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Research Review

Falls and Freezing of Gait in Parkinson's Disease: A Review of Two Interconnected, Episodic Phenomena

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Abstract: Falls and freezing of gait are two "episodic" phenomena that are common in Parkinson's disease. Both symptoms are often incapacitating for affected patients, as the associated physical and psychosocial consequences have a great impact on the patients' quality of life, and survival is diminished. Furthermore, the resultant loss of independence and the treatment costs of injuries add substantially to the health care expenditures associated with Parkinson's disease. In this clinically oriented review, we summarise recent insights into falls and freezing of gait and highlight their similarities, differences, and links. Topics covered include the clinical presentation, recent ideas about the underlying pathophysiology, and the possibilities for treatment. A review of the literature and the current state-of-the-art suggests that clinicians should not feel deterred by the complex nature of falls and freezing of gait; a careful clinical approach may lead to an individually tailored treatment, which can offer at least partial relief for many affected patients. © 2004 Movement Disorder Society

Key words: Parkinson's disease; falls; gait; freezing; pathophysiology; treatment

In recent years, falls and freezing of gait (FOG) received increasing recognition as debilitating and somewhat enigmatic features of Parkinson's disease (PD). Falls and FOG are generally thought to be closely intertwined, for various reasons. First, both symptoms seem most common in advanced PD but are deemed to be rare in earlier stages of the disease. Second, sudden FOG is likely to disturb balance and thereby represent a common cause of falls in PD. Third, recent observations have shed new light on the poorly understood pathophysiology underlying falls and FOG and suggested the possibility of shared and common pathologic mechanisms. Fourth, falls and FOG often respond poorly and sometimes paradoxically to treatment with dopaminergic medication, perhaps pointing to a common underlying pathophysiology. Fifth, the episodic and unpredictable nature of falls and FOG underscores the possible connections between these phenomena in PD. Finally, falls and FOG pose substantial threats to the well-being of patients with PD, not only because of the direct clinical impact on affected individuals,[1] but also in terms of mounting health care costs for society.[2] While some of these widely held assumptions are correct, there are also important differences between falls and FOG, as we discuss later. Here, we present a clinically oriented review of falls and FOG, with emphasis on recent insights into the presentation, pathophysiology, and treatment options. We also discuss new directions for further research.

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EPIDEMIOLOGY

Falls

Subjective complaints about tremor generally dominate the early stages of PD. However, as the disease progresses, balance impairment and falls become in-

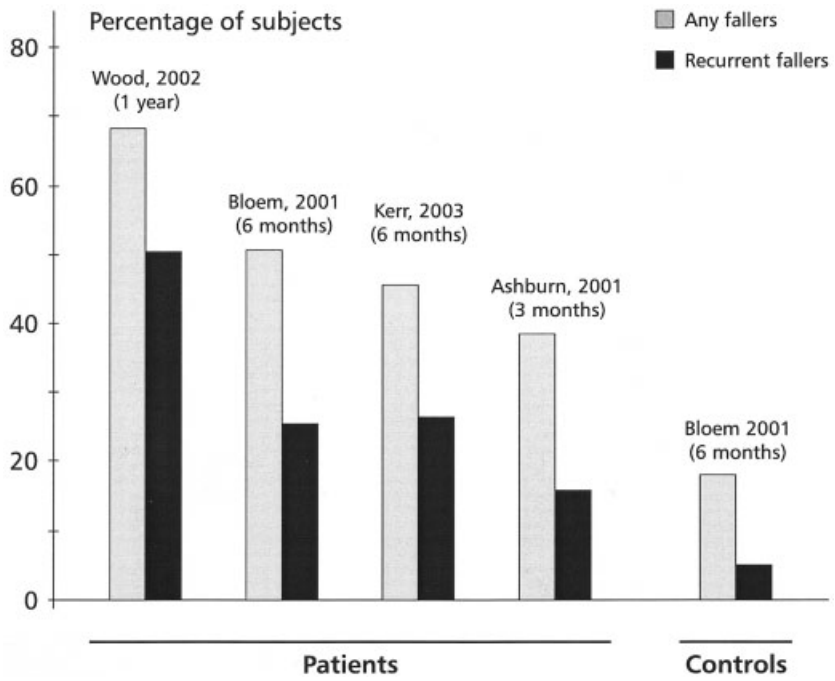

FIG. 1. Fall rates in Parkinson's disease, as observed in four prospective studies.[5–8] Despite the differences in duration of follow-up, a fairly consistent pattern crops up with falling incidences that continue to increase with longer follow-up. The final two columns depict the incidence of falls in age-matched controls, as observed in one study.[6] We did not show a fifth prospective study with a 3-month follow-up because "near falls" were lumped with actual falls[4]; not surprisingly, the observed fall rates in this study were higher compared to the study that merely included complete falls during 3 months.[5]

creasingly important and develop into one of the chief complaints among PD patients and their caregivers. Balance is typically preserved early in the course of idiopathic PD, and falls are rare during the first few years after disease onset.[3] However, eventually most patients will sustain recurrent falls. In the past few years, five prospective surveys of PD patients[4–8] have documented the incidence of falls and their consequences. The observed fall rates were rather impressive, as almost 70% of patients fell during a 1-year follow-up (Fig. 1). Recurrent falls occurred in approximately 50% of patients during 1 year. Proportionally lower fall rates were noted in studies with a shorter follow-up. Compared to healthy subjects, the relative risk of sustaining recurrent falls during a 6-month period was 9.0 (95% confidence interval, 2.0–41.7) for PD patients.[6] Not surprisingly, fall rates were even higher in studies that also included "near falls" where, despite a loss of balance, an actual impact with a lower surface could be avoided by grasping for external support.[4,9]

Intuitively, the incidence of falls should increase as a function of disease duration and severity. However, most studies found no relation between disease duration and falls. This paradoxical observation is explained by the fact that falls are initially absent early in the course of the disease, then become increasingly prevalent as balance becomes progressively impaired, but eventually disappear again when patients become progressively immobilised in late-stage PD.[1] Indeed, a recent meta-analysis of all five prospective surveys confirmed the existence of such a "bell-shaped" relation between disease duration and falls (R. Pickering and B.R. Bloem, unpublished observations).

