Atypical Parkinsonism
Diagnosis and Treatment

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KEYWORDS

• Progressive supranuclear palsy • Corticobasal degeneration
• Multiple system atrophy • Atypical parkinsonism • Diagnosis

KEY POINTS

- Careful clinical examination is important for the differential diagnosis of atypical parkinsonism from Parkinson disease.
- The expanding phenotypic spectrum of atypical parkinsonism and the expanding pathologic spectrum of classic atypical parkinsonian phenotypes make the early differential diagnosis challenging.
- Investigations may be supportive, but their sensitivity and specificity are low.
- There are currently no biomarkers available.
- There are currently no neuroprotective treatments available, although there are some symptomatic and supportive treatments with usually no sustained effect.

Video of progressive supranuclear palsy accompanies this article at http://www.neurologic.theclinics.com/

INTRODUCTION

Parkinsonism is defined according to the UK Brain Bank Criteria as the presence of bradykinesia and at least one of the following: rest tremor, rigidity, or postural instability.[1] Once the presence of parkinsonism has been established, the main question for the clinician is whether the patient has the most common cause of parkinsonism (eg, Parkinson disease [PD]) or an atypical parkinsonian condition [AP]. Although the term "atypical" implies the presence of features "atypical" for PD, and there are numerous disorders causing parkinsonism,[2] typically this term is used to describe 3 particular sporadic parkinsonian conditions, namely progressive supranuclear palsy

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(PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA), which are the conditions that are further discussed here.

PSP, CBD, and MSA are distinct pathologic entities. Despite ongoing research, their cause and pathophysiology are still unknown, and there are no biomarkers or effective treatments available. One important reason that may account for that is that their early differential diagnosis is still challenging. Clinicopathologic studies have shown that the most common misdiagnoses occur between these 3 disorders and also PD, Lewy-body dementia, frontotemporal lobar degeneration, and Alzheimer disease (AD).[3–8] Moreover, the early differential diagnosis is complicated by patients with pathologically proven PSP, CBD, or MSA that may present clinically with phenotypes other than the classic ones.[9–12] Conversely, patients with the classic AP phenotypes may turn out to have other pathologic abnormalities.[9–12] Here, a guide on how to diagnose these conditions is provided and the limited available treatment options are discussed.

PROGRESSIVE SUPRANUCLEAR PALSY

PSP is a neurodegenerative disease characterized by symmetric parkinsonism, supranuclear palsy of vertical gaze, early postural instability with falls backwards, subcortical dementia, dysarthria, and dysphagia.[7] The prevalence of PSP is approximately 5 per 100,000, and men and women are equally affected. Average age at onset is 63, and mean time from symptom onset to death is 7 years. No pathologic proven cases have begun before the age of 40.[7]

PSP is a tauopathy with an unknown cause. PSP is almost always sporadic, and only a few familial cases have been reported, mostly carrying mutations in the *MAPT* (microtubuli associated protein τ) gene.[13,14] A genome-wide association study has confirmed that the most common risk allele for PSP is the H1 haplotype of the *MAPT* gene, and further risk loci have been identified.[15] Mitochondrial dysfunction and oxidative stress have been implicated in the pathophysiology of PSP.[16]

Diagnostic Approach to Progressive Supranuclear Palsy

Clinical features

PSP is typically characterized by symmetric and axial parkinsonism, postural instability with early falls particularly usually backwards, vertical supranuclear gaze palsy, and a frontal-subcortical dementia. This classic PSP phenotype is now termed Richardson syndrome (RS; see Phenotypic spectrum of PSP section). Postural instability and falls occur also in PD, however usually later in the disease course. In PSP, the prevailing axial rigidity causes head and trunk hyperextension sometimes with retrocollis (although rarely), unlike the posture in flexion in PD. The typical pill-rolling asymmetric rest-tremor typically seen in PD is usually absent (**Table 1**).[3,7,17,18] Gait may be slightly broad-based and typically not the short-stepped gait seen in PD. Freezing of gait is common and may lead to diagnostic confusion with MSA.

The characteristic sign of PSP is the supranuclear palsy of vertical gaze followed by abnormalities of horizontal gaze (Video 1). The ocular motor dysfunction begins with a slowing of vertical saccadic movements, downward in particular. Markedly reduced blink rate and closure of eyelids due to eyelid dystonia or levator inhibition (also known as apraxia of eyelid opening) results in overactivity of the frontalis muscle, in an attempt to keep eyelids open, leading to a characteristic surprised look. Horizontal saccade intrusions named square wave-jerks, occurring while staring at an object, are frequently present in PSP patients, while ocular-vestibular reflexes are preserved. Thus, on doll's eye maneuver, there is improved range, as vestibulo-ocular reflex is preserved, confirming the supranuclear nature of the gaze palsy.[7,18–25]