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Management of Freezing of Gait in Parkinson's Disease

Sang-Myung Cheon
Department of Neurology, Dong-A University School of Medicine, Busan, Korea

Freezing of gait is common in Parkinson's disease. Patients with freezing of gait experience sudden arrest of forward stepping while their trunk continues to move forward. Sudden and unexpected nature of freezing of gat can lead to falls and injuries, and cause significant restriction of daily life in patients. Management of freezing of gait is currently unsatisfactory, but various efforts have been made. Current status of pharmacological and surgical treatment for freezing of gait is summarized in this review.

Key Words: Parkinson's disease, Freezing of gait

Introduction

Freezing of Gait (FoG) is type of episodic movement breakdown in locomotion and can be defined as a 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk'.[1] It is a common and disabling motor symptom in Parkinson's disease (PD), most commonly experienced during gait initiation, turning, and when negotiating obstacles or other tasks. Patients with freezing of gait experience sudden and often unexpected episodes during which their feet subjectively become 'glued to the floor' while their trunk continues to move forward. Sudden and unexpected nature of FoG can lead to falls and injuries, and cause significant restriction of daily activities and poor quality of life in patients with PD.[2]

FoG can present as akinesia, showing as start hesitation which occurs at gait initiation, or as motor arrest, showing arrests during ongoing gait such as in festination, during turning, reaching a destination, or triggered by external circumstances, based on phenomenology (Table 1).[3] It can be classified pharmacologically based on response to dopaminergic medication (Fig. 1). Off-state FoG is most frequent type, which can be relieved by dopaminergic medication. Pseudo-on-state FoG states FoG seen during seemingly optimum on-state, but which is actually improved with dopaminergic medication. On-state FoG is rar-

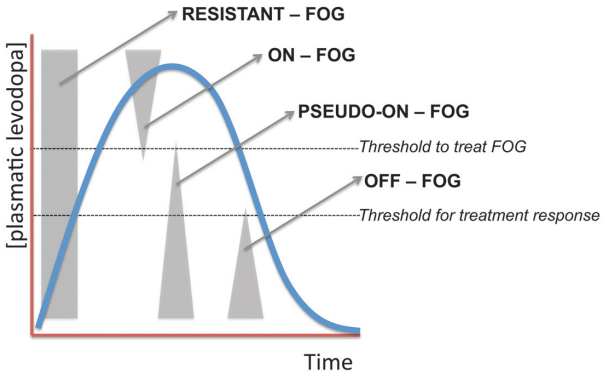

Figure 1. Pharmacologic classification of freezing of gait. Adopted from Fasano et al. 2013.

Sang-Myung Cheon
Department of Neurology, Dong-A University School of Medicine,
26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
Tel:051-240-5266 Fax:051-244-8338
E-mail:smcheon@dau.ac.kr

Table. Classification of freezing of gait. Adapted from Fasano et al. 2015

Phenomenological classification	
Akinetic freezing of gait	Start hesitation Total akinesia
Motor freezing of gait	Freezing without alteration of the motor pattern : on an open runway
	Freezing with alteration of motor pattern : during turning, reaching a destination or an obstacle, passing through a doorway or increasing gait velocity
	Triggered by external circumstances - eg. anxiety or dual taking
Pharmacological classification	
Off-state freezing of gait	Most frequent type, relieved by dopaminergic medications
Pseudo-on-state freezing of gait	Seen during seemingly optimum on-state, but which improves with increased dopaminergic medication
On-state freezing of gait	Rarest form, induced by dopaminergic medication
Resistant freezing of gait	Indifferent to changes in dopaminergic medication

est form (might be less than 5% of all FoG), which is induced by dopaminergic medication. Resistant (or unresponsive) FoG is indifferent to changes in dopaminergic medication.

