Freezing of gait after a hemorrhagic stroke can respond to venlafaxine and rivastigmine

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Whereas frontal leukoaraiosis is associated with gait disorders,^{1,2} stroke rarely causes freezing of gait (FOG).¹ When present, poststroke FOG is usually refractory to medications. We describe successful treatment of FOG developing after a hemorrhage with venlafaxine and rivastigmine.

Case description

A 65-year-old man who frequently jogged at moderate speed developed right hemiparesis and aphasia after a hemorrhagic stroke arising from the left thalamus (figure). Eight weeks later he started to notice subtle gait hesitation; by 4 months, he developed frank FOG during gait initiation and turning and while walking down narrow corridors, but he remained able to run. Freezing was not distractible and improved with visual cues, as seen in parkinsonian patients. There was no known exposure to dopamine blockers or family history of movement disorders.

We first evaluated him 11 months after his stroke. He reported 3 falls, short-term memory impairment, and prominent treatment-refractory anxiety. He scored 3 (range 0–4) on item 14 of the Unified Parkinson's Disease Rating Scale (UPDRS), which addresses freezing severity by history.

Examination confirmed impaired fluency, executive function, and memory. He had moderate hypophonia, mild right hemiparesis, diffuse hyperreflexia with a right Babinski sign, and mild bilateral hand tremors, which likely were not enhanced physiologic tremors given they were present only on intention. There was no bradykinesia, resting tremor, or dysmetria. Sensation was intact. Gait was slow and wide-based, with freezing upon initiation, turning, going through doorways, and avoiding obstacles. His gait was scored as 2 (range 0–4) on item 29 of the UPDRS, suggesting freezing with independent ambulation. Postural reflexes were intact.

Venlafaxine extended-release (ER) 37.5 mg nightly led to subjective FOG improvement by 2 months. Seventy-five mg caused confusion, which resolved after adding transdermal rivastigmine 4.6 mg daily.

Practical Implications

Since freezing of gait is difficult to treat, alternative strategies such as cholinesterase inhibitors and antidepressants, which act on multiple neurotransmitters such as norepinephrine, should be considered.

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Figure Temporal evolution of a left hemorrhagic stroke in a 65-year-old man

(A) Axial head CT scan performed within hours of stroke onset demonstrates an acute hemorrhage of the left hemisphere with intraventricular extension, mass effect upon the left lateral ventricle, and minimal right-sided shift. Left basal ganglia and right thalamic lucencies are identified and thought to represent old lacunar infarcts. (B) Axial T2-weighted fluid-attenuated inversion recovery brain MRI without contrast performed 11 months after symptom onset reveals a collapsed hemosiderin-lined cavity in the left thalamus indicating the site of origin of the patient's hemorrhage. The small lucencies in the left basal ganglia and right thalami seen in (A) are found to correspond to foci of old hemorrhages, as suggested by axial gradient echo images (not shown). (C) Axial head CT scan performed 17 months after symptom onset confirms left thalamic and basal ganglia hypodensities, residual from previous hemorrhages in these areas, as noted on the prior MRI. Extensive, patchy, confluent, and stable periventricular signal changes, consistent with chronic microvascular ischemic changes, are present on all 3 scans.

A month later, FOG was present only on initiation and turning. Cognition and anxiety improved. He scored 1 on UPDRS items 14 and 29. Over the following 9 months, venlafaxine ER and rivastigmine were titrated up to 187.5 mg and 9.5 mg daily, respectively, with dose-related clinical changes. A year later, symptoms and imaging remained stable (figure).

DISCUSSION

This is the first description of FOG after a hemorrhage responding to rivastigmine and venlafaxine. FOG is a motor block³ that can be overcome by visual cues and worsen with anxiety.³ Its pathophysiology is complex, likely involving the spinal cord gait generator, cortex, brainstem, cerebellum, and visual and vestibular systems.³

Although we presume his thalamic injury was the most likely contributor to the development of FOG, we cannot exclude possible roles of capsular damage, intraventricular blood extension, and preexistent subcortical microvascular disease burden, as evident in the figure. Since FOG affected both of his feet, a multifactorial model of disease seems possible; we speculate that the hemorrhage may have triggered the development of FOG bilaterally by disrupting already-vulnerable circuits.

Different neurochemicals likely mediate the thalamus's role in gait. Noradrenaline, serotonin, and acetylcholine are known to modulate its glutamatergic and GABAergic activity.⁴ Furthermore, reduced frontal noradrenergic tone may disturb motor networks,⁴ as seen in patients with Parkinson disease, who are known to have reduced thalamic noradrenaline. This deficit presumably precipitates pathologic motor oscillations that project to the supplementary and presupplementary motor areas via thalamocortical connections, causing parkinsonism.⁵ Considering this mechanism of disease, an acquired thalamic noradrenergic deficit causing FOG in our patient seems plausible.

Our patient also exhibited considerable anxiety, which likely exacerbated his gait disorder and tremors. As previously suggested,⁶ we suspect venlafaxine, an inhibitor of norepinephrine, serotonin, and dopamine reuptake, was efficacious in treating both FOG and anxiety.

The therapeutic role of rivastigmine, a cholinesterase inhibitor, may have been through augmentation of thalamic cholinergic inputs from the pedunculopontine nucleus, pars compacta, and lateral pontine tegmentum, or by improving cognitive processing speed and alertness.⁷ Improved gait and balance with donepezil and galantamine use has been reported.⁷

Although we presume a causal relationship between our patient's stroke and gait symptoms, there are limitations to our observations. FOG may have developed in this patient regardless of the hemorrhage. We did not perform functional neuroimaging to exclude an underlying neurodegenerative disease given the patient's improvement and lack of other parkinsonian features. We also cannot rule out improvement secondary to poststroke plasticity or to a placebo effect, but we consider these unlikely given his clear dose-related symptom responsiveness. Finally, we cannot exclude the presence of subtle FOG prior to the hemorrhage, but we doubt this possibility, as the patient was athletic and would likely have noticed any gait changes. Documentation of similar cases may clarify these uncertainties.

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