Freezing of Gait

Similar to falls, FOG is usually regarded as a "late" feature of PD. However, recent studies revealed that FOG may occur in very early stages of idiopathic PD, in fact up to 26% of patients who were not yet exposed to levodopa (L-dopa).[10–13] Long-term follow up of patients in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study established that appearance of FOG early in the course of the disease should not be used as a "red flag" for atypical parkinsonism.[12] For patients with more advanced PD and prolonged exposure to L-dopa, the prevalence of FOG ranges between 20 and 60% of patients.[11,13,14] Because of the difficulties in ascertaining whether patients actually have FOG (see below), these figures are possibly even higher. On the other hand, a sizable number of patients—by some accounts 80%—will never experience FOG at any stage of the disease. This finding suggests that FOG may be associated with a specific pathology that is not present in all patients.

Although FOG is not unique to PD, it has only been described in association with hypokinetic, extrapyramidal movement disorders. FOG can occur in all parkinsonian syndromes, particularly in progressive supranuclear

palsy (PSP) and its subtype, the "pure freezing syndrome," as well as in vascular parkinsonism.[15,16] FOG is rare in neuroleptic-induced parkinsonism.[15,17] Early retrospective studies also considered FOG to be rare in multiple system atrophy (MSA),[15] but recent clinicopathological studies frequently observed FOG in MSA patients of the parkinsonian type.[18,19] In patients with MSA, FOG was associated with parkinsonism but correlated poorly with the severity of cerebellar features.[18]

CLINICAL PRESENTATION

Balance Impairment and Falls

Most falls in PD are intrinsic in nature, that is, they are caused primarily by the underlying balance disorder and not by an obvious environmental cause such as a collision or loose rug on the floor.[6] Many falls result from sudden changes in posture, in particular turning movements of the trunk, or attempts to perform more than one activity simultaneously with walking or balancing. Most PD patients can maintain a routine conversation while walking[20] but have difficulties performing under different dual task conditions,[9,21–24] leading to FOG or loss of balance. Performance deteriorates further as the tasks become more complicated.[25] It appears as if, under complex conditions, PD patients have particular problems lending priority to what is most important, i.e., maintaining a safe gait and upright stance. Instead, patients typically try to perform all tasks equally well, but pay a price in terms of poor gait or balance.[25] Falls are also common during transfers, such as rising from a chair or bed. Falls due to trips or slips are relatively rare.

PD patients fall mostly forward (45% of all falls), and some 20% of falls were laterally directed.[26] The characteristically stooped posture increases the likelihood of forward falls, because the associated forward shift of the centre of gravity (COG) provides relative protection against a backward fall.[27] In contrast, patients with PSP fall mostly backward, perhaps because these patients stand more erect.[28] A striking feature in PSP is the incidence of seemingly "spontaneous" falls, almost as if these patients propel themselves backward. Such falls are not usually seen in idiopathic PD.

Syncopal falls caused by orthostatic hypotension are rare in PD.[6] Patients presenting with parkinsonism and syncopal falls most likely have MSA, or perhaps dementia with Lewy bodies. Excessive dopaminergic therapy is often held responsible when symptomatic orthostatic hypotension does occur in PD,[29] but recent evidence suggests that orthostatic hypotension can occur in untreated patients due to sympathetic failure.[30] However, postprandial hypotension, defined as decreases in systolic blood pressure of $\geq$20 mm Hg occurring within 2 hours after the start of a meal, is common in PD[31]; this condition can lead to symptomatic hypotension and transient loss of consciousness, thereby causing falls.

Most falls in PD occur indoors, usually in the patient's own familiar environment, particularly in the bedroom.[6] This high incidence of indoor falls may reflect the patients' inability or unwillingness (due to a fear of falls) to leave their house. In addition, the high incidence of falls in the bedroom likely reflects problems with transfers, particularly at night. Nighttime orthostatic hypotension after prolonged recumbence may further contribute to falls in the bedroom.

Freezing of Gait

Three different subtypes of FOG can be differentiated.[32] Perhaps the best-known clinical presentation is that of a patient who suddenly, for no apparent reason, becomes unable to start walking or fails to continue to move forward ("akinesia"). Such a complete absence of movement is actually not the most common presentation. Indeed, video analyses revealed that FOG is frequently associated with an effort to overcome the block,[32] causing the legs to "tremble in place." The third type of presentation consists of shuffling forward with small steps. These observations may have clinical implications, because it suggests that patients who "accept" the block and wait for spontaneous resolution may be less likely to fall.

In early stage PD, FOG is generally short in duration and mainly seen in the form of start or turning hesitation,[32] causing relatively mild functional impairment and rarely leading to falls. Most FOG episodes last less than 10 seconds and only a few last more than 30 seconds.[32] With disease progression, FOG becomes more frequent and disabling, often leading to falls.[11,13,14] FOG is much more common in the *off* state, and the complete akinesia form does not occur frequently during the *on* state. Freezing of only one leg occasionally occurs, particularly in patients with asymmetrical parkinsonism.

Most FOG episodes occur during turning movements and while patients attempt to initiate walking ("start hesitation"). However, FOG may also appear during straight, unobstructed walking, while crossing narrow spaces, when reaching a target or trying to negotiate obstacles. Mental aspects and visual inputs can have both positive and negative influences on FOG. On the one hand, FOG is more common in crowded places and in time-restricted, stressful situations. The negative effect of vision is reflected by the frequent occurrence of FOG when patients approach a target or attempt to cross a narrow passing. Attention, which may be related in part

