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REVIEW ARTICLE

Freezing of gait: overview on etiology, treatment, and future directions

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Abstract

Background Freezing of gait (FOG) is a disabling motor symptom occurring mainly in the advanced stage of Parkinson's disease (PD).

Methods This review outlines the clinical manifestation of FOG and its relationship with levodopa treatment, the differential diagnosis with respect to other neurodegenerative and secondary forms and the available treatment.

Results We report the proposed models explaining the FOG phenomenon and summarize the available knowledge on FOG etiology's potential genetic contribution. A complete understanding of the mechanisms underlying FOG in PD is essential to find the best therapy. Different treatment options exist but are still not entirely successful, and often a combination of approaches is needed.

Conclusions Further studies focusing on the potential genetic role in FOG may increase the knowledge on the FOG etiology and pathophysiology, allowing further individualized treatment strategies for this very disabling phenomenon.

Keywords Freezing of gait (FOG) · Genetic and FOG · Treatment of FOG · Etiology of FOG · Differential diagnosis of FOG

Introduction

The freezing phenomenon refers to transient episodes, usually lasting seconds, in which the motor activity attempted by an individual is interrupted. Freezing occurs in several neurological disorders such as Parkinson's Disease (PD), and other degenerative and acquired parkinsonisms [1]. Although freezing mainly affects walking, it can also involve arms, face movements, and speech. The less frequent upper limb freezing manifests mainly during daily living activities such as teeth brushing or handwriting [2]. Speech freezing instead presents as palilalia, which refers to the involuntary repetition of the first syllable of words or phrases [3]. Freezing can also occur as eyelid freezing or levator palpebrae inhibition of supranuclear origin [4]. Freezing of gait (FOG), the focus of this review, is defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [5]. FOG usually lasts a couple of seconds and occasionally exceeds 30 s [6]. It is a highly debilitating symptom that usually appears in advanced idiopathic PD [5] with an increasing prevalence (10 to 90%) according to the stage of the disease [7]. FOG is more frequently associated with the PD postural instability and gait disorder (PIGD) phenotype [8] and with several non-motor symptoms such as cognitive impairment (e.g., set-shifting deficit), anxiety, and sleep disturbances (e.g., REM behavior disorders) [9–12]. The high fall risk [13] and reduced quality of life [14] represent the major issues related to this phenomenon.

Despite its clinical relevance and extensive research, the pathophysiology of FOG is not fully understood, and available treatment strategies are poorly effective. Little is known on the possible genetic predisposition/contribution to develop FOG.

In this review, we revised the knowledge on FOG clinical presentation and etiology, focusing especially on genetic factors, pathophysiology, and therapeutic approaches.

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Literature and search methods

A literature search was performed using PubMed as a primary information to identify publication on for several aspects of freezing of gait primarily focused on genetics. The following MeSH terms and/or keywords were used: freezing of gait genetics and/or gene variants and/or gene polymorphisms, pathophysiology, clinical presentations, differential diagnosis, and treatment.

The eligibility criteria for articles includes were articles published up to December 2020, written in English and currently published journal articles.

Clinical features and classification of FOG

The clinical evaluation of FOG is challenging mainly due to its episodic nature. Nevertheless, some studies point to the fact that in patients with FOG, the gait pattern is continuously impaired beyond FOG episodes, mainly due to increased gait asymmetry and variability or reduced step length [15–17]. Therefore, a careful anamnesis, physical examination, and evaluation of the effect of medications will help in assessing FOG properly [18]. FOG can appear when initiating walking (start hesitation), or during walking particularly when turning, crossing a narrow or tight quarter (e.g., doorway) or crossing the streets with several input, or when approaching a destination (target hesitation), or as an open space hesitation [19] (Table1). In addition to these known environmental factors, other stressors such as cognitive tasks (e.g., dual task) and sensory stimuli (e.g., doorbell, color-changing traffic light) can exacerbate FOG [20, 21]. FOG can also appear without any trigger, along with the disease progression.

