntengroep zelfs een vijfmaal verhoogd risico. Dit impliceert dat het gebruik van sedatieve medicatie bij valgevaarlijke patiënten zou moeten worden voorkomen.

Het frequent vallen leidde tot een groot aantal weke delen verwondingen en een toename van angst om te vallen. Deze angst om te vallen kan een vermindering van lichamelijke activiteiten tot gevolg hebben. Ernstige verwondingen kwamen in onze studie weinig voor, maar dit is toe te schrijven aan de relatief korte follow-up. In retrospectieve studies wordt een verhoogde incidentie van heupfracturen bij de ZvP gevonden[14,15]; een risico dat ook verhoogd wordt door de toegenomen osteoporose bij de ZvP.[16,17]

In het voorkómen van vallen is het belangrijk om vallen in de toekomst te kunnen voorspellen. In **hoofdstuk 3** hebben wij mogelijke voorspellers van vallen bestudeerd. De aanwezigheid van twee of meer vallen in het afgelopen jaar gaf de beste voorspelling van nieuwe vallen in de toekomst. De sensitiviteit (68%) en specificiteit (81%) waren echter niet hoog. Bovendien zou het beter zijn het verhoogde risico te onderkennen voordat de eerste vallen plaatsvinden. Angst om te vallen zou mogelijk vooraf kunnen gaan aan de eerste val, maar het vragen hiernaar had slechts een matige sensitiviteit en specificiteit.
Een interessante bevinding bleek dat geen van de momenteel veel gebruikte klinische testen voldoende toekomstig vallen kon voorspellen. Ook de zeer bekende en veel gebruikte retropulsietest kon vallers niet van niet-vallers onderscheiden. Omdat er over de uitvoering van de retropulsietest veel discussie is, hebben wij deze in onze studie zes maal achtereen uitgevoerd en apart geanalyseerd. Dit gaf ten eerste verschillende resultaten, wat er op wijst dat de uitvoering gestandaardiseerd zou moeten worden, en ten tweede was geen enkele test in staat toekomstige vallers te onderscheiden. Uit deze bevindingen blijkt dat het belangrijk is om andere risicofactoren te bestuderen en nieuwe testen (zoals bijvoorbeeld elektrofysiologische metingen van lopen en balans) te ontwikkelen die een verhoogd risico op vallen in de toekomst adequaat kunnen voorspellen.

In **Hoofdstuk 4** hebben wij de epidemiologie van vallen bij de ZvH bestudeerd. Deze studie was het eerste gedetailleerde onderzoek naar valfrequentie en omstandigheden bij de ZvH. Het bleek dat ook bij deze ziekte de valfrequentie hoog was. Zestig procent van de patiënten rapporteerde meerdere vallen in het afgelopen jaar. In een prospectieve periode van 3 maanden was dit 20% en 40% viel één keer. Een latere studie vond vergelijkbare retrospectieve valfrequenties.[18]
Evenals bij de ZvP vonden de meeste vallen binnenshuis plaats en hadden zij veel kleine verwondingen tot gevolg. Opvallend was dat patiënten met de ZvH echter weinig angst om te vallen bleken te hebben, terwijl zij wel een verminderd vertrouwen in hun balans rapporteerden. Mogelijk wordt dit veroorzaakt door de gedrags- of cognitieve stoornissen die gepaard gaan met de ZvH, waarbij er onvoldoende besef kan zijn van de mogelijke gevolgen van een val. Een andere verklaring zou kunnen zijn dat er ook weinig ernstige gevolgen werden gezien.

Ook bij de ZvH konden klinische balans testen vallers niet onderscheiden van niet-vallers. In een recente retrospectieve studie bleek de Tinetti Mobility test een redelijk voorspellende waarde te hebben (sensitiviteit 74%, specificiteit van 60%).[19] Een andere studie toonde significante verschillen tussen vallers en niet-vallers bij de Berg Balance test en de Timed Up en Go test.[18] Deze studie bevatte echter een kleine groep patiënten.

Om andere mogelijke voorpellers te onderzoeken hebben we kwantitatieve meetinstrumenten toegevoegd in de vorm van accelerometers, bevestigd aan de romp, en een drukgevoelige loopmat (zie box 1.3 in **Hoofdstuk 1**). Hierbij bleek er bij vallers sprake te zijn van een significant hogere laterale rompzwaai, wat correleerde met klinische chorea scores. Bij analyse van het looppatroon waren verlaagde loopsnelheid en een kleinere paslengte significant geassocieerd met een verhoogd valrisico. Deze bevindingen zijn een eerste stap in de richting van het ontwikkelen van een objectieve test maat, waarmee toekomstige vallen voorspeld zouden kunnen worden.

Hoofdstuk 5 behandelt de consequenties van balansstoornissen, vallen en angst om te vallen voor de kwaliteit van leven bij de ZvP. Vele factoren, zoals ziekte-ernst, motoriekstoornissen en gedragsstoornissen, bepalen de kwaliteit van leven bij de ZvP. [20,21] Balansstoornissen, vallen en angst om te vallen waren in onze studie allen geassocieerd met een verlaagde kwaliteit van leven. Angst om te vallen bleek hiervan de belangrijkste factor te zijn en dit is in overeenstemming met een eerdere studie, waarin angst om te vallen belangrijker was dan loopstoornissen of daadwerkelijk vallen.[22] Dit impliceert dat bij behandelingen, gericht op het verbeteren van de kwaliteit van leven bij de ZvP aandacht voor angst om te vallen een belangrijke plaats moet innemen.

