Practical approach to freezing of gait in Parkinson's disease

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/practneurol-2013-000743).

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Published Online First
14 February 2014

ABSTRACT

Freezing of gait in Parkinson's disease and related disorders is common and very disabling. It usually occurs in the advanced stages, although mild forms may develop earlier. Freezing can occur on turning, in narrow spaces, immediately before reaching a destination, and in stressful situations. Dual tasking (motor or cognitive load) aggravates the problem. Freezing of gait in Parkinson's disease usually occurs in the 'off' rather than in the 'on' state. It is, therefore, not entirely drug-resistant; the first step in medical treatment is to ensure adequate dopaminergic stimulation to reduce the 'off' state. There is no good evidence for any specific drug to alleviate freezing. Visual or auditory cues are very helpful as behavioural therapy. Assistive devices, such as a wheeled walker sometimes help. Deep brain stimulation of the subthalamic nucleus may alleviate freezing in the 'off' state. Because of the complexity of freezing, individual patients need a careful assessment—particularly in relation to motor fluctuation—to optimise their treatment.

INTRODUCTION

Freezing of gait is a unique and disturbing disorder where parkinsonian patients cannot start or continue to walk.[1–5] It is characterised by difficulty in stepping forwards—either at the start of or during walking—with the patient unable to lift the foot from the floor and with trembling of the legs.[1 2] Because sudden freezing usually disturbs balance, parkinsonian patients may fall.[3] Figure 1 shows the vicious cycle of freezing of gait and falls. It is common in Parkinson's disease but may be even more common in atypical parkinsonisms, such as pure akinesia,[6] progressive supranuclear palsy, vascular parkinsonism, and normal pressure hydrocephalus (table 1).

CLINICAL CHARACTERISTICS

When a patient with freezing of gait attempts to lift a foot to step forward, the foot feels 'stuck' to the ground.[2 3] The 2010 Washington DC workshop defined freezing of gait as 'a brief, episodic absence or a marked reduction of forward progression of the feet despite the intention to walk'.[7] There are three clinical patterns:

- *Trembling in place*, with alternating rapid knees movements (knee trembling)
- *Shuffling forward*, with very short, shuffling steps
- *Complete (or total) akinesia*, with no limbs or trunk movement.

Several situations can cause freezing of gait, but turning (turning hesitation) is the most provocative (table 2).[3 4 8] Most patients have their preferred direction of turning, but there is a complex relationship between turning direction and disease-dominant side.[2 5] Freezing is also common at the initiation of gait (start hesitation), when a patient is passing through a narrow space such as a door frame (tight-quarters hesitation) or immediately before reaching a destination (destination hesitation) (table 2). Time pressure also worsens the tendency: for example, when attempting to cross a busy street before the traffic signal changes, or when using an elevator. Sudden demands—such as a ringing telephone or a doorbell—may worsen freezing, as may cognitive load, such as a verbal fluency task and 'serial 7 calculation'.[5] The 'stop walking while talking' test—originally for demented elderly patients—increases cognitive load during walking. Motor dual tasking, such as carrying a tray or bags while walking, also aggravates freezing, as may cognitively challenging situations, stress, depression and anxiety.[9]

On the other hand, patients can usually step over a line drawn on the ground in front of them (kinesia paradoxa). Stern *et al*[10] described several methods for overcoming freezing in 61 patients (box 1). The most frequently used method is to provide verbal or auditory stimuli, such as

To cite: Okuma Y. *Pract Neurol* 2014;**14**:222–230.