Three phenotypical FOG patterns have been described: (i) trembling in place, (ii) shuffling, and (iii) akinetic freezing (less common) [6] (Table 1). Both (i) and (ii) are due to the inability to produce a voluntary movement caused by the co-contraction of agonist and antagonist muscles [24].

Since FOG occurs more frequently in the OFF-state, levodopa (LD) is the most common treatment to reduce its occurrence. However, LD can also worsen FOG [22, 25]. These and further observations led to a pharmacological classification based on the response to the dopaminergic

Table 1 Classifications of FOG

Phenotypical FOG manifestations (Fahn et al. 1995) [1]	
Start hesitation	FOG appears when patient initiate walking
Turn hesitation	FOG appears during turning
Apparent hesitation in tight quarters	FOG appears passing through doorways
Destination-hesitation	FOG appears when the patient approaches a target
Open space hesitation	FOG appears spontaneously
Phenotypical FOG patterns (Schaafsma et al. 2003) [6]	
Trembling in place	The patient attempts to move the feet to overcome the block and produce short and incomplete steps (i.e., alternating trembling (3–8 Hz) of the legs) remaining in the same place
Shuffling	The patient moves forward with very short steps
Akinetic freezing	The patient experiences a total arrest of the movement of the legs and feet
Pharmacological FOG classification (Espay et al. 2012) [22]	
OFF-state FOG	It disappears during the ON phase due to the levodopa treatment efficacy
OFF–ON- resistant/unresponsive FOG	Indifferent to the dopamine intake
ON-state FOG	Provoked by the L-Dopa assumption
Pseudo-on-state FOG	Present during likely on-state but ameliorate with increased dopaminergic treatment
Biphasic FOG	It appears in the transition phase between the OFF and ON phases
Phenomenology FOG classification (Ehgoetz Martens et al. 2018) [23]	
Asymmetric motor	Elicited during turning or gait initiation or through narrow passage
Anxious	Provoked by talking or distractions while walking, being in hurry or anxious
Sensory attention	Elicited while walking in the dark, in a disarrayed environment or in a sloped surface

medication [22]. The *OFF-state FOG*, which is frequently seen in the stage of early-fluctuations, is relieved by LD treatment. The *OFF–ON-resistant/unresponsive FOG*, which usually emerges with the progression of the disease, partly due to the additive degeneration of non-dopaminergic areas, is not relieved by LD. The *ON-state FOG* is caused by LD intake and disappeared when LD is reduced even in profound OFF state. It has been related with the impairment of cholinergic or glutamatergic system [26]. The *Pseudo-on-state FOG* is seen during an outwardly optimum on-state, but which nevertheless improves with increased dopaminergic medication [27]. A new form of LD-induced FOG has been recently described a *Biphasic FOG* that appears in the transition phase between the OFF and ON states [28, 29] (Table 1). Differentiating between these forms has consequences for treatment; OFF state FOG improves with higher LD dose or with different cueing modalities, while ON state FOG with LD tapering. The response to the medication or to the cues provides information also in relation to the underlying etiology allowing a differential diagnosis and tailored treatment strategies [30]. Ehgoetz Martens et al. [23] introduced an interesting tool, the characterizing FOG questionnaire (C-FOG), to classifying subtypes of freezers which consider the heterogeneity and the different triggering situations causing FOG. They differentiate FOG in three subtypes according to its underline phenomenology: (i) *asymmetric motor*, (ii) *anxious*, and (iii) *sensory attention* (Table 1). LD reduced FOG duration in the *asymmetric motor* and *sensory attention* subtypes, while no effects were shown in the *anxious* subtype. According to the phenomenology, different strategies can be used to overcome the different FOG subtypes: a "metronome" or "stepping over someone feet" are efficacious in the *asymmetric motor* and *sensory attention* subtypes, "take a deep breath" in the *anxious* subtype [23].