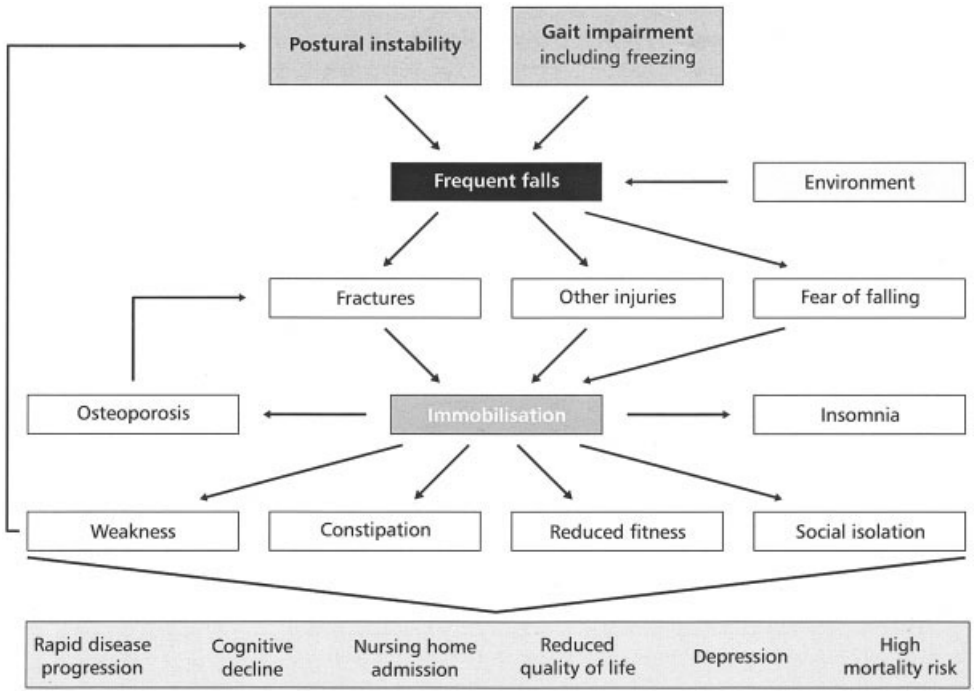

FIG. 2. Clinical impact of falls and freezing of gait in Parkinson's disease. Note the vicious circle that arises because weakness further aggravates the underlying balance disorder. The combination of secondary consequences listed in the bottom row is sometimes referred to as "malignant" parkinsonism.

to stress, can also promote development of FOG. For example, performing a secondary task while walking can cause some PD patients to freeze.[10,21,23] On the other hand, when attention is focused on each step, for example by means of external cueing to change gait from automatic to attention-driven stepping, FOG may be alleviated.[33]

In the DATATOP cohort, the main risk factors for development of FOG included gait as the initial motor symptom and more advanced disease, especially with respect to gait, balance, and speech.[12] Cognitive decline and depression were also associated with earlier appearance of FOG. Conversely, the presence of tremor as the initial motor symptom and higher scores on the UPDRS tremor items were strong protective factors for future development of FOG at any stage of the disease. In general, FOG is seen more frequently in older patients,[34] but an older age at onset of the disease does not increase the risk of future development of FOG.[12]

Extrapyramidal gait disorders can be subdivided into continuous and episodic forms.[35] The continuously present gait disturbances generally progresses slowly, enabling patients to adjust the daily routine to their altered gait. This condition differs from the episodic gait disorders (including FOG) where patients are unable to adjust to the transient gait interruptions, causing significant insecurity. Furthermore, one would expect that the sudden and unpredictable gait blocks should frequently lead to falls,[4] but this finding was not observed in all prospective surveys of falls.[6] This discrepancy may be related to difficulties in ascertaining whether FOG was present just before the fall.

CLINICAL IMPACT

The mobility problems related to falls and FOG have a devastating impact on the patients' lives (Fig. 2). Indeed, patients often report that gait impairment, falls, loss of mobility and reduction of social activities are the main determinants that negatively influence their quality of life.[36,37] Hip fractures are perhaps the most feared consequence of falls, as these are associated with a high morbidity and mortality in PD[38] and commonly lead to nursing home admission. Within 10 years after diagnosis of the disease, approximately 25% of patients will have developed a hip fracture.[39] "Minor" injuries such as joint dislocations, bruises, or skin lacerations are very common and represent a major source of discomfort to patients.

A common, yet frequently overlooked, consequence is a fear of future falls, which can be incapacitating in its own right as it leads to restriction of daily activities.[6,40]

The reduced mobility causes loss of independence and deprives patients of their social contacts, leaving some patients largely isolated. Not surprisingly, falls in PD are often associated with depression.[41] The immobility is further associated with constipation, pressure sores, and poor sleep quality. Prolonged periods of immobility eventually promote the development of osteoporosis, which facilitates future fracture development.[42] Patients with severe instability, FOG, recurrent falls, or a hip fracture often require admission to nursing homes.[4,43] Finally, patients with gait or balance disorders have an increased mortality risk. Average survival is reduced to approximately 7 years, once recurrent falls are present.[44] This high mortality is in part a direct result of falls, for example, in the case of a massive epidural hematoma. However, the complications of falls such as pneumonia due to immobilization more commonly form the ultimate cause of death. Immobilisation also reduces the overall physical fitness and thereby increases the risk of cardiovascular morbidity or mortality.[45] Finally, many patients are unable to get up without help after a fall, which can lead to exhaustion, dehydration, or death.

CLINICAL ASSESSMENT

History Taking

Interviewing patients about prior falls is not always reliable because many fail to report their falls due to an amnesia or sometimes because patients conceal their balance problems for fear of nursing home admission.[1] It often proves difficult to clarify the precise fall circumstances, yet this is critical for implementation of fall prevention strategies. Useful information may be obtained by consulting the spouse, caregiver, or by using a falls diary. Clinicians should also inquire about fear of falling and also about balance confidence, as some patients feel overly confident, despite marked balance deficits. Such patients may be particularly at risk of falling. Specific questionnaires have been designed to assess fear and balance confidence,[46,47] but these are typically used more for research than in the clinic.

