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Bilateral Pedunculopontine Nuclei Strokes Presenting as Freezing of Gait

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Video



Abstract: The pedunculopontine nucleus (PPN) has been suggested to play an important role in locomotion, based on animal studies, but its function in humans has not been well defined. Autopsy studies have suggested that PPN pathology correlates with gait dysfunction in Parkinson's disease and in progressive supranuclear palsy but direct clinical evidence is lacking. We report a patient with bilateral PPN infarcts whose dominant clinical feature was freezing of gait, thus providing evidence that PPN is involved in human locomotion and that damage to the PPN may lead to abnormal gait. © 2008 Movement Disorder Society

Key words: pedunculopontine nucleus; freezing of gait; stroke.

The pedunculopontine nucleus (PPN), located between the medial lemniscus and superior cerebellar peduncle in the pons and part of the mesencephalic locomotor region, consists mainly of cholinergic neurons, but also neurons containing γ -amino-butyric acid (GABA) and glutamate.¹ The PPN projects to and receives connections from the limbic system, ipsilateral prefrontal motor cortex, and the cortico-tegmental tract, basal ganglia nuclei, and the brainstem reticular formation, and provides input into thalamic nuclei, globus pallidus, substantia nigra, subthalamic nucleus, ventral tegmental area, medullary, and pontine reticular formation, and descending spinal pathways.^{1,2} Electrophysiologic studies of PPN during locomotion and various PPN lesion experiments have established the relationship

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of PPN to locomotion in animals. At autopsy, the extent of PPN degeneration in Parkinson's disease (PD) correlates with premortem gait dysfunction.³ Recent reports suggest that low-frequency deep brain stimulation (DBS) of PPN may ameliorate levodopa resistant gait dysfunction in PD.⁴⁻⁶ However, direct evidence that PPN functions as a locomotor region in human is still lacking. Here, we report a patient with bilateral PPN strokes presenting with freezing of gait (FOG) suggesting that PPN is involved in human locomotion and that damage to this structure may result in FOG.

CASE REPORT

This 70-year-old right-handed Hispanic gentleman with a history of hyperlipidemia and depression presented with a chief complaint of worsening gait, particular initiation of gait. He also reported an intermittent right leg rest tremor. The patient also complained of mild leg stiffness, but denied upper body slowness or stiffness, micrographia, hallucinations, cognitive dysfunction, or acting out of dreams. None of his symptoms responded to medical therapy, including ropinirole 3 mg TID, amantadine 100 mg BID, carbidopa/L-dopa 25/250 mg QID, or carbidopa/L-dopa/entacapone 37.5/150/200 mg QID. Except for hyperlipidemia he had no other apparent stroke risk factors and he had no family history of cardiovascular, cerebrovascular disease, or neurodegenerative disorders.

On examination, the patient obtained a score of 29 of 30 on the mini-mental status examination, missing one point for delayed recall. Extraocular movements, including smooth pursuit and saccades, were intact. Muscle strength was normal without spasticity, and deep tendon reflexes were 2+ throughout with bilateral flexion plantar responses. Sensory examination showed intact and symmetric pinprick, light touch, vibration, and proprioception. Finger-nose-finger, heel-to-shin, and heel taps were all performed without difficulties. On the unified Parkinson's disease rating scale (UPDRS) the patient scored 11 points in Part II (activities of daily living) and 24 points in Part III (motor subsection). He had minimal hypomimia and no rest or kinetic tremors. His bradykinesia and rigidity were more profound in the lower extremities than in the upper extremities. He required the use of his arms to arise from a chair, and walked with moderately stooped posture. Initiation of the gait was severely impaired along with marked FOG while initiating gait and while attempting to turn (3 of 4 UPDRS item 14, 2 of 4 item 29). After overcoming poor gait initiation, he ambulated with a normal stride length. Visual cueing with a specially designed cane improved gait initiation and FOG while turning. He also had marked postural

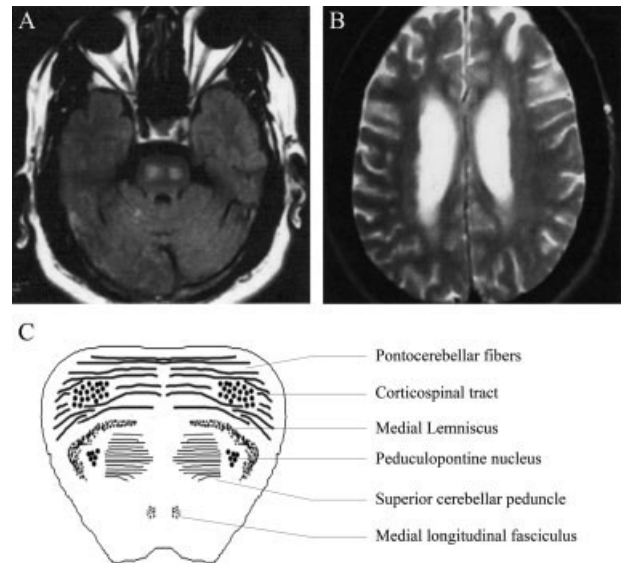


FIG. 1. (A) Axial brain MRI with FLAIR sequence shows, small, well-circumscribed, bilateral PPN infarcts. (B) Axial brain MRI with T2 sequence reveals no prominent periventricular or frontal subcortical white matter ischemic changes. (C) A diagram showing the anatomy of pons and the location of PPN which corresponding to the lesions.

instability as evidenced by an inability to recover from the pull test, 2 of 4 UPDRS item 30 (Video, available online at <http://www.interscience.wiley.com/jpages/0885-3185/suppmat.>).

