Clinical and single-photon emission computed tomography study of pure akinesia with freezing of gait

Imen Kacem, MD, Amina Gargouri, MD, Mouna Ben-Djebara, MD, Riadh Gouider, MD, PhD.

Pure akinesia with freezing of gait (PAFG) was first described in the mid 1970s by Narabayshy and Imai as an entity in which freezing of gait (FOG) is the prominent symptom. This condition is characterized by major akinesia with freezing phenomena including frozen gait, frozen hand, and frozen speech, in the absence of rigidity or rest tremor. These last signs distinguish it from primary progressive freezing of gait (PPFG), or gait ignition failure (GIF). Pure akinesia with freezing of gait was closely associated with atypical Parkinsonian syndromes due to its phenomenology with no response to levodopa, and thought to be a particular phenotype of progressive supranuclear palsy (PSP). In fact, in some patients with pure akinesia (PA), apraxia of eyelid-opening and upgaze, and convergence difficulties were noticed at the late phase, which was considered consistent by some authors with a clinical diagnosis of PSP. However, PAGF is still considered an independent condition although it is rarely reported in the literature and its pathophysiology remains unclear. We report a case of PAGF and review the literature for clinical features, imaging results, and therapeutic options. Our objective in reporting this particular case is to highlight the unusual clinical course of such pathology and the challenging differential diagnosis.

**Case Report.** Our patient is a 60-year-old man, without relevant medical history, who started experiencing difficulty in walking, with initiating gait hesitations and falls, at the age of 52. He also reported progressive slowness of movements and swallowing difficulties. Physical examination showed akinesia, masked facies and eyelid apraxia, his voice was slow, hypophonic, and sometimes unintelligible because of stuttering. His posture was slightly stooped, with retropulsion. Freezing appeared frequently at the initiation of gait, and he walked in small steps with frequent falls. Hand freezing appeared in rapid alternating movements and finger tapping. All muscle stretch reflexes were normal, and the plantar response was flexor bilaterally. There was neither tremor, signs of autonomic dysfunction, nor extra ocular movement abnormalities both in vertical and horizontal
planes. Cognitive assessment showed a slight dysexecutive functioning (frontal assessment battery=16/18), but a global normal cognitive efficiency. This later remained stable after 8 years of follow-up. Brain MRI showed only a small ischemic lesion in the caudate nucleus. Cerebral single photon emission computed tomography (SPECT) (HMPAO-Tc99m), performed 3 years after the onset of symptoms, showed hypoperfusion of the frontal and temporal lobes (Figures 1 & 2). No midbrain perfusion abnormalities were noticed on that exam. He underwent physiotherapy and treatment with levodopa 750 mg/d, with initially, a mild and partial improvement of gait disturbance. After 7 years of follow up, at the age of 60, his symptoms did not improve with gait worsening and frequent falls. He became wheelchair confined 4 years after the onset of symptoms. At the last examination, his cognition was still unaffected, but he developed restriction of his vertical gaze.

Discussion. Freezing of gait is the most frequent initial symptom in PAGF. While it is common in atypical parkinsonism, it is also seen in advanced Parkinson's disease (PD) and hence, has been classified as the fifth cardinal feature of this disease. The pathophysiology of gait disorders has not been determined yet, but most recent studies in PD patients suggest a number of fundamental problems leading to FOG. Hallet in a recent review, explained that in such patients, automaticity is impaired and patients must depend more on voluntary movements. Yet, self-initiation of movement is also particularly difficult for these patients due to slowness in ability to increase the excitability of the motor cortex (especially the supplementary motor area). Moreover, he reported the studies that demonstrated that internal triggering, coming from the frontal lobe, hypothalamus and limbic system, were deficient while the extrinsic triggers had a stronger influence. For Hallet, the other important element in the genesis of freezing is the difficulty in shifting control from intrinsic and extrinsic drivers, which incriminate failure in attentional control. Brain imaging, especially PET studies, showed reduced uptake of 18F-dopa in the striatum in PD, PSP, and PAGF patients suggesting a role of dopaminergic mechanism. However, a marked decrease in glucose metabolism in the frontal cortex and striatum was only found in PAGF and PSP patients. In our patient, HMPAO-Tc99m SPECT performed in the rest condition, showed a frontal hypoperfusion. Kurata et al, by performing ECD-SPECT (ethyl cysteinate dimmer), found a hypoperfusion in the frontal lobe both in PSP and in PA patients with a more severe change in the frontal eye field in the first one than the latter. They also found different patterns of clinical symptoms between the 2 groups of patients suggesting that PAGF and PSP are distinct disorders.

In contrast to this previous report, Park et al, suggested, more recently, that both PAGF and PSP may be part of the same pathophysiologic spectrum of disease. By comparing changes in brain glucose metabolism using FDG-PET (fluorodeoxyglucose), they showed similar topographic distribution of glucose hypometabolism in the midbrain in PAGF and PSP when compared with controls, with, however, a reduction in the frontal cortex in PSP patients.

Furthermore, pathologic studies have demonstrated that autopsy findings in PAGF are consistent with those of PSP, thus, Williams et al tend to consider PAGF as the third phenotype of PSP. However, whether PAGF represents a subtype of PSP or is merely a syndrome with considerable clinical and pathophysiologic overlap has
not yet been determined. In fact, idiopathic PAGF is a condition that seems to stand within a wide spectrum of PSP, but there also exist patients who still have only PA even after 10 years of illness duration. In our patient, PSP’s clinical criteria were not fulfilled after 7 years of follow up.

Considering the therapeutic options, FOG is known to be one of the dopamine resistant motor symptoms of parkinsonism. This can explain that treatment of PAGF is still limited. However, anecdotic improvements were reported. Yener et al. reported a patient with PAGF in which treatment with donepezil (10 mg/day) resulted in dramatic improvement within several days. They supported their clinical observation with the ascertainment of a markedly increased perfusion in the bilateral frontoparietal cortex on the control of PET scan. On the other hand, Watanabe et al. reported a marked clinical and SPECT improvement with tandospirone citrate (30 mg/d) in their PSP patient presenting initially as pure akinesia syndrome. Non pharmacological treatment was more effective than medications in our observation. Indeed, the gait rehabilitation was very helpful in many cases of FOG; these training methods need to provide settings for optimal movement timing and amplitude interaction.

In conclusion, our patient had clinical features of PAGF with an 8 years evolution without additional signs suggesting PSP. This long evolution is unusual, but the diagnosis of PSP cannot be excluded regarding the presence of frontotemporal hypoperfusion on brain SPECT. Neuropathological proof is still needed to ascertain this diagnosis.

Acknowledgment. We extends our thanks to Dr. Ben-Brahim, Radiologist in the Department of Nuclear Medicine at the Hôpital Militaire de Tunis, for his assistance with this study.

References