Lundin-Olsson et al[23] publiceerden de 'stops walking when talking test' (SWWT) en introduceerden hiermee een nieuw inzicht in balansstrategieën van ouderen. Het onvermogen om te kunnen lopen en praten tegelijkertijd bleek geassocieerd met een verhoogd risico om te vallen in de volgende zes maanden bij ouderen. Bij het bestuderen van de waarde van deze test voor patiënten met de ZvP werd in onze studie echter geen onderscheid gevonden tussen toekomstige vallers en niet-vallers (**Hoofdstuk 6.2**). Slechts enkele patiënten stopten met lopen tijdens het praten. Mogelijk werd dit veroorzaakt door het feit dat de Lundin-Olsson studie veel patiënten bevatte met geheugenstoornissen en depressie, terwijl ernstige geheugenstoornissen een exclusie criterium waren voor onze studie. Dit zou erop kunnen wijzen dat het onvermogen om dubbele taken uit te voeren eerder een marker is voor cognitieve stoornissen dan voor motoriekstoornissen.

In navolging van de SWWT volgen er meer studies die het effect van dubbele taken op lopen en balans onderzoeken. In **Hoofdstuk 6.2** worden deze artikelen besproken en hoewel alle studies een wat verschillende opzet hadden, lieten zij wel een verslechtering van het lopen en de balans zien wanneer er een tweede taak moest worden uitgevoerd. Dit gold voor zowel cognitieve (bijvoorbeeld rekenen) als motorische taken (bijvoorbeeld het dragen van een dienblad). Eén van deze studies suggereerde dat een multipele taken test mogelijk duidelijkere verschillen kon laten zien bij patiënten met de ZvP zonder geheugenstoornissen.[24] Hiervoor werd de zogenoemde 'multiple task test' ontwikkeld, waarbij er toenemend steeds meer taken (zowel cognitief als motorisch) werden toege-

voegd, totdat er acht taken tegelijk moesten worden uitgevoerd. Dit liet verschillende strategieën zien bij parkinsonpatiënten en gezonde controlepersonen. De controles gaven voorrang aan de motorische taken boven de cognitieve taken en de patiënten probeerden tevergeefs alle taken tegelijk uit te voeren. Parkinsonpatiënten leken daarbij minder goed in staat om een zogenaamde 'posture first' strategie te hanteren, waarbij de balans voorgaat op andere taken. Het onvoldoende voorrang geven aan de balans zou daarom wellicht onderdeel moeten uitmaken van valpreventie programma's bij de ZvP. Hierbij kan bijvoorbeeld geleerd worden om extra taken tijdens het lopen uit te stellen totdat er sprake is van een veilige positie. Een recente studie wijst juist op een andere meer succesvolle strategie, waarbij er juist geadviseerd wordt om te oefenen meerdere taken tegelijk uit te voeren, hiermee ook beter tegemoet komend aan de dagelijkse situatie.[25]

In **Hoofdstuk 7** wordt een concept ontwikkeld voor een multifactorieel valpreventie programma voor de ZvP. Dit programma zou gericht moeten zijn op zowel interventies gericht op de ZvP, als op algemene preventie strategieën die voor ouderen gelden. In dit kader hebben we de een literatuur review verricht, waarbij alle beschreven valrisicofactoren en valpreventie strategieën werden geëvalueerd met daarbij de huidige nationale en internationale valpreventie richtlijnen. Hierop werd een concept protocol gebaseerd waarin er een overzicht werd gegeven van de mogelijke interventies, passend bij specifieke risicofactoren. Deze interventies moesten dan ook geschikt zijn voor patiënten met de ZvP. Zo is bijvoorbeeld het kruisen van de benen een veel gebruikte strategie om orthostatische hypotensie te verminderen tijdens staan. Dit is uiteraard geen geschikte methode indien er sprake is van een bijkomende ernstige balansstoornis.
Het voorgestelde preventieprogramma bevat onder meer de volgende interventies (afhankelijk van het specifieke risicoprofiel van de individuele patiënt): het optimaliseren van de dopaminerge therapie (bijvoorbeeld verminderen van 'off'-freezing); het verminderen of staken van sedativa; fysiotherapie ter verbetering van lopen en transfers; balanstraining en het vergroten van het vertrouwen in de balans; het bevorderen van lichamelijke activiteit; trainen van het gebruik van hulpmiddelen; ergotherapie; behandeling van orthostatische hypotensie, urine incontinentie en visusstoornissen. Dit valpreventie programma wordt momenteel getest en wordt beoordeeld door een internationaal panel van experts ter verdere verfijning.

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Curriculum Vitae

Yvette Grimbergen was born on October 12, 1971 in Uden, the Netherlands. She attended secondary school at the Thomas More College (Atheneum) in Oudenbosch and graduated in 1990. In 1991 she finished her 'propedeuse' Spanish language at the University of Leiden and continued studying Latin-America Studies until 1993. In 1993 she decided to follow her primary interest and started her medical training at the same university. In 1997 she started a prospective study on falls in Parkinson's disease under supervision of prof. dr. B.R. Bloem and prof. dr. R.A.C. Roos. In 1999 she graduated from medical school and started her residency at the department of Neurology of Leiden University Medical Centre (head: prof.dr R.A.C. Roos). During her residency she continued her research for this thesis. From 2002 onwards she has been a member of the European Huntington's disease network (EHDN), participating in the motor working group. Since 2009 she has been working as a neurologist at the Sint Franciscus Gasthuis in Rotterdam.

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