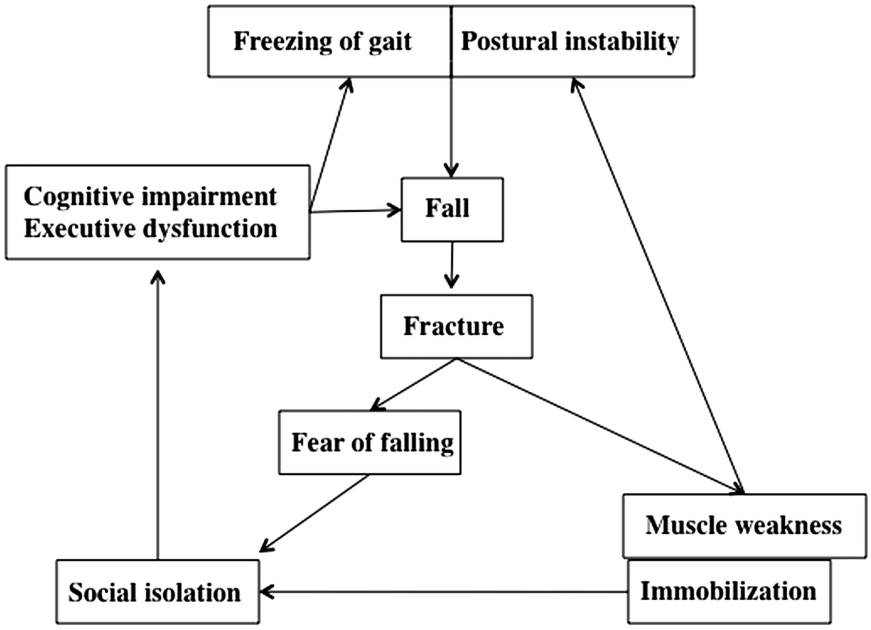

Figure 1 Clinical impact of freezing of gait. Note the vicious cycle of muscle weakness or cognitive impairment aggravating postural instability and freezing of gait.

a soldier's marching command. Others include visual stimuli, such as stepping over inverted walking sticks, another person's foot, or carpet patterns.[10] Patients who show freezing on the floor can easily climb stairs; climbing stairs involves a vertical leg movement and uses a different motor programme from that in horizontal walking. Also, stairs act as a strong visual cue. Although freezing worsens in stressful situations that limit time or space, moderate emotional stress often improves it. Thus, a patient can, for example, walk without freezing in a doctor's office when focusing attention on the act of walking. Thus, videotaping freezing of gait in outpatient clinics is difficult.[5] By contrast, many patients show the worst freezing while at home,[2–4] perhaps because their walking attention is distracted. It is not clear why sensory stimuli can facilitate and block movement.

Festination is unique to Parkinson's disease. Sir James Parkinson, in 'The Shaking Palsy' described festination as 'The propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and forepart of the feet, … irresistibly impelled to make much quicker and short steps, and thereby to adopt unwillingly a running pace.'

We have found that with a little shortening of stride during festination, gait speed increases (to running pace) because of the increased cadence; when there is marked shortening of stride (strong sequence effect), walking speed decreases despite the increased cadence; and freezing occurs. Thus, gait festination is associated with freezing, suggesting a common pathophysiology, such as disturbance of the central timing mechanism.[11 12] However, this theory cannot explain 'start hesitation'.

Table 1 Freezing of gait in parkinsonism

Disease	Frequency
Pure akinesia or pure freezing syndrome	Always present
Progressive supranuclear palsy	Very common
Vascular parkinsonism	Very common
Normal pressure hydrocephalus	Common
Parkinson's disease	
Early	Less common, but present
Mid to advanced	Common
Multiple system atrophy	Common
Corticobasal degeneration	Common
Drug-induced parkinsonism	Less common

RELATIONSHIP TO DISEASE PROGRESSION AND DOPAMINERGIC TREATMENT

Freezing of gait occurs more commonly in advanced Parkinson's disease.[2 4 13] Despite this, duration of levodopa treatment does not necessarily relate to the

Table 2 Provocation of freezing of gait

Type of freezing	Occasion	Frequency
Turning hesitation	Freezing when turning	Very common
Start hesitation	Freezing when gait is initiated	Common
Reaching destination hesitation	Freezing when approaching target	Common
Tight quarter hesitation	Freezing in narrow space	Common
Open space hesitation	Freezing in open space	Less common

Box 1 Trick movements or strategies for alleviating freezing of gait

- Gait modification by unaccompanied patient
  - Altering distribution of body weight
  - Walking sideways 'crablike'
  - Consciously lifting one leg higher
  - Sliding one foot backwards then walking forward
- Assisted by another person
  - Rhythmical pulling or pushing
  - Passively elevating patient's knee
- Verbal or auditory stimuli
  - Marching to command like a soldier
  - Walking or dancing to music or metronome
  - Another person giving verbal commands
- Visual stimuli
  - Stepping over object, another person's foot, paving stone, carpet patterns
  - Using L-shaped cane or laser beam cane
  - Watching other people walk

