Paradoxical worsening of gait with levodopa in Parkinson disease

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Despite many recent advances in the treatment of Parkinson disease (PD), levodopa is still the most effective medication for PD. While there are many "nondopaminergic" features of PD that do not improve with levodopa, PD motor symptoms generally improve with dopaminergic medications. However, not all the motor manifestations of PD are improved to the same extent and some may not respond at all to levodopa. Tremor is often less responsive to levodopa than bradykinesia. Different aspects of bradykinesia may even respond differently. For example, recent studies showed that with self-paced finger and hand movement tasks similar to those used in the Unified Parkinson's Disease Rating Scale, levodopa improved the speed of movement but had little effect on the amplitude of movement and on movement fatigue, although impairment of movement amplitude was more prevalent than impairment of speed in PD.[1,2] In contrast, when finger tapping was paced to an external rhythm, patients with PD had a dramatic reduction in the amplitude of movement when the tapping rate was higher than 2 Hz and this reduction in amplitude did not improve with levodopa.[3]

Gait disturbance in PD is often difficult to treat with levodopa. While many patients with PD have gait freezing in the "off" medication state that improves with dopaminergic medications,[4] it is well known that there are patients with PD in whom gait freezing and falls do not respond to levodopa.[5] Although worsening of gait with levodopa that cannot be attributed to dyskinesia has been described,[6,7] it is not well recognized. An early study reported difficulty in initiating walking in 6 out of 51 patients with PD and it improved with lower doses of levodopa,[7] perhaps related to high doses of levodopa used in the 1960s and 1970s,[4] which were typically 3 to 4 g (without peripheral decarboxylase inhibitor) per day.[7] In this issue of *Neurology*®, Espay et al.[8] carefully evaluated and documented worsening of gait with levodopa in 4 patients with PD. The study is limited by the few patients examined, by the lack of blinding of either the patients or the evaluators to the medication states, and by the fact that the medication states were tested in a fixed order. Nevertheless, it clearly demonstrated that the phenomenon of "on" state freezing of gait in PD existed and that it may occur in patients who took much lower doses of levodopa than those in the early reports.

It is interesting that "on"-state freezing began about 5 years after symptom onset and persisted over time. The phenomenology of "on"-state freezing seems to be different from the more common "off"-state freezing and gait freezing unresponsive to levodopa. Most patients had "trembling in place," which is also seen in other types of gait freezing. Unlike the more recognized gait freezing in PD, "on" state freezing appeared to be as severe with straight walking as in turning. It is also associated with freezing of repetitive hand movement in the "on" medication state.

There are many unanswered questions regarding "on"-state freezing. The true incidence and prevalence of this condition is not known but it is likely underrecognized and underreported. Whether most patients with PD would have "on"-state freezing when administered a sufficiently high dose of levodopa is not clear. Further studies are needed to characterize the phenomenon and the type of patients in whom it occurs. Do patients with "on"-state freezing belong to a distinct subtype of PD and have a distinct pattern of dopaminergic deficit? We also have no knowledge of the pathophysiologic basis of "on"-state freezing, although our understanding of the more common "off"-state freezing is also poor. Physiologic and functional imaging studies may elucidate the pathophysiology of "on"-state freezing and could lead to better treatment in the future.

Treatment of patients with "on"-state freezing is difficult. In the 4 patients reported, the dosages of levodopa were limited by "on"-state freezing even though other PD motor symptoms improved with levodopa. Increasing the dose of dopaminergic med-

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ications does not seem to be an option for these patients. Whether they will respond to other treatment modalities such as subthalamic nucleus deep brain stimulation remains to be established. New deep brain stimulation targets, such as the pedunculopontine nucleus,[9] which plays an important role in gait, may need to be considered. The role of physical therapy and gait training also needs to be evaluated.

What are the implications for the practicing clinician? The most important is the recognition that this condition exists. Most clinicians have encountered patients with PD who reported worsening of their symptoms with levodopa. The different clinical features of "on" state freezing compared to the more commonly recognized forms of gait disturbance in PD may be helpful in identifying patients with this phenomenon. When patients reported worsening of gait with dopaminergic medications, they need careful evaluations in the "off" and "on" medication states, and in some cases, in the "super on" state as utilized by Espay et al.,[8] to arrive at the appropriate diagnosis that will guide further treatment options.

DISCLOSURE

Dr. Chen serves on scientific advisory boards for Medtronic, Inc., Allergan, Inc., Biovail Corporation, and EMD Serono, Inc.; has received speaker honoraria from Merz Pharmaceuticals, LLC and Allergan, Inc.; serves on the editorial boards of *Neurology*, *Canadian Journal of Neurological Sciences*, *Journal of Motor Behavior*, *Muscle and Nerve*, and *Clinical Neurophysiology*; receives research support from Medtronic, Inc., the Canadian Institutes of Health Research, the Michael J. Fox Foundation for Parkinson's Research, and the Dystonia Medical Research Foundation; and has provided expert testimony and affidavit in welding related litigations.

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