Pathophysiology of FOG

Different supraspinal/brain regions are involved in gait: the pontomedullary reticular formation (pmRF), the midbrain locomotor region, which, in turn, includes pedunculopontine nucleus (PPN) and cuneiform-subcuneiform nucleus, the basal ganglia (BG), the cerebellum, and the cerebral cortex [31]. PPN in particular has an important role in gait and posture control through cholinergic neurons. PPN receives inputs from BG and cortex neurons and projects to pmRF to initiate and modulate the spinal neural circuitry to control posture and gait [26, 32]. Cortical and striatal cholinergic denervation through PPN and thalamus is related to FOG [33]. BG receives inputs from cerebral cortex and controls voluntary motor movements through GABAergic projections to other brain regions. The supplementary motor area (SMA) and premotor area (PM) are also indispensable for locomotion control. The SMA and PM projected to both the spinal cord and the brainstem reticular formation, which are associated with movement initiation [34]. The processing of afferent information and its integration at the cortical level is of strategic importance. Only when the temporoparietal cortex timely integrates the visual, proprioceptive and vestibular sensations, PM and SMA can precisely release the motor program [35].

The pathophysiology of FOG in PD is still not well understood. FOG episodes appear to be related to different network failure. Several hypotheses have been proposed so far. Nieuwboer et al. [36] summarized the pathological mechanisms in the following four models: (1) The *cognitive* model explains FOG as related to the inability to process conflicting response which reflects an executive dysfunction and leads to behavioral incongruence [37]. (2) The *threshold* model implies that along with the disease progression, several motor gait dysfunctions accumulate leading to a point of motor breakdown [38]. (3) The *interference* model proposes that the concurrent cognitive and limbic information presented during a motor task caused locomotion interruption triggering FOG, increasing the synchronization within the BG circuitry, leading to an excessive inhibition of the thalamus and PPN [39]. (4) The *decoupling* model interprets FOG as a disconnection between the pre-planned motor program and the actual motor response [40]. Most of these models are focused on a single component, either the motor or the cognitive or the limbic one. Lewis and Barker [32] proposed a model where a "cross-talk" between competing inputs from parallel and segregated pathways (motor, cognitive, and limbic) [31] targeting the striatum, where a significant loss of dopamine is present, results in the overactivity of the output nuclei of the BG (globus pallidus internus-GPi and substantia nigra pars reticulata-SNr) which inhibit the already disordered PPN leading to FOG episodes, due to a decreased rhythmic gait control.

The impaired corticostriatal and corticothalamic system [39] leads also to an increased (hyper)-direct way activity thorough the STN that activates the GPi/SNr which contains GABAergic inhibitory neurons and further inhibits the PPN. The STN is an intermediate nucleus in the BG that integrates information from the frontal cortex to GPi/SNr.

Neurophysiological studies have shown abnormal prolonged STN firing rates in PD-FOG [41] and a decoupling between cortical and STN firing [42]. STN is also linked to the cerebellum thorough excitatory output [43] which increased the inhibitory cerebellar output. The cerebellum is involved in gait rhythm, taking and processing simultaneously the sensory feedback from the spinal cord and feed-forward information from the cortex. A recent meta-analysis on gait impairment in PD patients compared to controls showed that the cerebellar locomotor region is the most consistently gait area activated, while the supplementary motor area (SMA) is the less activated [44]. Abnormal

functional activation and connectivity in the cerebellum [45] and an increased activity in the parieto-occipital and cerebellar areas were shown in PD-FOG compared to PD-non-FOG patients suggesting a compensatory role of these areas towards the reduced activity in the BG [46]. Similarly, in PD-FOG, patients compared to non-FOG have also been shown an overactivation of the parietal cortex and a reduced activation of the frontal premotor cortex (SMA and premotor cortex) and deregulation of the output from BG [47]. However, in both studies, the authors did not specify whether the two groups differ in disease duration which may be relevant since FOG is prevalent with disease progression and in more severe PD phenotype (e.g., PIGD). Barthi et al. [48] have recently systematically reviewed the available literature on neuroimaging in PD with FOG (see review for details).

The different hypotheses highlight the complexity of FOG pathophysiology, and it is still not clear whether the involvement of different areas/networks may be responsible for the heterogeneity of FOG between patients. This certainly points out the need of further exploring it.

