Movement Disorders
CLINICAL PRACTICE
CASE REPORT

"Rapidly" Progressive Supranuclear Palsy

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PSP has a typical duration of 5 to 7 years, sometimes longer,[1] and a slow course is part of the diagnostic criteria.[2] Although rare cases of PSP with more rapid progression have been described, they are typically over 2 to 3 years. Faster rates of a PSP phenotype suggest an alternative diagnosis, such as prion disease. We describe a patient whose course with pathologically confirmed PSP was under 2 years.

A 73-year-old woman presented with slow walking for 1 year without falls. Several months before being observed at our center, she was diagnosed with Parkinson's disease and treated with levodopa 100/25 mg twice-daily, entacapone 200 mg twice-daily, and low doses of ropinirole without benefit. Doses, however, were limited by bothersome orofacial dyskinesias. There was no family history of parkinsonism or dementia. Our initial examination revealed a Montreal Cognitive Assessment score of 23/30, mildly attenuated fast phases with vertical optokinetic nystagmus (OKN) testing,[3] orobuccal dyskinesia, symmetric mild rigidity and bradykinesia, and slow gait with falling on the pull test. Entacapone and ropinirole were discontinued and L-dopa was escalated gradually to 600 mg/day. After initial mild improvement, her gait progressed rapidly; the orofacial dyskinesias persisted and the patient stopped the L-dopa with resolution of these movements. Within weeks, she declined further, fell frequently, and was unable to complete activities of daily living. Six months after presentation to our center, she was unable to walk, spoke in a whisper, and followed only some one-step commands. There was vertical ophthalmoplegia and horizontal ophthalmoparesis, with a few fast phases with horizontal OKN, but not vertical. She had severe axial and appendicular rigidity and bradykinesia. An MRI of the brain revealed mild global atrophy and previous lacunar infarcts in the basal ganglia. Cerebrospinal fluid showed normal cell count, protein, glucose, cultures, and negative cytology. She became unable to drink or eat and died within 1.5 years of symptom onset.

On postmortem examination, prefixation brain weight was 1,240 g. Gross pathology showed only mild generalized atrophy. Serial coronal sections of the cerebral hemispheres were unremarkable, aside from mild atrophy of the STN. No frontotemporal atrophy was present. Serial axial sections of the brainstem revealed pallor of the SN. Neuropathological examination demonstrated loss of pars compacta neurons accompanied by globose neurofibrillary degeneration, prominent in tegmental brainstem nuclei and deep gray matter structures (Fig. 1A,B). Frontotemporal lobar degeneration was absent, as were ballooned, achromatic neurons. Abundant globose neurofibrillary tangles were present in widespread nuclei of the pontine and mesencephalic tegmentum, as well as deep gray matter structures, including the STN, thalamus, and globus pallidus. The changes were highlighted by phospho-tau (AT8) immunohistochemistry (IHC), which also showed tufted astrocytes (Fig. 1C), gliofibrillary tangles, coiled bodies, and extensive neuropil threads involving gray and white matter tracts. Astrocytic plaques were absent, as were Pick bodies and corticobasal bodies. There were no features of globular glial tauopathy. There were no neuritic plaques or other neocortical pathology that would explain the rapid progression. The findings were overall characteristic of PSP.

The symmetric parkinsonism poorly responsive to L-dopa, early falls, and supranuclear vertical ophthalmoplegia in this patient suggested PSP, but the very rapid progression was atypical, causing us to pursue a more extensive workup than is usually necessary for PSP. Orobuccal dyskinesias are also uncommon in PSP. In two series of patients with rapidly progressive dementia (Table 1), prion disease was the most common diagnosis. PSP was rare, accounting for 2 of 178 (1.1%) and 2 of 22 (9.1%) of cases,[4,5] with total disease duration reported as 1.5 and 3.5 years for the 2 patients in one series.[5] Neurodegenerative dementias as a group (n = 26) were the second-most common cause of rapidly progressive dementias in