likelihood of developing freezing of gait: longer disease duration and longer levodopa treatment commonly go together and their effects cannot be completely separated. Freezing of gait can develop at a relatively early stage of Parkinson's disease but is then mild and of short duration. Severe freezing in early disease is a red flag, suggesting atypical parkinsonism.[4] Giladi *et al*[14] looked at the natural course and risk factors for freezing of gait in the early stage of Parkinson's disease using data from the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study: the associated factors at disease onset were the absence of tremor and the presence of a gait disorder. The development of freezing during the course of Parkinson's disease strongly correlates to balance and speech problems, but less to worsening of bradykinesia, and is not associated with progression of rigidity. Bartels *et al*[15] also showed that freezing of gait does not correlate with bradykinesia. A recent study showed that non-gait freezing, increased dopaminergic drug dose, falls/near falls and cognitive problems are independent determinants of gait freezing in Parkinson's disease. Box 2 summarises the risk factors for developing freezing of gait.

A distinctive feature of freezing of gait in Parkinson's disease, as opposed to that in atypical parkinsonism, is the response to dopaminergic therapy. In patients with the wearing-off phenomenon, freezing is more common when 'off'. Schaafsma *et al*[8] studied 19 patients with gait freezing and showed that 95% experienced freezing when turning while in the 'off' state, but only 32% showed turning hesitation in the 'on' state. The duration of freezing when 'on' was significantly shorter than when 'off', suggesting that levodopa reduces freezing in most patients with

Box 2 Risk factors for developing freezing of gait in Parkinson's disease

- Onset of Parkinson's disease with a gait disorder
- Absence of tremor
- Development gait, balance, and speech disorders
- Longer disease duration
- Longer levodopa treatment
- Increased total dopaminergic drug dose
- Initial motor symptoms on the left side
- Disease severity
- Depression and anxiety
- Cognitive impairment

Parkinson's disease. Moreover, the ELLDOPA (Early vs Late LevoDOPA) study showed that a certain amount of levodopa delayed development of freezing in early Parkinson's disease.[16] By contrast, one report showed that high doses of levodopa therapy induce freezing of gait (hypotonic freezing) within years of starting treatment,[17] a phenomenon equivalent to the recently recognised 'on' freezing.[2 18] Concomitant dyskinesias may worsen freezing during the hypotonic 'on' state.[5] Recently, Espay *et al*[18] described four patients with 'on' freezing of gait, and stressed the importance of using supratherapeutic medication doses (at least twice the usual dose) to distinguish true 'on' freezing from 'pseudo-on' freezing. Table 3 summarises the influence of dopaminergic medications on freezing of gait.

PATHOPHYSIOLOGY

The pathophysiology of freezing of gait is not well understood. There are many hypotheses, which are not mutually exclusive (box 3). A better understanding of its mechanisms may allow effective treatments to develop.

Disordered central drive and automaticity

In Parkinson's disease, disruption of the 'basal ganglia to supplementary motor area' circuit for self-initiated movements reduces central driving and internal cueing to the motor cortex. The progressive reduction

Table 3 Influence of dopaminergic medication on freezing of gait

Types of freezing	Characteristics
Freezing in the 'off' state	Relieved by dopaminergic medication
Freezing in the 'on' state	
'Pseudo-on' freezing	Observed during a suboptimal motor state or even seemingly optimal 'on' state, but which nevertheless improves with stronger dopaminergic stimulation
'True-on' freezing	Induced by dopaminergic medication Reduction of medication may alleviate freezing, but other motor symptoms may deteriorate
Unresponsive freezing	Freezing in 'off' and 'on' states, not influenced by medication

Box 3 Pathophysiology

- Disordered central drive: disruption of basal ganglia-supplementary motor area loop for self-initiation
  - Sequence effect of progressive shortening of step length
  - Impairment of automaticity
- Abnormal gait pattern generation: disordered supraspinal facilitation
  - Increase in stride-to-stride variability
  - Impaired gait cycle coordination
- Rhythm formation disturbance (hastening) during freezing: fronto-striatal
- Abnormal coupling of posture and gait
  - Knee trembling might be a disrupted anticipatory postural adjustment
- Postural instability (inability to shift body weight to one leg)
- Perceptual malfunction
  - Abnormal perceptual processing of environmental constraints
- Frontal executive dysfunction:
  - Particularly of set-shifting

in step length before freezing episodes—a consequence of decreased motor drive or defective cue production—is the 'sequence effect'.[12] Spatiotemporal gait abnormalities, such as premature stepping, also occur just before freezing.[19] Physiological malfunction in Parkinson's disease causes a motor set mismatch between the step size that is cortically selected and that maintained by the basal ganglia (hypokinesia).[12]