Genetic and gait disturbances (including FOG)

Monogenic forms of PD may exhibit distinctive phenotypic features or show specific disease symptoms in different disease stages. Walking disturbances were investigated in cohorts of patients with *LRRK2* and *GBA* variants, which today represent the most frequent genetic risk factors for PD. Although the phenotypical presentation of motor and non-motor symptoms in PD patients with *LRRK2* G2019S mutation is similar to the idiopathic PD (IPD), some differences have been reported [49]. In particular, gait dysfunction was reported as a frequent symptom at the time of examination in G2019S-PD, after adjusting for the disease course [50]. In a study on early-onset PD, the PIGD phenotype appeared significantly more frequent in *LRRK2*-G2019S PD patients [51]. In familial PD, carriers of the *LRRK2* G2019S mutation display a PIGD subtype three times more common and have more difficulty walking, displaying increased gait rhythmicity variability under challenging condition [52]. An increased gait variability under challenging conditions (i.e., dual-task) and worse cognitive performances has been reported in *LRRK2* mutation carriers with no PD diagnosis compared with non-mutated subjects [53, 54]. Some studies specifically assessed the genetic association of FOG.

Da Silva et al. reported a higher FOG frequency in *GBA*-PD and IPD compared to *LRRK2*-PD mutation carriers [55]. Similarly, postural instability and gait disorders were more frequent in *GBA*-PD (61%) than in *LRRK2*-PD (48%) and IPD (49%) in a study on a large cohort of Chinese PD patients ($n = 1638$) [56]. However, the difference was not statistically significant. Concerning the young-onset monogenic forms, being rare forms, there are no systematic data on the frequency of walking disturbances. Walking is often affected by feet and lower limbs dystonia, which is frequent in these forms. Nevertheless, the impact of lower limb dystonia on gait can be distinguished from FOG by the lack of hesitation and the presence of the abnormal posture interfering with the quality of the steps. Doherty et al. reported FOG as a late feature in PD with Parkin mutations, suggesting a possible role of mutations of this gene in the onset of FOG in the late stage of the disease [57].

Due to the known role of both norepinephrine and dopamine signaling dysfunctions in determine FOG, Tekin et al. [58] investigated in PD patients whether the presence of a common tyrosine hydroxylase (TH) polymorphism (V81M) affects the clinical outcomes in 101 PD patients. They observed higher scores at the FOG questionnaire (FOG-Q) and a more severe FOG in those homozygous for the V81M variant after controlling for disease duration. The severe dopaminergic denervation in the presynaptic striatum has been reported as a predictor for the later development of FOG in 400 early PD patients [59]. A study investigated the *SLC6A3* rs393795 (AA) allelic variant effect on cerebral spontaneous neuronal activity and showed that this variant could aggravate the severity of gait disorders altering the SMA and inferior frontal gyrus (IFG) function and inducing compensatory activation of the right inferior temporal gyrus (ITG) [60].

Moreover, the *SLC6A3* rs3836790 polymorphisms appeared to be associated with the response to LD observed in advanced PD patients with gait disorders [61]. Based on the known effect of methylphenidate (MPH), a known dopamine transporter inhibitor, on gait disorders, the authors evaluate whether the above-mentioned *SLC6A3* gene variant was associated with different MPH response in ON-LD condition. They reported an effect of MPH on the number of FOG episodes, number of steps, and completion time of the stand-walk-sit test in PD patients with the *SCL6A3* rs3836790 genotype [61]. These patients were all implanted with deep brain stimulators, and the authors suggest that the findings could not be extended to less severely affected patients. Miller et al. [62] studied whether the rs1076560 *DRD2* (G > T) and rs4680 catechol-o-methyltransferase (*COMT*) (Val158Met) or brain-derived neurotrophic factor (rs6265 *BDNF* Val66Met) genetic polymorphisms were associated with gait function. They found that the *DRD2* polymorphism (T allele), but neither *COMT* nor *BDNF*, was consistently associated with worse gait and greater dopamine responsiveness in the patients compared to patients who were homozygous for the G allele (Table 2).