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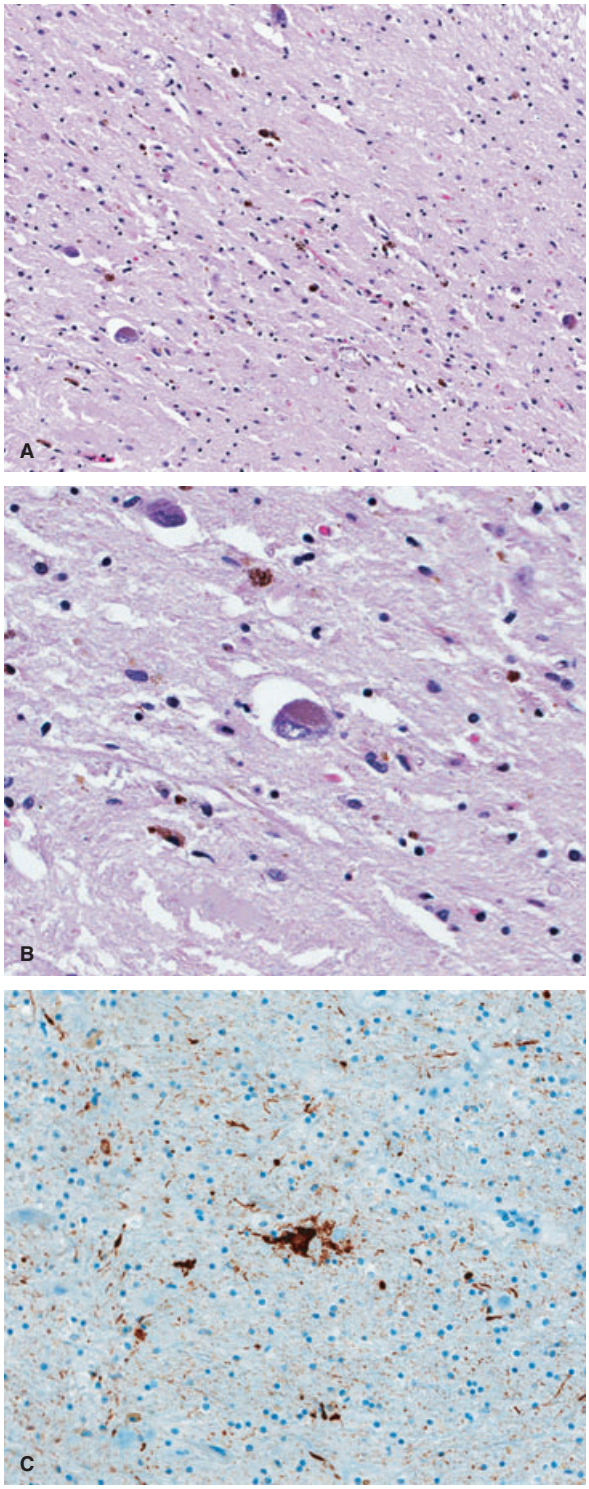

Figure 1 (A) Medium magnification photomicrograph of the SNc shows significant loss of pigmented neurons (scale bar = 100 μm). (B) High magnification of the same region shows a globose neurofibrillary in a residual viable neuron, with pigment incontinence (scale bar = 30 μm). (C) IHC stain for phosphorylated tau protein (AT8) demonstrates tufted astrocytes (center) and neuropil threads (scale bar = 50 μm).

TABLE 1 Common causes of rapidly progressive dementias

Josephs et al.[5] (n = 22)	Geschwind et al.[4] (n = 178)
Prion disease (n = 8; 36%)	Prion disease (n = 110; 62%)
FTLD with MND (n = 5; 23%)	Autoimmune[a] (any, n = 15; 8%)
Tauopathy (PSP or CBD = 4; 18%)	Tauopathy (PSP or CBD = 10; 7%)
Diffuse Lewy body disease (n = 3; 14%)	Frontotemporal dementia (n = 7; 4%)
Alzheimer's disease (n = 2; 9%)	Alzheimer's disease (n = 5; 3%)
	Dementia with Lewy bodies (n = 4; 2%)

[a]Neurodegenerative dementias as a group (n = 26) were the second-most common cause of rapidly progressive dementias (15% of all cases and 39% of nonprion cases). Autoimmune causes accounted for 22% of nonprion cases.
FTLD with MND, frontotemporal dementia with motor neuron disease; CBD, corticobasal degeneration.

the other series,[4] accounting for 15% of all cases. Shorter disease duration in PSP is associated with higher tau burden,[6] though, interestingly, the single patient in this study with a disease course <2 years had only moderate tau involvement (PSP-tau score: 2).[6] Our patient had severe tau burden, consistent with the described association between pathologic severity and disease duration.

The National Institute of Neurological Disorders and Stroke (NINDS) and Society for Progressive Supranuclear Palsy criteria for PSP require a "gradually progressive" course for both possible and probable PSP.[2] PSP typically progresses to death in 5 to 7 years,[1] with Richardson syndrome having the fastest rate of progression.[7] Other clinical features associated with a more rapid progression of pathologically confirmed PSP include older age at onset,[7] male gender,[7] early falls,[1,8] dementia,[8] early dysphagia,[1] incontinence,[1] and a short interval from disease onset to one of seven clinical milestones (frequent falls, wheelchair dependence, unintelligible speech, severe dysphagia, urinary catheter, cognitive impairment, and residential care).[7] Similar predictors were described in a clinically diagnosed cohort of PSP patients.[9] Although our patient had many of the symptoms and signs associated with a worse prognosis, her very rapid progression was still atypical for PSP. Rapid progression of a PSP phenotype should lead to an investigation for an alternative diagnosis, such as prion disease.[4,5] Other neurodegenerative diseases, such as frontotemporal lobar degeneration with motor neuron disease resulting from transactive response DNA binding protein 43 kDa proteinopathy, can also have PSP-like presentations and rapidly progressive courses.[10] This case illustrates, however, that PSP may rarely have a rapid course leading to death in less than 2 years.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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