Brain magnetic resonance imaging (MRI) revealed hyperintense lesions on the fluid attenuation inversion recovery (FLAIR) sequence localized to the region of bilateral PPN (Fig. 1A) without any significant evidence of T2 hyperintensity involving subcortical white matter (Fig. 1B). PPN is localized in dorsal pons between medial lemniscus and superior cerebellar peduncle (Fig. 1C) corresponding to bilateral PPN pathology in this patient's MRI.

DISCUSSION

The primary aim of this report is to provide evidence that PPN plays an important role in locomotion control not only in animals but also in humans and to hypothesize that PPN damage can lead to FOG. PPN has been found to be connected reciprocally with multiple basal ganglia structures including globus pallidus internus (GPI), subthalamic nucleus (STN), and substantia nigra (SN) and it receives inputs from the spinal cord, limbic system, ascending reticular activating system, premotor, and supplementary motor areas and projects to the thalamus, striatum, limbic system, and reticular formation.^{1,2,7} Lesions in bilateral PPN and inhibition of bilateral PPN by high frequency of stimulation at 100 Hz

produced akinesia in normal monkeys.^{8,9} In primates made parkinsonian with 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), bicuculline injection in PPN reversed their akinesia, suggesting this cardinal parkinsonian sign is caused by inhibition of PPN possibly from activation of globus pallidus GABAergic projections to the PPN.¹⁰ Electrical stimulation of PPN at low frequency improves akinesia in MPTP-treated primates whereas inhibition of PPN with high frequency stimulation worsens the motor symptoms.¹¹ Despite the data based on animal studies, the role of PPN in human locomotion is unclear. Masdeu et al. reported a case of intracerebral hemorrhage involving the pontomesencephalic junction and the right PPN causing failure to generate stepping movements, but the hemorrhage was quite large raising the possibility that FOG could have been caused by damage to neighboring structures.¹² Another case series reported three patients with unilateral midbrain tegmentum stroke causing hesitation of gait initiation and ataxia.¹³ In these cases, PPN may have been involved; however, the primary brain lesions were at the midbrain level. Also, gaze palsy and ataxia coexisted with gait problems suggesting the involved brain regions were extensive.

Our case is unique in that the lesions, presumably small infarcts, seem to be confined to the pontine region involving bilateral PPN. The location of the lesions is essentially identical to the area of PPN as demonstrated by various autopsy and imaging studies, including diffusion tractography using data acquired at 1.5 T MRI.¹⁴ It is possible that adjacent areas might be involved; however, the patient demonstrated no signs of upper motor neurons, sensory, or cerebellar dysfunctions, suggesting PPN is the structure primarily involved other than corticospinal tract, medial lemniscus, or superior cerebellar peduncle. We believe that the lesions are causally related to the FOG, observed in our patient, thereby providing evidence that intact PPN function is necessary for normal ambulation in humans.

FOG is a common symptom among PD patients but may be also observed in patients with normal pressure hydrocephalus, and various atypical parkinsonian disorders including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD).¹⁵ Factor et al. followed patients with primarily FOG symptoms over 6 to 16 years and found that they eventually developed pallidonigrolyusian degeneration, dementia with Lewy bodies, PSP, and CBD, suggesting FOG is a presentation in diverse diseases.¹⁶ The mechanism of FOG is not well understood but it has been postulated to be due to damage or dysfunction of frontal lobes and basal ganglia.¹⁷ PPN receives important

reciprocal connections between frontal lobes and basal ganglia and it probably serves as the relay center for locomotion. Degeneration of PPN was observed in autopsy studies in patients with PD and PSP, and the extent of PPN degeneration, especially the cholinergic neurons, correlated with degree of gait dysfunction.³ In addition, FOG was also found to be associated with urinary incontinence which is commonly caused by the dysfunctions of basal ganglia and brainstem nuclei including pontine micturition center.¹⁵

In patients with PD, FOG is among the most difficult symptoms to treat. Though dopamine depletion and basal ganglia dysfunction are the primary neurological deficits in PD, gait and balance problems only partially respond to L-dopa, suggesting other neurotransmitter systems are involved. Conventional STN- or GPi-DBS improves many motor symptoms in PD patients but this therapeutic intervention usually provides only modest, if any, improvement in gait problems and FOG rarely, if ever, improves. Mazzone et al. first implanted PPN-DBS in 2 patients with PD and noted the unique electrophysiology of human PPN, characterized by small and broad multiunit discharges.⁴ Two patients with PD and dominant FOG and postural instability showed moderate improvement of these symptoms after bilateral PPN-DBS surgery.⁵ Stefani et al. implanted bilateral STN-DBS and PPN-DBS in 6 patients with severe PD.⁶ Combined STN and PPN stimulation in conjunction to PD medications improved motor symptoms significantly than either target stimulation alone, especially in gait and posture. These results suggest that PPN might be a promising target for DBS and PPN-DBS may provide benefit for medication-resistant FOG in PD, vascular parkinsonism, and other neurodegenerative disorders.

LEGEND TO THE VIDEO

The patient displayed hypomimia and lower extremity bradykinesia along with FOG. After initiation, he was able to walk with normal stride length. Instructions to "march" rather than merely walk and visual cueing provided by a specially designed cane was associated with modest improvement in FOG.

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