Overall, conclusive results linking rare monogenic forms or common genetic risk factors of PD with gait disturbances are still lacking. This gap of knowledge warrants future

Table 2 Summary of genetic studies in gait disturbances including FOG

Authors	Gene and SNPs	Gait abnormalities	Gait in early/late stage	Treatment
Marras et al. 2011 [50]	*LRRK2* G2019S (n. 25) IPD (n. 84)	Not specified Gait dysfunction > *LRRK2* (adjusted for disease duration)	28% (7/25) 0–5 y 8% (2/25) 6–10 y 20% (5/25) 11–15 y 40% (10/25) 16 + y Initial symptom 1 (4%) *LRRK2* 11 (14%) IPD	NA
Alcalay et al. 2009 [51]	*LRRK2* G2019S (34 (3.7%) Total n. 925	Not specified PIGD phenotype > frequent in *LRRK2* G2019S	NS	NA
Mirelman et al. 2013 [52]	*LRRK2* G2019S (n. 50) IPD (50) 9 (17%) PIGD phenotype	Increased stride time variability in 3 walking conditions (> dual task) TUG longer in *LRRK2* 32 (64%) PIGD phenotype	Initial motor symptom in 22% of G2019S-*LRRK2* mutation carriers compared with only 4% of non-carriers	The LD daily dose was higher in carriers
Mirelman et al. 2011 [53]	All healthy subjects *LRRK2* G2019S carriers (n. 25) Non-carriers (n. 27)	*LRRK2* G2019S carriers showed an increased stride time variability during dual-task walking condition		NA
Da Silva et al. 2017 [55]	Total n. 131 *LRRK2* (n. 16) *GBA* (n. 21) *GBA* and *LRRK2* (n .1) IPD (n. 93)	High frequency of FOG in *GBA* (72.22%) and IPD (77.42%) versus *LRRK2* (47.06%)	NA	All dopamine treatments
Wang et al. 2014 [56]	Total n. 1638 *LRRK2* (n. 223) *GBA* (n. 49) IPD (n. 1366)	PIGD > frequent in *GBA* (61.2%) than in *LRRK2* (48.4%) and IPD (49.1%) although the difference was not statistically significant	NA	NA
Doherty et al. 2013 [57]	Parkin mutation (n. 5)		FOG as a late feature in 2 of the 5 cases presented	NA
Tekin et al. 2016 [58]	V81M TH (rs6356; G to A change position at 241 in coding region) Total (n. 101) FOG + (n. 80): Homozygous (13) Heterozygous (n. 35) Wild type allele (n. 32)	FOG (measured with FOG-Q) worse in homozygous compared to hetero and homozygous for wild type allele		NA
Wang et al. 2019 [60]	*SLC6A3* (rs393795 AA) PD-FOG + (n. 50): AA 16 (32%)/CA 20 (40%)/CC 14 (28%) HC (n. 45): AA 14 (31%)/CA 26 (58%)/CC 5 (11%)	AA genotype was related to increased activation of right ITG and positively correlated with FOG-Q score	Disease duration AA = 3.71 ± 4.86 CA/CC = 4.75 ± 3.18	NA

Table 2 (continued)

Authors	Gene and SNPs	Gait abnormalities	Gait in early/late stage	Treatment
Moreau et al. 2015 [61]	FOG/gait disorders (n. 61) genotyped for *SLC6A3* (rs3836790)	Co-dominant model (genotype 6/6): the SNP is associated with the improvement after LD only on FOG episodes Recessive model (6/6 vs 5/5 and 5/6): the is associated with the improvement after LD of number of FOG episodes, number of steps and completion time		The SNP associated with the ON state after methylphenidate treatment
Miller et al. 2018 [62]	*DRD2* rs1076560 (G > T) (n. 36) *COMT* rs4689 (Val158Met) (n. 36) *BDNF* rs6265 (Val66Met) (n. 36) 30 HC	GAITRite ® Gait parameters collection *DRD2* patients (T allele carriers compared to G homozygote patients) had worse gait impairments (slower walk, shorter steps, more time of the gait cycle on double support) and higher LD effect	Mild-to-moderate stage Parkinson's disease	Medication responsiveness of gait function in Parkinson's disease mainly in T allele carriers of *DRD2* gene