With respect to FOG, it is usually insufficient to simply ask about "freezing", because not all patients interpret this question correctly. It is better to specifically ask patients about the characteristic subjective sensation of the feet becoming "glued to the floor." A specific set of questions has been bundled into the Freezing of Gait Questionnaire that can help clinicians screen for the presence of FOG and assess subjective severity.[48] Finally, it is worth evaluating the use of walking aids. Some patients are ashamed to use these, whereas others use them improperly, e.g., by carrying the walking frame instead of using it for extra support.[49]

Physical Examination

Isolated clinical tests have, by themselves, a poor predictive capacity for falls in daily life.[6] The examination, therefore, should include a battery of functional tests to capture the full repertoire of balance and gait abnormalities in PD (see Bloem and Bhatia[50] for a comprehensive review of clinical tests). It is particularly important to judge the safety of turning movements, transfers, and gait during dual task conditions. Additional tests should evaluate anticipatory postural control (lifting objects, for example) and the defensive postural reactions (compensatory stepping and reaching with the arms). These defensive postural reactions are typically measured with the retropulsion test, which is usually performed as a sudden shoulder pull from behind, sometimes as a push to the chest. Drawbacks to this test include the difficulty in standardising execution and the lack of a generally accepted scoring system. The most valid variant consists of a single and unexpected shoulder pull, where taking >2 steps backward is considered abnormal.[51] However, the retropulsion test does not discriminate well between moderately affected patients and controls and is a poor predictor of falls in PD.[6]

Many of the above tests are included in standardised rating scales,[52,53] but not all scales, e.g., the Tinetti Mobility Index, were specifically designed for use in PD and lack responsiveness in this population.[54] Whenever possible, patients should be examined both during optimal response to treatment and in a "defined *off* state" (after withdrawal of antiparkinson medication for at least 12 hours).[32,53]

It is often difficult to elicit FOG in the physician's examination room.[55] It is better to examine patients as they walk along a specifically developed trajectory, periodically passing through narrow paths and performing turns of 180 or 540 degrees to elicit FOG.[32] Dual tasking (cognitive loading) can be applied during portions of the gait trajectory, and performance can be videotaped to objectively evaluate the type of freezing, the duration of each episode, and the frequency of FOG.[32]

Some balance and gait tests are usually normal in idiopathic PD, and abnormal findings suggest the presence of an atypical form of parkinsonism. For example, tandem gait is normally preserved, even in fairly advanced PD.[6] Impairment may suggest the presence of MSA (with cerebellar involvement) or PSP. Stance width during gait is also typically normal in PD, and a wide-based gait suggests a different disorder.

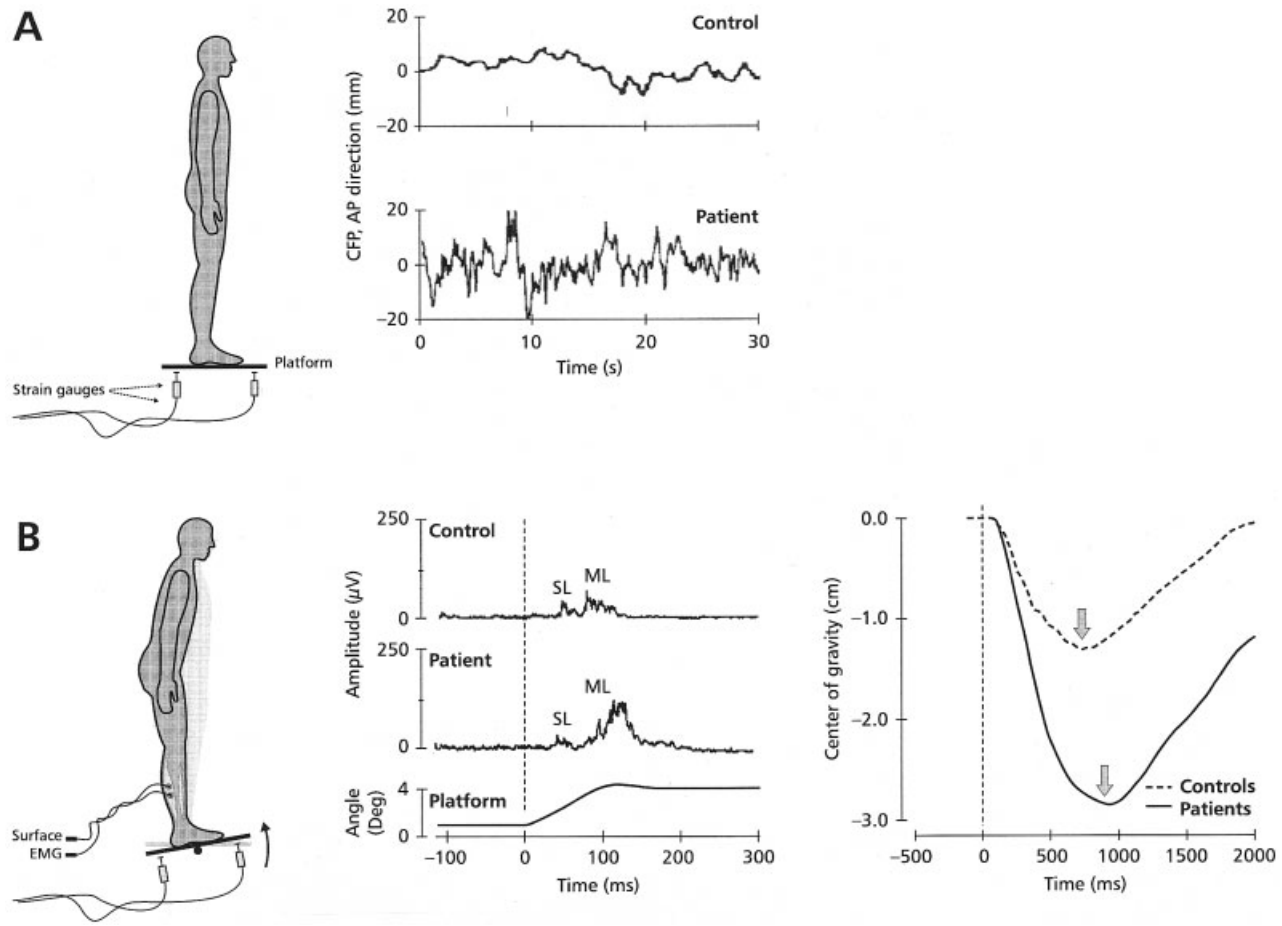

FIG. 3. A: Static posturography. Subjects stand quietly on a stable support surface with imbedded strain gauges (usually in all four corners), which can record excursions of the centre of foot pressure (CFP). The individual traces show an increased displacement path for the patient with Parkinson's disease (PD), suggesting more instability. Tremor and dyskinesias may also lead to changes in CFP displacement. AP, anteroposterior. **B:** Dynamic posturography. Subjects stand quietly on a movable support surface that, in this particular example, suddenly rotates upward and displaces the subject backward ("toes-up" rotational perturbations). Surface electromyograph (EMG) recordings show short latency (SL) reflexes and medium latency (ML) balance correcting responses in the stretched medial gastrocnemius muscle of a control subject and a PD patient. In this experimental condition, ML stretch responses are typically increased in PD, and this finding is associated with an increased backward displacement of the centre of gravity (modified from Bloem and colleagues[69]).