Skilled movements, such as gait, are automatic and require less attention.[20] In Parkinson's disease, there is impaired automaticity, putting more stress on voluntary mechanisms, and increased pressure on cognitive resources. Parkinson's disease patients without freezing may compensate for automaticity deficits by switching to increased cognitive control, but those with freezing cannot. Impaired automaticity explains why freezing of gait frequently occurs while performing secondary cognitive or motor tasks (dual tasking).[20]

Abnormal gait pattern generation

Ambulatory gait analysis using pressure-sensitive insoles show that freezing of gait is associated with increased stride-to-stride variability, bilateral uncoordinated gait, and marked gait asymmetry.[21] Although these could result from abnormal output from the central pattern generators of the spinal cord, there is probably also disordered supraspinal facilitation (driving).

Rhythm formation disturbance (hastening) during freezing

Knee trembling is the most characteristic feature of freezing of gait. Yanagisawa *et al*[1] first recorded floor reaction forces of this using a force plate. The frequency of trembling is very similar to that in a hastened response during alternating voluntary movements in Parkinson's disease, such as finger tapping.[22] Since hastening also develops in patients with striatal lesions from stroke,[23] the basal ganglia and its frontal projections may be an essential lesion site for freezing of gait.[5] Another hypothesis is that there is impaired postural adjustment in preparation for stepping. Jacobs *et al*[24] showed that multiple anticipatory postural adjustments induce the knee trembling, and that freezing associated with a forward loss of balance is caused by inability to couple normal anticipatory postural adjustments to the motor programmes for stepping.

A perceptual malfunction

Patients with Parkinson's disease find difficulty in passing through narrow spaces such as doorways. Almeida and Lebold quantified the 'walking through different-sized doorways' task in Parkinson's disease.[25] They found decreased step length and increased gait variability while approaching a narrow doorway, but only in those patients with freezing of gait. Thus, freezing is found to result from an underlying perceptual mechanism interfering with online movement planning.[25] Parkinson's patients estimate wider 'just passable door width' than healthy controls,[26] but the estimate is similar between those with and without freezing of gait.[27]

Frontal executive dysfunction

Patients with freezing of gait may have a frontal lobe dysfunction or a disconnection between the frontal lobe and the basal ganglia. Thus, Amboni *et al*[28] studied frontal executive function in early stage, non-demented Parkinson's patients, and found significantly lower frontal assessment battery scores, verbal fluency and 10-point clock test scores in patients who freeze than in those who do not. Freezing of gait also selectively correlates with poorer performance in tasks of set shifting, but not with a range of other executive tasks. These results support a frontostriatal dysfunction in Parkinson's disease patients with freezing of gait, disrupting ability to keep different tasks online.

Cholinergic degeneration contributes to disordered gait and balance problems[29] but with no clear direct relationship to freezing. Reduced thalamic volume and related visual recognition are associated with freezing, possibly reflecting cholinergic degeneration of the pedunculopontine nucleus.[30] However, a PET study using a cholinergic ligand would be needed to prove this relationship.

ASSESSMENT

Because freezing episodes are rare in the clinic, a careful history is most important. It is insufficient simply to ask about 'freezing', because not all patients

interpret this question correctly. To ensure the patient understands what freezing of gait is, it helps to show a typical freezing episode to the patient and also to the spouse or other caregivers. Physical examination should be carried out during the 'on' and 'off' states, because most patients freeze only when 'off'. Evaluation tests include passing through a narrow space such as a doorway, dual tasking and rapid 360° axial turns, and reaching a target destination, such as a chair. Evaluation of responses to external cues helps to determine the possible therapeutic interventions. Performance can be videotaped to evaluate objectively the type and degree of freezing. A freezing of gait questionnaire (FOG-Q) can help to assess freezing,[31] and comprises six items; four assessing severity and two assessing gait difficulty in general. It includes general gait items, which reduces its specificity. A new more specific FOG-Q uses short video clips, and reliably detects and evaluates the impact of freezing.[32]

It is important to make the correct diagnosis of Parkinson's disease, because it can respond to dopaminergic treatment, but atypical parkinsonism may not. Therefore, most patients require neuroimaging to detect underlying lesions, especially in the frontal lobes or their connections to the basal ganglia and brainstem. Even in typical Parkinson's disease, imaging may help by finding associated white matter lesions or cortical atrophy.