FOG freezing of gait; *FOG-Q* freezing of gait questionnaire; *HC* healthy controls; *IPD* idiopathic Parkinson's disease; *ITG* inferior temporal gyrus; *LD* levodopa; *NA* not available; *NS* not specified; *PIGD* postural instability and gait disorders; *SNPs* single nucleotide polymorphisms; *TH* tyrosine hydroxylase; *TUG* time up and go test

effort in collecting prospective phenotypic and genetic data from large cohorts of patients. In this view, new emerging consortia will hopefully provide data for association studies of gait disturbances, such as FOG in PD, and genetic factors.

Freezing of gait: differential diagnosis

A marked impairment of gait, with early disappearance of postural reflexes and FOG, is typical of all degenerative parkinsonisms. In PD, FOG is present in about 7% of patients in the first 2 years of the disease, in about 28% within 5 years, 39% within 10 years, and 58% after 10 years. As illness progresses, the risk of developing FOG increases [10].

FOG also commonly occurs in atypical and vascular parkinsonism (VP). Despite there are no specific FOG-related features that allow a differential diagnosis with other parkinsonism (e.g., PSP and MSA), in the latter, FOG is typically more severe [63]. VP with gait disturbance could be caused by a strategic lesion in the brainstem or BG and/or chronic diffuse vascular damage of the subcortical white matter, as in Binswanger's disease related to different causes (e.g., atherosclerosis, thromboembolism, CADASIL). Binswanger's disease manifests with dementia, urinary incontinence/urgency, and gait abnormalities. VP accounts for 4.4–12% of all parkinsonism [64] and is predominantly characterized by lower body parkinsonism, postural instability, FOG, absence of tremor, and dopamine efficacy with also corticospinal tract signs [65].

Higher level gait disturbance (HLGD) is the definition adopted for "disexecuted gait disturbance" or "apraxia of gait" [66, 67]. The FOG represents one of the main features of HLGD together with the reduced cadence, short steps with marked variability, preservation of arm swing, hesitation, and postural instability directed backwards. Other features are a variable combination of cognitive decline, parkinsonism, frontal release, and/or corticospinal tract signs.

Pure akinesia or primary progressive freezing of gait (PPFG) refers to syndromes where freezing is the predominant symptom and usually presents early during the disease course suggesting a diagnosis other than IPD. PPFG may present as in idiopathic freezing of gait without other features of parkinsonism except for the loss of postural reflexes and mild bradykinesia [68, 69]. Patients with PPFG, and in addition an abnormal dopaminergic imaging measured by DAT-SPECT, may slowly evolve to pure akinesia with freezing of gait (PAGF) or progressive supranuclear palsy (PSP), whereas those PPFG with normal DAT-SPECT may evolve towards cortical basal syndrome (CBS) or motoneuron disease (MND). In amyotrophic lateral sclerosis (ALS), patients with an abnormal dopaminergic imaging have been reported the occurrence of FOG [70].

Non-degenerative, potentially treatable FOG causes include chronic subdural hematoma [71] and normal pressure hydrocephalus (NPH). NPH is suspected in the presence of ventriculomegaly disproportionate to cortical atrophy and radiologically defined by an Evans index greater than 0.3 [72]. NPH is also supported by the narrowing of the cerebrospinal fluid spaces at the cranial vertex and by the dilatation of the Sylvian fissure and disproportionately enlarged subarachnoid space [73, 74]. NPH gait is characterized by small, slow shuffling steps with FOG and deterioration in dual-task conditions. Accessory symptoms may be urinary incontinence (frequency and urgency followed by outright incontinence) and dementia with dysexecutive predominance in later disease stage [75, 76].

Subdural hematoma, stroke, space occupying, and trauma lesions mainly occurring in the frontal lobes can cause subacute and asymmetrical isolated gait impairment whit FOG. In these forms, the sudden symptoms onset significantly differs from the slower progression typical of parkinsonisms or NPH. FOG have been also reported following hypoxic injury of the BG [77]), carbon monoxide [78] and manganese intoxication [79], and wasp sting allergy [80].