PATHOPHYSIOLOGY

Falls

The underlying pathophysiology leading to falls in PD is complex. It was hoped that some insights might be derived by describing patients with the highest risk of falling, but unfortunately, this process proved difficult. Only few factors were independently and consistently associated with faller status, including a moderate disease severity (in particular Hoehn and Yahr stage 3) and presence of earlier falls.[50] Daily use of alcohol and intake of benzodiazepines were also associated with falls in some studies.[4,6]

More detailed knowledge has been obtained using objective assessment techniques, in particular static and dynamic posturography techniques.[56] *Static* posturography studies (Fig. 3A) have provided interesting insights into the pathophysiology of postural abnormalities in PD,[57–60] but it can be difficult to separate primary balance abnormalities from postural tremor or medication-induced dyskinesias. One important finding was the predominance of sway abnormalities in the mediolateral plane.[57,58,61] This side-to-side instability may play a role in the pathophysiology underlying hip fractures that typically result from lateral falls onto the trochanter (remember that approximately 20% of falls in PD were laterally directed[26]). *Dynamic* posturography techniques use stance perturbations, using either a moving support surface or an external force applied to the body (Fig. 3B).

Such studies point to a multifactorial pathophysiology, with closely intertwined contributions from primary disease processes, secondary disease processes, and various compensatory strategies. A comprehensive analysis of these different factors can be found in recent reviews.[1,35,50,62–64] Here, we will provide some topical examples, derived mainly from our own work.

Primary disease processes refer to mechanisms that can be traced back directly to the underlying neuropathology in PD. Various groups have used dynamic posturography to study these primary disease processes. A recent development involves exposing subjects unpredictably to a random series of perturbations in multiple directions,[65,66] to reduce habituation of postural responses that occurs when identical balance perturbations are delivered in a predictable manner.[67] By using such an approach, we observed that the protective arm movements in PD are inadequately directed, such that the arms are adducted against the trunk during a fall, instead of stretched out to grab for support or to protect against the impact of an impending fall.[65] These abnormal arm movements could partially explain why wrist fractures seem relatively rare in PD, because these are typically caused by falls on the outstretched hands.[26]

Secondary disease processes largely reflect the immobility in advanced PD. For example, lack of mobility may lead to cerebrovascular disease, joint degeneration, muscle weakness, and reduced tendon flexibility. All these factors, in turn, can negatively affect postural control. For example, a recent study demonstrated that cerebrovascular comorbidity was associated with poorer balance and more prior falls among patients with otherwise typical PD.[60]

Compensatory strategies may help patients to avoid falls. An example of a seemingly *"beneficial" compensation* relates to the stooped posture. When asked to balance on a movable platform, PD patients are predominantly unstable when they are toppled backward.[65] However, in daily life, patients may purposely aggravate their natural tendency to stand stooped and so shift their COG further forward, away from their disease-related preferential fall direction. There is some experimental evidence for this protective mechanism in PD. In early PD, the centre of foot pressure (CFP) during quiet stance is shifted backward, rather than forward.[68] This finding may reflect the true effect of PD itself and underlie the propensity to fall backward, as identified on a movable platform. In later stages of the disease, the CFP position at rest shifts forward,[68,69] possibly because patients now attempt to compensate for their tendency to fall backward. Of interest, when such patients are asked to close their eyes, the CFP again shifts backward,[70] suggesting that patients use visual feedback to actively keep the CFP away from the disease-related preferential fall direction. A stooped posture is indeed biomechanically effective in protecting against backward falls,[27] but the price paid may be an increased likelihood of forward falls.

A striking example of an apparently *adverse compensation* relates to trunk stiffness. When young subjects are tilted laterally (e.g., to the right) by a moving platform, the trunk rapidly moves away (that is, to the left) from the direction of the impending fall.[71] This trunk hinging is partially passive in nature, because it occurs very early after the perturbation (after approximately 30 msec), well before postural reflexes become biomechanically active. The inertial trunk movement helps to stabilise posture because it keeps the COG away from the imposed fall direction. The early trunk movements are markedly diminished for patients with PD, causing their trunk to fall "like a log" into the perturbation direction.[65] A commonly accepted explanation for this reduced trunk flexibility is increased muscle stiffness, caused by rigidity, tonic increases in background muscle activity, cocontraction or secondary changes in intrinsic muscle properties. However, recent observations suggest that stiffening could represent a purposely selected compensatory strategy, with certain advantages. For example, stiffening reduces the degrees of freedom that need to be controlled and, thus, simplifies postural control. Of interest, the "decision" to stiffen up could be driven by fear of falls, which is common in PD.[6,40] Indeed, stiffening strategies with elements reminiscent of those observed in PD could be induced in healthy subjects who were made artificially fearful by placing them on an elevated platform.[72] It seems as if PD patients control their upright stance in an all-or-nothing approach, using trunk stiffening to maximise stability under relatively static (unperturbed) conditions, but this comes at the expense of inflexibility (loss of shock-absorbing trunk flexion) in the case of sudden postural perturbations.