There are various quantified assessments of gait, such as electromyography and tests using a force plate, a three-dimensional (3D) camera, and an ambulatory gait analysis system with pressure-sensitive insoles. However, these apply more to the laboratory than the clinic. There are also inertial sensors that come as waist-mounted wearable triaxial accelerometer to measure trunk acceleration during everyday activities.[33] Figure 2 shows data from an advanced-stage Parkinson's disease patient with start and turning hesitations in an outpatient clinic. While walking, the sensors record the 'locomotor' (0.5–3.0 Hz) band of acceleration; during freezing, there is a higher-frequency (3–8 Hz) component of acceleration. Figure 3 shows the acceleration and trunk angle changes during a fall in a patient with Parkinson's disease, with rapid oscillation of acceleration due to knee trembling (freezing) and abrupt inclination of trunk angle (lower trace) caused by a forward fall.

TREATMENT

Dopaminergic medication

The medical treatment of freezing is difficult because its mechanism is multifactorial and poorly understood. Although freezing has long been considered as a dopamine-resistant symptom of Parkinson's disease, freezing in the 'off' state clearly improves with levodopa and other dopaminergic medications. Figure 4 shows a treatment algorithm. When the patient is undertreated without wearing off, increase the dopaminergic drugs. When the disease progresses and there is freezing particularly in the 'off' state, follow the management regimen for wearing off:

- start the combination of levodopa and a dopamine agonist
- use a catechol-O-methyltransferase (COMT) inhibitor and/or monoamine oxidase (MAO) type-B inhibitor
- increase the frequency/dose of levodopa
- perform deep brain stimulation to reduce the 'off' state.

When there is freezing of gait in the 'on state, there are two possibilities. Most freezing in the 'on' state is 'pseudo-on' freezing, occurring in the motor state only with suboptimal parkinsonism control, or even seemingly good control, but insufficient to alleviate freezing. In these cases, freezing may improve with stronger dopaminergic stimulation. 'True-on' freezing is relatively rare, and reducing dopaminergic medications may alleviate it,[18 34] but sometimes with deterioration of other motor symptoms. Box 4 shows a useful series of questions to help to differentiate 'true-on', 'pseudo-on', 'off', and 'unresponsive' freezing of gait. Two double-blind, prospective studies in early stage Parkinson's disease showed that freezing of gait is more likely on dopamine agonists than on levodopa. This could be because of the milder benefit to motor symptoms from a dopamine agonist.[34] We need further research to clarify whether dopamine agonists have a negative impact on the development of freezing.

A large, randomised controlled study showed that the MAO-B inhibitor selegiline delays the development of freezing,[35] but once freezing had developed, the inhibitor rarely reduces it. Rasagiline also modestly helps the freezing score, but its clinical significance is not clear.[34] Amantadine may reduce frequency of freezing (retrospective study), but this needs confirming prospectively.[13]

Specific medications

Recently, two groups have investigated methylphenidate for freezing of gait in Parkinson's disease in double-blind, placebo-controlled trials, but with contradictory results,[36] probably through differences in study design. L-threo-dihydroxyphenylserine (L-DOPS), or Droxidopa, is a precursor of norepinephrine, with modest efficacy in a double-blind, placebo-controlled study.[37] However, this effect awaits confirmation in Western countries. Caffeine, an adenosine A2A antagonist, might also help freezing in Parkinson's disease. Although botulinum toxin injections into the calf muscles helped in an open-labelled study, recent double-blind placebo-controlled studies showed no benefit to freezing in Parkinson's disease.[34]

Behavioural approaches, rehabilitation, assistive devices

Box 1 shows various tricks with or without assistance of the accompanying person. Particularly helpful advice to patients include:

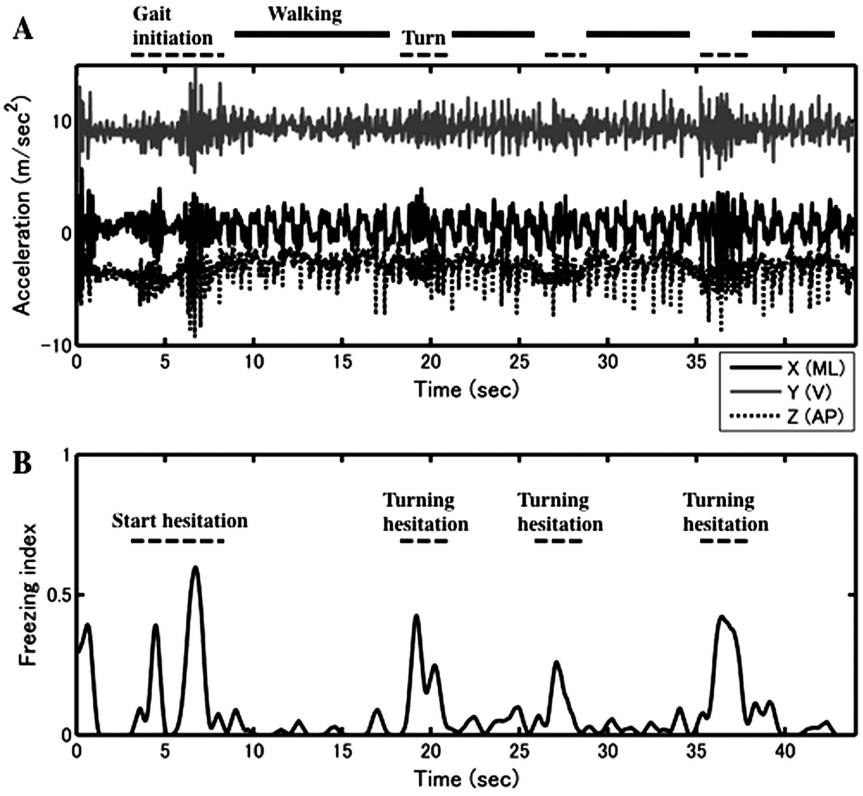

Figure 2 A 40-second recording of acceleration recorded by a triaxial accelerometer mounted on the waist during gait initiation, walking and turning in advanced Parkinson's disease. (A) A higher-frequency component of acceleration during start and turning hesitations. (B) Freezing index: The rhythmicity of knee trembling between 3 and 7 Hz is estimated by a cross-correlation calculation, based on the mathematical method of 'pattern matching'. The freezing index increases from 0 to 1 as the trembling becomes more rhythmic. The freezing index increases during start and turning hesitations.

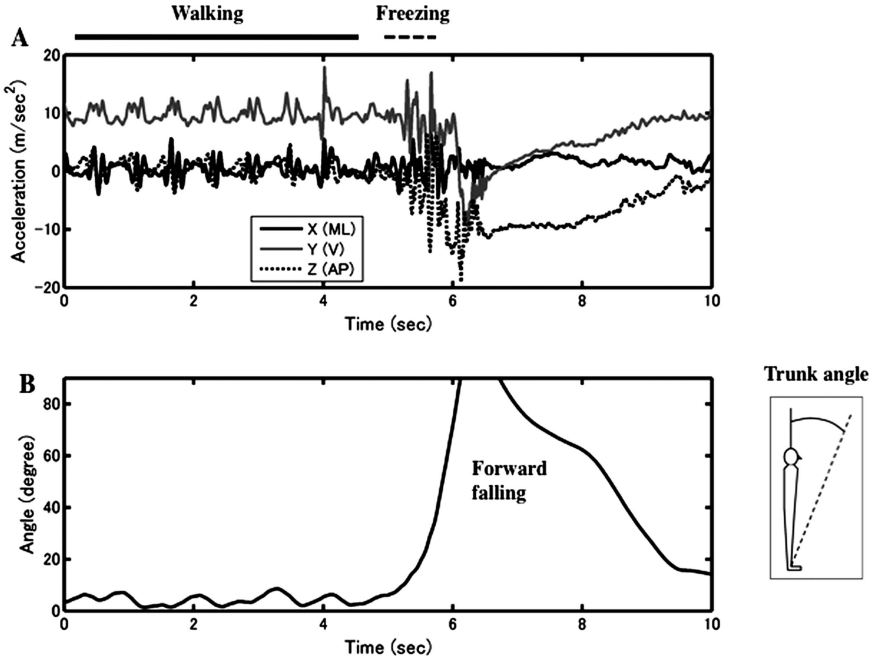

Figure 3 A fall detected by the triaxial accelerometer worn on the waist. (A) Acceleration of walking, freezing of gait, and a forward fall in a Parkinson's patient in everyday life. A rapid oscillation of acceleration corresponds to knee trembling (freezing). (B) A trunk angle change calculated from the vertical (gravity) component of acceleration indicates an abrupt forward inclination of the body.