A brain imaging study (i.e., MRI) is required to define the underlying etiology of these forms. Recently, asymmetrical FOG was reported as presenting symptom of a lesion of the anterior corpus callosum, revealing an unknown link between the interhemispheric pre-SMA connections and FOG [81].

A study on 14 already described cases with lesion-induced FOG, using a lesion network mapping technique previously described, showed that the different lesions resulting in FOG were connected to a focal area in the dorsal midline cerebellum [82]. Although these findings may differ from the FOG in PD and or atypical parkinsonism, all these clinical observations highlight the diverse etiology underlying FOG and pointed to different critical areas involved in a functional network. The implication of distributed functional network has been showed also in neuroimaging studies in PD (for a review, see Fasano et al. [83]) although with some heterogeneity in the results across the studies.

Finally, a careful examination might be necessary to exclude functional neurological disorders (FNDs). Different positive motor, sensory, and gait functional signs are recommended to be used in the diagnosis of FNDs with a high specificity (93 to 100%) [84]. Among gait signs, hesitation has also been reported to occur more often in patients with FND than in patients with "organic" lesions [85]. In addition, several studies have reported the presence of FNDs in association with different neurological (e.g., migraine, stroke) and neurodegenerative disorders including PD [86–88].

Treatment

Although the pathophysiology of FOG in PD remains largely unknown, evidence in favor of a role of the dopaminergic and some non-dopaminergic pathways is provided [89, 90]. Several studies consistently demonstrated that dopamine replacement therapy with LD is the first choice for FOG treatment in PD [91, 92]. However, the relationship between FOG and LD is not fully predictable. LD relieves FOG episodes in some conditions, while in others may act as a trigger [22]. This paradoxical effect of LD could be explained both by the presence of segregated parallel BG loops (motor, cognitive, and limbic) [39] and the long-term post-synaptic changes at the dopamine receptor level [93].

Several studies suggest that continuous infusion of levodopa-carbidopa intestinal gel (LCIG) could be a useful therapeutic strategy in patients with FOG refractory to oral therapy [94–97]. There are different potential explanations for the beneficial effect of LCIG on levodopa-resistant FOG. First, LCIG is administered via the jejunum, which provides greater bioavailability of LD compared with oral administration, avoiding the pulsatile dopamine stimulation in striatum by oral LD which, in turn, can induce the overstimulation of fronto-striatal pathways [94]. Improvement of FOG has been reported in several studies with the use of monoamine oxidase type B inhibitors, methylphenidate and L-threo-3,4-dihydroxyphenylserine (L-DOPS, droxidopa), while variable efficacy on FOG has been reported for amantadine and botulinum toxin into the calf muscles with few adverse effects (e.g., risk of fall) [98]. The reported efficacy of L-DOPS that is a precursor of noradrenaline suggests a potential role of noradrenergic neurons in the pathogenesis of LD-resistant FOG [99].

Exercise and physical therapy have proved to be efficacious in reducing FOG episodes and preparing for upcoming FOG such as sensory cueing (auditory, three-dimensional visual cues or transversal and regular line, Google Glass) [100], gait feedback, gait training (dual-task or environmental factors such as a narrow doorway), motor learning approach (e.g., action observation), and fall prevention. Cueing improves the ability of shifting from habitual to goal-directed gait control [101, 102]. The development of assistive and neuromodulating technologies (wearable sensors, robotics, virtual reality, transcranial current stimulation) is also an emerging rehabilitative approach [103–106].

Cosentino et al. [107] performed a meta-analysis providing evidence that physiotherapy compared to no intervention is effective in improving FOG in the short term and that retention effect is present mainly with the action observation approach. Evidence from another study

previously showed that retention is impaired in PD patients with severe FOG [108] suggesting that an earlier intervention in those at risk of FOG may be beneficial.

DBS of the STN is an effective treatment for PD [109], but the effect on FOG or axial signs is controversial [110]. Few authors have reported FOG induced by STN-DBS [110–113] leading to consider initially FOG as a contraindication for DBS [114].