FoG is common and reported point prevalence of 7-47%, which is strongly correlated with Hoehn and Yahr stages.[2,4,5] Community cohort study reported the prevalence from 27% to 63% during 12 years and incidence rate was 124.2 per 1000 person-years.[6] It usually occurs at the late stage of the disease, and correlated with longer disease duration, higher UPDRS score, higher levodopa equivalent daily dose (LEDD), motor fluctuation, and specific motor symptoms (positively with severity of gait disturbance and axial symptoms, and negatively with severity of tremor).[2,4,5,7-9] It is also associated with non-motor symptoms, such as apathy, visual hallucination, and cognitive impairment (especially, attention, visuospatial and executive dysfunction).[10] Those association of FoG with non-dopaminergic symptoms or signs implies that FoG originates from beyond nigrostiatal system, and numerous studies suggest pathologies of various regions of cortex and brainstem. Researchers proposed hypotheses to explain FoG, but the pathophysiology of FoG is still far from understanding, and it also is beyond the scope of this review. Here, management of FoG in PD patient will be reviewed briefly, focused on pharmacologic and surgical treatment.

Though the mechanism of clinical correlates of FoG in PD patients are not known, they deserve to mention because they could suggest some clues for the management of FoG. Studies suggested that FoG was associated with exposure to antimuscarinics, dopamine agonist, depression, and anxiety, which all could be manageable.[1,2,11] Monoamine oxidase inhibitor, selegiline, was shown to be associated with decreased risk of future FoG.[12] Also, another monoamine oxidase inhibitor, rasagiline, might have some benefits in selected patients with FoG, and recent pilot study suggested that responder to rasagiline showed lower UPDRS gait score, higher LEDD, lower anxiety score, and higher dose of amantadine, and use of pramipexol, higher anxiety, and higher gait score were associated worsening following rasagiline treatment.[13] Cholinergic deficit in patients FoG, proved by prior history of exposure to antimuscarinics, specific cognitive dysfunction, plasma level of Aβ-42, and evidences of functional imaging studies could propose the role of cholinergic treatment, though recent trial failed to improve FoG.[2,10,14-16]

Pharmacologic treatment of freezing of gait

The first step of management of FoG would be the identification of FoG according to dopaminergic medication. The unpredictable nature of FoG could make it hard to assess by simple question, whether or not freezing of gait is present. Demonstration or showing video clip of FoG could help to identify the events during the day by the patients. Severity and disability of FoG can be evaluated by structured questionnaire, such as new freezing of gait questionnaire.[17] Occurrence, duration, and disability due to FoG events related to medication time can reveal the response of FoG to dopaminergic medication. Because the majority and earlier stage of FoG would be off-state FoG, and there could be a pseudo-on-state FoG, levodopa should be increased until the dose at appearance of dyskinesia if tolerable. Adjustment of dopaminergic medication using dopamine agonist would not be recommended. Besides the limitation of daily dose of dopamine agonist, some researchers suggested association of dopamine agonists with increased risk or worsening of FoG and even recommended to discontinue the dopamine agonists.[11,18] However, recent study showed that rotigotine patch attenuated the severity of FoG.[19] The authors found no benefit in ropinirol and pramipexol group, and postulated the benefits of rotigotine from similar binding affinity to dopamine receptors with dopamine and steady-state pharmacokinetics.

Sufficient increment of levodopa dose can reveal the on-state and resistant FoG. There are limited studies about the management of levodopa-resistant FoG. In a small study, patients with documented resistant FoG were treated with 24 hour levodopa-carbidopa intestinal gel.[20] Although the study could not found significant change in freezing of gait questionnaire, actual events of FoG reduced. The possibility of known correlation between sleep disturbance and fall was suggested by the authors. Pharmacokinetic benefit of intestinal gel and rotigotine patch could share common therapeutic mechanism.