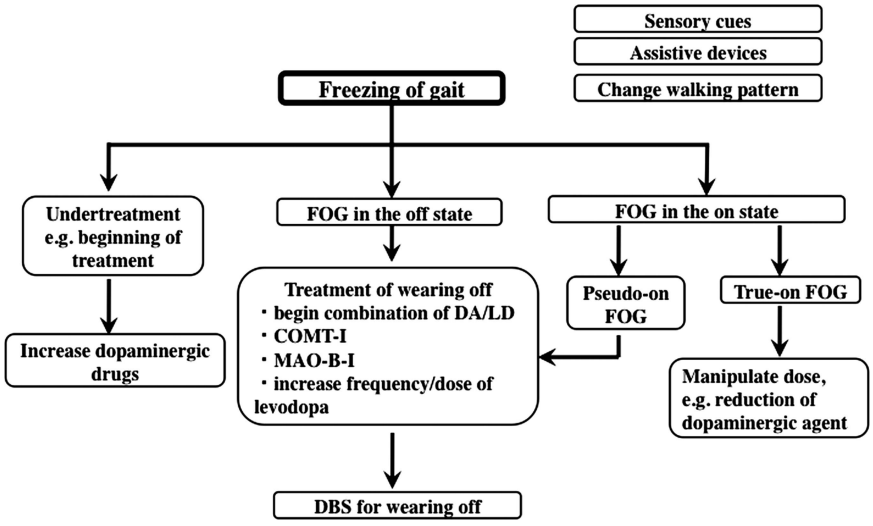

Figure 4 Algorithm for treating freezing of gait. freezing of gait, freezing of gait; DA, dopamine agonist; LD, levodopa; COMT-I, catechol-*O*-methyltransferase inhibitor; MAO-B-I, monoamine oxidase type-B inhibitor; DBS, deep brain stimulation.

- consciously lift one leg higher and march like a soldier (figure 5A)
- slide one leg backwards and then walk forward (see online supplementary video 1)
- step over another person's foot (see online supplementary video 2)
- strike the heel on the ground first when walking to prevent shuffling gait (figure 5B)
- step over transverse lines drawn on the floor (figure 5C) or 3D objects
- do not make a steep/sharp turn, but make a round/wide turn when possible (see online supplementary video 3).

Box 4 Questions that can help distinguish 'on' freezing from 'off' freezing

- Does freezing occur in the 'off' state, but disappear in the 'on' state?
  - Yes → 'off' freezing
  - No → 'undertreated' or 'unresponsive'freezing
- Does freezing of gait occur in the 'on' state, but disappear in the 'off' state?
  - Yes → 'true-on' freezing
  - No → go to the next question
- Does freezing of gait occur in the 'on' state, but improve with stronger dopaminergic medications?
  - Yes → 'pseudo-on' freezing
  - No → go to the next question
- Does freezing occur in the 'on' state, and aggravate with stronger dopaminergic medications?
  - Yes → 'true-on' freezing, if freezing disappears in the 'off' state
  - No → 'pseudo-on' freezing or 'unresponsive' freezing

Rehabilitation strategies for freezing have received much attention over the last decade.[38] Parallel lines, modified inverted sticks, virtual reality glasses and ordinary rhythmic auditory cues all have immediate cueing, but the results are contradictory, probably because of small patient numbers, and because patients are mostly evaluated in the 'on' state.[38] However, external cues helped in three out of four patients with 'on' freezing of gait.[18] Training exercises, with and without cues, also help. 'The Rehabilitation in Parkinson's disease: Strategies for Cueing' (RESCUE) trial (a randomised crossover study) studied the effects of a home physiotherapy programme based on rhythmical cueing on gait.[39] Most patients chose auditory cueing, and there were significant improvements in posture, gait and freezing of gait scores. There were two other randomised controlled studies, both with improvements in freezing[38]:

- 6-month supervised group exercise on fall risk factors
- treadmill training with auditory and visual cues.