Several factors should be considered to explain the controversial results on the efficacy of STN-DBS on FOG: the frequency of stimulation, the uni- or bilateral stimulation, inappropriate réglage, suboptimal electrode positioning far from the dorsolateral edge of STN, and causes not dependent on the stimulation. In many patients, despite optimal post-surgery therapy, gait impairments continue to progress with time, becoming less responsive to treatment [111, 115–120]. In addition, approximately 10% of STN-stimulated patients will not improve or even develop FOG after surgery [121].

New technologies offer innovative strategies to increase the beneficial effects so as to reduce side effects from DBS-STN, including those on gait. To overcome the modification in stimulating current delivered and to reduce troubleshooting gait disorders induced by DBS in the early programing phase, new manufactures have introduced current continuous neurostimulation device and the use of multiple independent current sources. Furthermore, the stimulation with segmented electrodes in comparison with the spherical configuration typical of antecedent devices could control better the current spread away from the internal capsule and increase the threshold for gait deterioration [122].

Alternative to STN, other DBS targets have been proposed such as GPi, SNr, and PPN. After DBS-GPi, improvement of FOG was seen only in the ON state and not in the OFF state, arguing towards a major role played by LD rather than DBS [123]. An effect was reported by both higher frequency [124] and low-frequency SNr-DBS [125].

Recently, a meta-analysis provided evidence that PPN-DBS may improve FOG and falling [126]. A combined stimulation (PPN and STN) approach has shown improvement on gait [127].

Based on the observations that modulation of locomotion is mediated by supra-spinal region and different cortical areas (e.g., primary motor area), few studies provide evidence of the application of neuromodulation in ameliorating FOG.

The use of a single or multiple session of 10 Hz repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex of the lower leg and the dorsolateral prefrontal cortex (DLPFC) was effective for FOG but not over the supplementary motor area [128, 129]. DLPFC is involved in executive function which has been implicated in FOG. Five consecutive days of anodal transcranial direct current stimulation (tDCS) over the primary motor cortex (corresponding to the leg the patient used to start walking after a FOG episode) showed efficacy on FOG episodes' number and duration [130]. Lu and colleagues reported no effects on gait initiation of anodal tDCS over the supplementary motor area [131].

Conclusion

FOG is a disabling symptom particularly frequent in advanced PD but also present in other parkinsonisms and in non-degenerative conditions. Extensive research has focused on understanding this phenomenon, and several drug treatments available can be helpful in terms of reducing the number and duration of freezing episodes. An optimal clinical characterization of the FOG in terms of phenotypical subtypes will be important for the association analyses and to guide the appropriate patient-oriented therapy choice.

Dopamine replacement therapy with LD, albeit with reported limitations, is the first choice for FOG treatment in PD. LCIG has shown a beneficial effect on FOG with consistent results, but it is an invasive approach, which limits its clinical application to some extent. Dual sites DBS proved to be a promising non-pharmacological approach, and novel technologies offer new strategies and innovative solutions to increase the beneficial effects so as to reduce side effects from DBS.

From a physiotherapy perspective, wearable pointing devices appear to be generally effective and promising, but the effectiveness of various cueing devices needs to be further tested in clinical trials on PD patients with FOG.

Overall, the clinical and genetic observations highlight the diverse etiology underlying FOG and pointed to different critical areas involved in a functional network that converge to a common pathway [40]. Both clinical and genetic aspects should be carefully investigated and consider in future studies. A detailed clinical evaluation comprising motor and non-motor aspects (e.g., cognitive and mood profile) is essential also in genetic studies. These data could implement the understanding of FOG pathophysiology and potentially unmasked therapeutical target.

The identification of risk factors will be fundamental for early diagnosis and also useful for understanding the FOG mechanism and set up the most appropriate clinical management. The contribution of genetics is still little known, but it is in its very early times. Further insights into the correlation between genetics and FOG are expected to come from systematic collections of clinical and genetic information from new emerging consortia (i.e., IPDGC) that will combine exome or whole genome sequencing and phenotypical data.

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Declarations

Conflict of interest The authors declare no competing interests.

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