Freezing of Gait

Early retrospective studies showed that FOG is associated with both disease progression and duration of L-dopa treatment but could not differentiate between these factors.[10,11] However, the prospective assessment of FOG in the DATATOP cohort of untreated PD patients showed that disease progression alone could be responsible, at least in part, for development of FOG.[12]

Another debate in the literature concerns the role of bradykinesia in the pathogenesis of FOG. Some have suggested that FOG is an extreme form of bradykinesia, frequently called akinesia.[73] However, analysis of the DATATOP study did not support a strong interaction

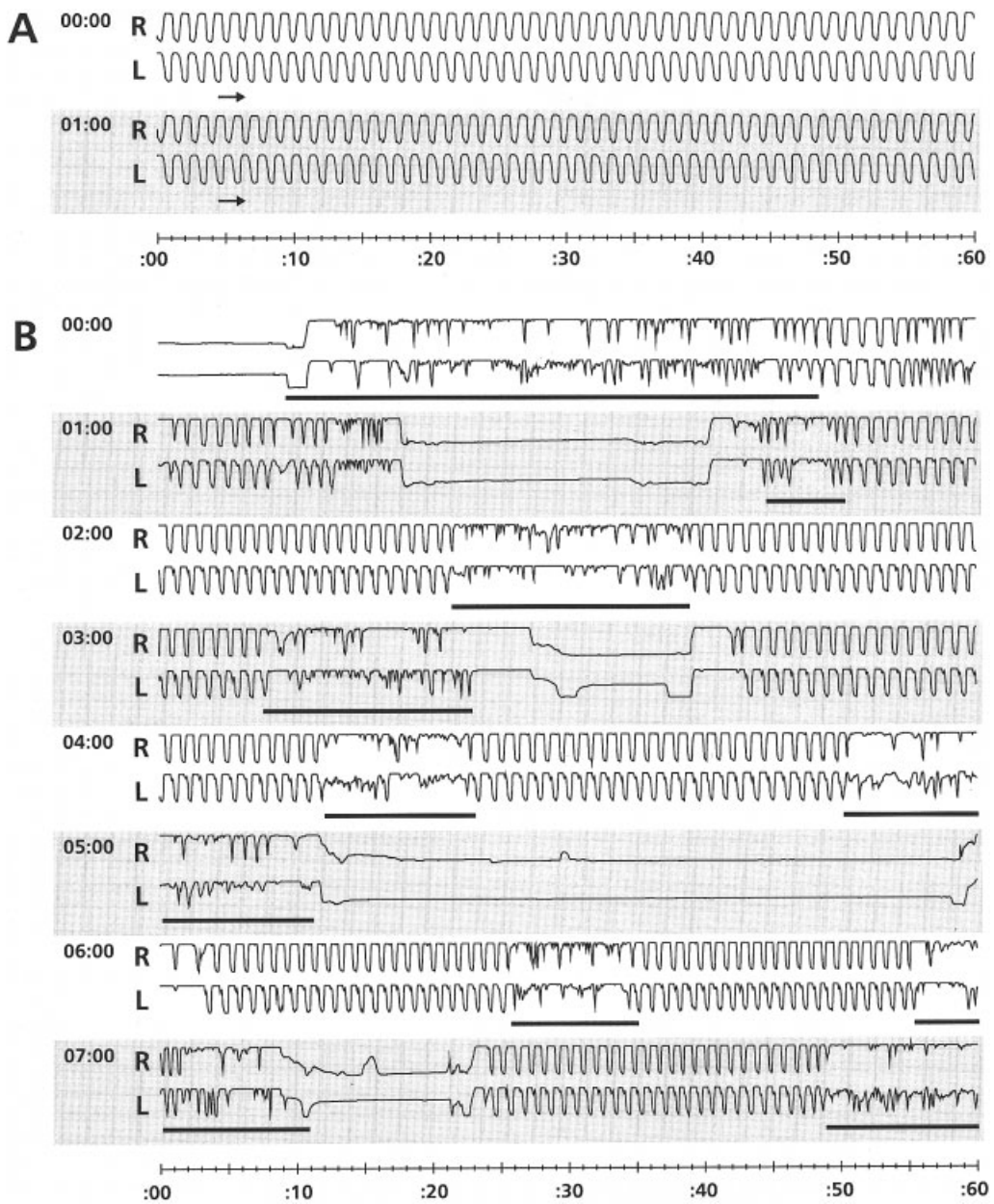

FIG. 4. A strip chart-like recording of insole forces (a measure of the ground reaction forces) for the left (L) and right (R) foot of a control subject (**A**, 2 minutes) and a Parkinson's disease patient with freezing of gait (FOG; **B**, 7 minutes). During walking, a clear cyclic rhythm can be observed. When there is no movement (sitting or standing), a flat line is observed. FOG is distinguished by the small, noisy fluctuations in the signal (and is underlined with a horizontal bar). The episodic and unpredictable nature of FOG is clearly apparent.

between worsening of bradykinesia and the development of FOG or between the development of micrographia (a classic hypokinetic symptom) and the development of FOG.[12] Another study neither observed a strong relation between FOG and bradykinesia.[74] It appears, therefore, as if FOG is an independent feature of parkinsonism.[15,75]

A new objective method for evaluating FOG consists of an ambulatory gait analysis system with pressure sensitive insoles that continuously record walking, synchronised with a video recording.[76] By using this system, the episodic and unpredictable nature of FOG can be quantified and assessed over several minutes (Fig. 4). Given the transient nature of FOG, a longer walking evaluation period, i.e., minutes rather than just a few seconds, is preferred. In addition, the "tremor-like" shaking of the legs during FOG can be analysed using time