When it found to be an on-state FoG, increasing dose of dopaminergic medication results in worsening of FoG, and dopaminergic medication should be reduced. Dopamine agonist could be the first, and then followed by levodopa. Reduction of dopaminergic medication may induce the aggravation of other parkinsonian symptoms, and some group suggest deep brain stimulation (DBS) targeting subthalamic nucleus (STN-DBS), not for the FoG as a goal but for the reduction of dopaminergic medication.[18]

Amantadine has been tried for the treatment of FoG in several studies, but the results were inconsistent. Some study showed the benefit of amantadine in dopamine-responsive FoG, but it was ineffective in resistant FoG.[21-23] But the benefit in selected patients was shown, so amantadine can be tried with caution, especially in elderly.

L-threo-3,4-dihydroxyphenylserine (L-DOPS), a precursor of noradrenaline, could have potential role in resistant FoG based on thesis of pathologic involvement of noradrenergic neuron in development of FoG. It was tried in combination with entacapone in small case series.[24] Only combination of droxydopa and entacapone group showed improvement of FoG including seemingly on-state FoG. Due to small number of patients and poor study design, more evidence is needed.

Methylphenidate, an inhibitor of dopamine transporter, has been suggested to show benefit at FoG in earlier studies.[25,26] Beneficial effect of methylphenidate was found again in advanced patient undergone STN-DBS at recent study.[27] An increase in dopaminergic and noradrenergic activity is suggested to be associated with the effect of methylphenidate.

Surgical treatment of freezing of gait

Since DBS has been introduced for the management of parkinsonian motor symptoms, axial symptoms were not perceived as goals of DBS, regardless of target structure. Actually, resistant or on-state FoG has been acknowledged as contraindication of DBS. And, the results of DBS targeting globus pallidus interna for the management of FoG has

not been reported. So, most of studies reported results about responsive FoG in DBS targeting STN (STN-DBS).

Recent review regarding the effects of high frequency STN-DBS on FoG analyzed the results of 7 studies up to more than post-operative follow-up period of 48 months, using score of UPDRS item 14.[28] Main finding of the review was that high frequency STN-DBS showed long-term improvement FoG at medication-off/simulation-on condition compared to baseline medication-off condition but there was no change or slightly worsening at medication-on/stimulation-on condition compared to baseline medication-on condition. Because baseline medication-on state was very mild, the authors suggested that it could not be improved with STN-DBS. And they also suggested the aggravation of FoG was not due to reduction of dopaminergic medication, though it was not known to be related to DBS or to disease progression. Recent prospective trial targeting FoG as primary end point confirm the benefits of STN-DBS in reducing the severity and the development of FoG compared to best medical treatment.[29]

The results of STN-DBS were not always fruitful. STN-DBS induced FoG or aggravation of FoG also have been reported.[30-32] Those findings could imply intrinsic limitation of STN-DBS, but other factors such as malpositioning of the electrode or diffusion of electric current outside the STN should be considered.[33] Anterior, medical and dorsal displacement of electrode can deteriorate gait and induce FoG.[34] Current diffusion to pallidofugal fibers can also worsen gait.[35] However, when the axial symptoms are disabling in patient undergone high frequency STN-DBS, low frequency stimulation (LFS) can be applied. Several studies suggested that LFS could improve speech, swallowing, gait, and freezing with minimal change in other motor symptoms.[36-39] But some critics mentioned the limitation of LFS due to the absence of stereotactic coordinates of active contacts and its benefit only seen at the presence of detrimental effect of high frequency stimulation.[40] Still LFS warrants more evidences but it could be applied in patient with disabling axial symptoms at high frequency STN-DBS.

Conclusion

Management of freezing of gait in Parkinson's disease warrants careful approach and judicious trial of dopaminergic medication. Though the results are still inconclusive for non-dopaminergic medication, discreet use could have role in selected patients. Deep brain stimulation targeting subthalamic nucleus can be an option in appropriate candidate with dopamine-responsive freezing of gait. Further explorations are needed to manage the heterogeneous complex of freezing of gait.

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