A 1-month open-label study of a laser light cue for using a cane or a walker also improved freezing; a laser cane may, therefore, be useful. Assistive devices such as a four-wheeled walker might consistently improve mobility and safety.

Surgery

Deep brain stimulation of the subthalamic nucleus may alleviate freezing when in the 'off' state much more than in the 'on' state.[40] Reducing the frequency of stimulation may also improve freezing. Although there are favourable preliminary open-label data on deep brain stimulation of the pedunculopontine nucleus, small double-blinded trials seem less promising.[41 42] For example, there have been studies of bilateral pedunculopontine nucleus stimulation after bilateral subthalamic nucleus deep brain stimulation,

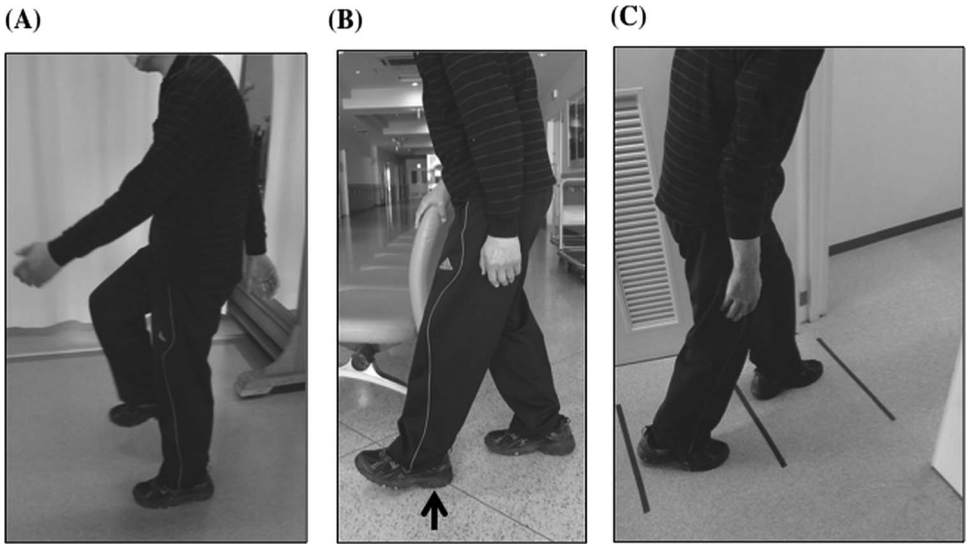

Figure 5 (A) Consciously lifting one leg higher and marching like a soldier to overcome freezing. (B) Consciously striking the heel first on the ground may prevent shuffling forward or festinating. (C) To overcome the doorway effect, stepping over transverse lines drawn on the floor may help.

(possibly because of the severity of motor complications and long disease duration),[41] and of unilateral pedunculopontine nucleus stimulation solely.[42] We need further controlled studies to know whether better patient selection, targeting and setting of stimulation parameters might improve the outcome.

Having motor fluctuations and dyskinesias increases the risk of developing freezing. A recent review article summarised how to introduce advanced therapies, such as apomorphine subcutaneous infusion, deep brain stimulation, and levodopa intestinal gel to manage intractable motor complications.[43]

In conclusion, although freezing of gait has been extensively analysed recently, it remains poorly understood. Careful observation of individual patients, particularly in relation to motor fluctuations, may lead to more effective treatments.

Practice points

- Ask about being 'glued to the floor' in daily life; freezing is difficult to elicit in a routine clinical examination, even if severe at home.
- Provide a demonstration of freezing; patients may not understand what freezing is.
- Consider atypical parkinsonism if freezing is severe in the early stage.
- Freezing in Parkinson's disease is not drug-resistant; 'off'related freezing can improve with levodopa and other dopaminergic medication.
- Try to increase dopaminergic therapy even when patients are seemingly 'on'. Most freezing, when 'on', is 'pseudo-on' freezing, which still improves with increasing levodopa. However, when there is dyskinesia, take care with increasing dopaminergic treatment.
- True 'on' freezing is rare and difficult to treat; try to reduce dopaminergic medications, but beware that this may worsen other motor symptoms.
- Deep brain stimulation of the subthalamic nucleus may reduce freezing in the 'off' state.

Contributors YO contributed to the reviewing of literature, drafting and writing of this review article.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Commissioned; externally peer reviewed. This paper was reviewed by Ralph Gregory, Poole, UK.

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