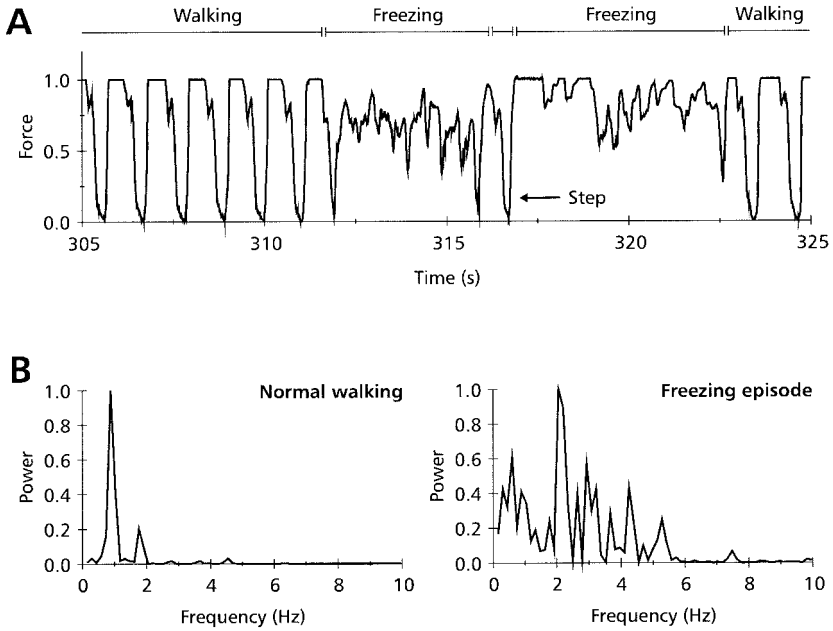

FIG. 5. Example of freezing of gait in a 77-year-old man with advanced Parkinson's disease (Hoehn and Yahr stage 3). The effects of "trembling-legs" during freezing of gait is reflected in the insole forces. The top panel shows insole forces before, during, and after a freezing episode. The bottom panel shows the results of spectral analysis for the walking period and for the freezing episode (the data before the break through step were analysed here). Note the large percentage of power in the 3 to 6 Hz band during freezing but not during walking. Reprinted with permission from Hausdorff and colleagues.[77]

series analyses. This quantitative analysis clarified that the trembling during FOG is distinct from classic tremor, both in terms of frequency and complexity of the leg fluctuations, but also distinct from normal locomotion.[76,77] In FOG, the legs fluctuate in a complex pattern with much of the power centred around 2 and 4 Hz (Fig. 5). Although the fluctuations may seem random, the legs in fact fluctuate in a fairly organised pattern. One possibility is that the movements during FOG are generated by an independent generator or by misfiring oscillators that force the legs to move too fast for effective stepping. Future studies are needed to evaluate if this trembling is activated involuntarily or as a result of the patient's effort to overcome the block.

Two recent studies showed that patients with FOG walk differently than patients who do not exhibit FOG, even in between the freezing episodes. One study reported that PD patients who experience FOG have an abnormal stride length and cadence during the three steps *prior* to freezing.[78] Another study observed that, while walking without apparent freezing episodes, PD patients with FOG have higher stride-to-stride variability compared to patients without FOG.[76] These observations suggest that a FOG episode may be the extreme form of gait dysrhythmicity, and that a loss of locomotion rhythm is perhaps the primary underlying neurophysiological disturbance in FOG. This desynchronisation might be the basis for the increased disturbance in gait dynamics and, more specifically, the increased stride-to-stride variability observed in patients with FOG.[76] This dysrhythmicity theory now seems more plausible than the idea that FOG might be caused by coactivation of antagonist muscles in the legs, which has only rarely been observed during FOG.

What does the response to treatment tell us about the pathophysiology of FOG? The frequent occurrence of FOG during the *off* state and the significant decrease in FOG in response to L-dopa indicate a relation to the hypodopaminergic state of the brain.[32,74] However, *off* state FOG did not improve when mesencephalic fetal cells were bilaterally implanted in the putamen to stimulate dopaminergic transmission.[79] Perhaps exogenous L-dopa acts to improve FOG at a site other than the putamen, suggesting a possible involvement for the caudate nucleus. Such an involvement of the caudate nucleus and its frontal projections could underlie the effects of mental processes on FOG and could explain why FOG can be observed in patients with frontal lobe lesions.[80] However, the preparatory cortical motor potential or Bereitschaftspotential was normal in patients with FOG.[81] Furthermore, frontal lobe blood flow perfusion as studied by SPECT did not differ between subjects with and without FOG.[82]

Interesting observations were made on patients with severe parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a condition that, at least in humans with acute exposure, appears to be a largely selective hypodopaminergic syndrome.[83] Freezing was not specifically reported when these patients were first discovered in an untreated state. However, shortly after initiation of treatment with L-dopa, these

patients developed freezing episodes similar to those seen after several years of therapy in PD.[84] These findings suggest that FOG, at least in part, is induced or aggravated by dopaminergic medication. This mechanism could explain the occurrence of FOG during the *on* state. However, it is important to note that some FOG during the *on* state may still result from a relative insufficiency of L-dopa dosage.

In prospective double-blind studies, the mono-amine oxidase type B inhibitor selegiline reduced the development of FOG in early[12] and more advanced PD.[14] In advanced PD, patients who participated in the DATATOP study, the effect of selegiline on FOG was not simply a symptomatic effect on general motor performance.[14] One possibility is that selegiline works through an improvement of the visuomotor system. Of interest, selegiline improves the P-300 latency in PD patients[85] and it improves visuomotor arm control in naive PD patients.[86] In clinical practice, patients with resistant FOG deserve a trial with selegiline, but the effects are often not impressive. Perhaps selegiline helps to prevent development of FOG but is less effective once the symptoms are fully developed.

TREATMENT

Drug Treatment

Some balance deficits seem primarily related to loss of central dopaminergic transmission, and for this reason, it is always worth trying to increase the dosage of L-dopa (Table 1). L-Dopa usually alleviates *off* state FOG[87] but is not very effective in preventing falls. In a prospective survey of fall circumstances during daily life,[6] most falls occurred when patients were in their best clinical condition (*on* state), possibly reflecting their increased mobility when symptoms are well controlled. In fact, one third of the falls occurred when patients were experiencing dyskinesias, some of which may have been sufficiently severe to perturb the patients and cause a fall. Quantitative analyses of postural reactions to sudden movements of a supporting platform also indicate that dopaminergic medication provides insufficient relief of most balance deficits, although some aspects improved partially.[69,88,89]

It is important to realise that dopaminergic medication can cause balance and gait deficits in PD. For example, dopaminergic medication can lead to orthostatic hypotension and thereby cause syncopal falls.[29] Confusion, hallucinations, and psychosis are other adverse medication effects that may induce falls by causing recklessness or dangerous wandering behaviour. Of interest, dopamine agonist treatment was associated with an increased frequency of FOG in two double-blind, prospective studies in early PD.[90,91]

The resistance of many gait and balance problems to dopaminergic treatment suggests that lesions within nondopaminergic nuclei might be involved in the pathophysiology.[69,92] These locations could include the adrenergic locus coeruleus and the cholinergic/glutaminergic pedunculopontine nucleus. Quite logically, attempts have been made to ameliorate balance and gait deficits using drugs aimed at restoring these nondopaminergic deficits. L-threo-DOPS (a synthetic precursor of norepinephrine) has received most attention. Beneficial effects on freezing, gait impairment, retropulsion, and postural instability were noted in small, poorly controlled studies.[93,94] Pending further evidence, there is presently no place for L-threo-DOPS or other nondopaminergic compounds in daily clinical practice.

TABLE 1. *Treatment options to reduce falls and FOG in PD*

Pharmacotherapy
Increase dopaminergic treatment for *off* state symptoms
Consider reducing medication for *on* state symptoms
Eliminate benzodiazepines whenever possible
Freezing of gait:
- Serotonin reuptake inhibitors
- Selegiline
- Botulinum toxin into calf muscles
- Reduce dopamine receptor agonists
Stereotactic neurosurgery
Young patient with mild and dopa-responsive axial symptoms
Avoid thalamic surgery and bilateral pallidotomy
Physiotherapy
Gait training (*e.g.,* use of cues)
Improve posture
Practice transfers (*e.g.,* chaining technique)
Balance training
Improve cardiovascular fitness
Train use of walking aids
Reduce fear of falling
Interaction with others
Other measures
Remove domestic hazards
Proper footwear
Heightened heels (to reduce backward falls)
Walking aids
Avoid daily alcohol
Treat symptomatic orthostatic hypotension
Treat associated depression
Electronic warning system
Avoid injuries
- Hip or wrist protectors (but poor compliance)
- Shock-absorbing surface
- Restriction of unsupervised activities
- Treat osteoporosis
Multidisciplinary team approach (including, *e.g.,* general practitioner, neurologist, geriatrician, rehabilitation specialist, physiotherapist, occupational therapist, psychologist, Parkinson's nurse specialist)

Deep Brain Surgery

Stereotactic deep brain surgery aimed at the internal globus pallidus or subthalamic nucleus can partially alleviate gait impairment and postural instability in well-selected patients with PD.[59,95–98] Bilateral interventions seem more effective than unilateral interventions,[99,100] and the effects were generally greatest for *off* state axial symptoms. A recent meta-analysis showed that bilateral pallidal stimulation and bilateral subthalamic nucleus stimulation were significantly more effective than unilateral pallidotomy in reducing gait and balance impairment during the *off* state.[101] Both unilateral and bilateral subthalamic nucleus stimulation can alleviate FOG,[99,102] but *on* state FOG may not improve much.[95] Thalamic surgery occasionally improves gait in PD, but the risk of postural deficits is considerable, particularly after bilateral approaches.[103] Pallidotomy also carries a risk of causing or aggravating gait and balance deficits, again mainly after bilateral procedures. Careful selection of appropriate candidates seems critical, because the effects on axial symptoms vary considerably among patients, and some do not improve at all. Younger patients with milder and dopa-responsive axial symptoms seem to respond best.[104] A particular concern is that several years after an initially good response, some patients develop severe gait and balance deficits that are often resistant to further therapeutic intervention.

Physiotherapy

Posture, balance, gait, and transfers can be targeted by physiotherapists.[105] Examples of possibly useful interventions include the use of cueing,[33,106] teaching of alternative motor strategies to make safer transfers,[107] gait training with external weight support,[108] and the use of exercises to improve stability, spinal flexibility, and general fitness.[64,109] Patients with FOG should be taught not to try and overcome their motor block during walking, as this may increase the risk of a fall. Physiotherapy is best delivered in the domestic situation, as the effects of home treatment exceeded those of hospital-based interventions.[110] However, recent meta-analyses concluded that there is little evidence to support or refute the use of physiotherapy, because of methodological flaws in published studies.[33,111,112] Further work is, therefore, needed.

Other Measures

A variety of additional measures can help reduce falls in PD. Symptomatic orthostatic hypotension can be treated in various ways, e.g., using elastic compression stockings or specific anti-orthostatic manoeuvres, such as standing with crossed legs or squatting.[113] Orthostatic hypotension can also be treated pharmacologically using fludrocortisone or sympathicomimetics such as midodrine, but a drawback is the increase in supine blood pressure.[114] Progression of osteoporosis can be arrested using the oral provitamin 1α-hydroxyvitamin D3 or vitamin K(2) (menatetrenone), resulting in a lower incidence of fractures.[42,115]

A novel approach to the treatment of FOG was motivated by the serendipitous observation that injection of botulinum toxin into a dystonic leg of a parkinsonian woman dramatically reduced FOG.[116] An open label trial, injecting botulinum toxin into the calf muscles of 10 PD patients with functionally significant FOG, showed that 70% of patients had some clinical benefit, which lasted for a mean duration of 6.6 weeks.[117] Based on the open nature of that study, these preliminary observations should be taken with caution. Several investigators have initiated double-blind studies, but the results are not yet available.

Individually tailored counselling by a PD nurse specialist is often appreciated by patients. However, a large randomised controlled trial showed that provision of community-based PD nurse specialists gave no improvements in transfers from a chair, frequency of bone fractures and mobility-related quality of life.[118] PD nurses may be more effective as part of a team, because the multifactorial pathophysiology underlying falls and FOG calls for a multidisciplinary approach. A recent study addressed this issue and found that an intensive multidisciplinary rehabilitation program—focused on patients and carers—significantly improved the patients' mobility and gait.[119] Of interest, patients with more advanced disease at baseline benefited most from treatment. The carers also responded positively. These findings should be expanded to design an optimal intervention program, to address such basic issues as cost-effectiveness, duration of effect, and compliance, and to distil the most effective components of the multidisciplinary rehabilitation program.

FUTURE PROSPECTS

With this review, we emphasised the clinical significance of falls and FOG for patients with PD. In addition, we clarified that, although falls and FOG are often difficult to treat, there is no room for therapeutic nihilism. The past few years have produced promising developments that offer hope for affected patients. At the same time, recent scientific evidence is beginning to shed new light on the complex pathophysiology underlying falls and FOG. Future developments will include randomised clinical trials to evaluate treatment strategies, and neuroimaging techniques that can functionally visualise the

neural circuitries involved in generating gait and postural responses in PD. In addition, focal lesion studies in animals will be instrumental to pinpoint the pathophysiology of axial mobility deficits, and to identify neural structures for novel therapeutic interventions.

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