Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria

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Abstract
All cases examined postmortem at the Mayo Clinic that met the classic neuropathological criteria for progressive supranuclear palsy (PSP) were identified for retrospective clinical analyses. The necropsy material was re-examined by a second neuropathologist to confirm the pathological diagnosis of PSP, yielding 12 cases. A range of clinical signs were documented in these patients, with numerous findings beyond those noted in the original descriptions of this disorder. Atypical clinical findings included absence of supranuclear gaze palsy (two cases), prominent asymmetry (two), arm dystonia (two), upper limb apraxia (two), myoclonus (two), chorea (one), eyelid opening apraxia (one), and respiratory disturbance (one). A definite clinical diagnosis of PSP had been made during life in only eight of the 12 patients. From the retrospective analysis of these 12 cases, a set of clinical criteria were developed for the premortem diagnosis of PSP emphasising differences from other akinetic-rigid disorders.

(Keywords: progressive supranuclear palsy; diagnostic criteria; neuropathology)

The initial clinical description of progressive supranuclear palsy (PSP) by Steele et al in 1964,1 emphasised a unique constellation of findings: "supranuclear ophthalmoplegia (especially downgaze), pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, and dementia." Although subsequent clinicopathological series substantiated the nosological validity of PSP,2-4 the phenotypic range of this condition has also expanded considerably with later publications. Numerous examples of non-ophthalmoparetic or late ophthalmoparetic PSP have been documented,4-9 as well as neuropathologically confirmed cases of "pure akinesia".9,9 Other less commonly reported features include dystonia,10 cricopharyngeal dysfunction,11 abnormalities of respiratory rhythm,12 dysphasia,12 non-tremorous involuntary movements,3 internuclear ophthalmoplegia,9,12 eyelid opening apraxia,12 and early severe dementia.7

It may be difficult to diagnose PSP in certain patients, given the overlap with other akinetic-rigid syndromes and the increasingly recognised clinical diversity. Atypical cases, sharing clinical features with Parkinson's disease,13-15 multiple system atrophy,16-18 or corticobasal degeneration17,18 may be a source of diagnostic confusion. Several authors have formulated clinical criteria for the diagnosis of PSP during life12,13,19-21; however, none have been based on a large necropsy series. Such diagnostic criteria may be suboptimal in that they have not been subjected to systematic neuropathological validation and furthermore, are necessarily biased toward clinically typical PSP cases.

We report our clinicopathological findings in a consecutive necropsy series of 12 patients with PSP studied at the Mayo Clinic. We confirm neuropathologically the expanded phenotypic diversity of PSP reported by previous authors, and outline clinical criteria based on a retrospective analysis of our cases. These criteria were developed for the premortem diagnosis of PSP, taking into account the sensitivity of premortem diagnosis of this condition.

Methods
All patients with the neuropathological diagnosis of PSP (or Steele-Richardson-Olszewski syndrome) based on postmortem pathological examination at the Mayo Clinic were sought. Cases were identified from the neuropathological diagnostic coding files of the Department of Laboratory Medicine and Pathology. Ascertainment was verified by a computer search of all clinically diagnosed cases of PSP seen at the Mayo Clinic, cross referenced for necropsy. Thirty patients, necropsied between 1973 and 1993, were initially identified. Neuropathological necropsy findings were confirmed in each instance (except in one patient) by a second, independent, neuropathologist (JEP) who was unaware of specific clinical details. To unequivocally substantiate the diagnosis in some patients, additional sections were cut from original tissue blocks and treated by various standard non-immunological staining techniques. In all cases, microscopic examination included the globus pallidus, subthalamic nucleus, midbrain, pons, medulla, cerebellum, hippocampus, and frontal and temporal neocortex, which were stained with haematoxylin and eosin. Selected sections were stained by modified Bielschowsky or Bodian methods for neurofilaments. In most cases, additional sections were also stained with luxol fast blue/periodic acid Schiff for myelin, Holzer, or glial fibrillary acidic protein for...
astroglia, and Congo red or thioflavin-s for amyloid. Criteria for the neuropathological diagnosis of PSP were those of previously published series.2 4 21 Of the original 13 patients, 12 showed the classic neuropathological changes described in previous published descriptions of this disorder; the only patient who failed to meet the neuropathological criteria was excluded from further analysis.

The neuropathological hallmarks of PSP, shown in all 12 cases, included the presence of widespread neurofibrillary tangles (NFTs), mainly of the globus type, associated with variable neuronal loss and gliosis in many subcortical areas, and relative sparing of the neocortex and hippocampus. Consistent sites of involvement included the internal segment of the globus pallidus (internal pallidum), subthalamic nucleus, substantia nigra pars compacta, periaqueductal grey, superior colliculi, red nucleus, Edinger-Westphal nucleus, pontomesencephalic tegmentum, pontomedullary reticular formation, and locus ceruleus. Degeneration in the cerebellar dentate nucleus was characterised by neuronal loss, gliosis, and rare NFTs. The NFTs, usually of globus configuration but occasionally flame shaped, were present in heaviest concentration in the internal pallidum, subthalamic nucleus, and substantia nigra compacta. As well as numerous NFTs, the substantia nigra pars compacta showed variable but relatively diffuse neuronal loss and gliosis without predilection for ventral and lateral areas characteristic of idiopathic Parkinson’s disease,23 and with a conspicuous absence of Lewy bodies. The ventral tegmental area was relatively spared. Axonal spheroids were occasionally present in the otherwise relatively uninvolved substantia nigra pars reticulata. Demyelination, presumably secondary to neuronal loss in the nucleus of origin, was restricted to tracts and was best shown in the medial pallidum, subthalamic region, and hilus of the dentate nucleus.

Clinical correlations were made based on a thorough analysis of the patients’ clinic records. All patients except one (case 2) had been examined by both a Mayo Clinic staff neurologist and ophthalmologist during life, and in the single exception detailed clinical records were available for analysis.

### Results

Patients in this series were predominantly men with onset of disease in middle to late life (table 1). The condition tended to progress fairly rapidly with death occurring a mean of 5-3 years after the onset of symptoms, although one patient lived for 10 years. There was no history of prior autoimmune disease, encephalitis ill, or exposure to known neurotoxins. None had a family history of neurological disease, except case 6 whose sister had been diagnosed with “St Vitus dance” earlier in her life.

 Pronounced imbalance with frequent falls was a prominent and early symptom in all patients. In half, this was an initial symptom and was a presenting complaint for 11 of 12 patients. It was present in all patients three years into the clinical course (table 1). Downgaze paresis, an important clinical hallmark of PSP, was not detected in 50% of the patients at the time of the initial exam; one third of patients had no gaze paresis of any type when initially examined (table 1). In two patients (cases 3 and 11), downgaze paresis was never detected; the last neuro-ophthalmological examination was conducted in these two patients 2-5 and 3-6 years respectively after clinical onset. Case 11 was seen in the final year of her life and noted to have only mild to moderate limitation of upgaze, which was not thought to exceed that which may occur as a consequence of aging.24 Case 3 was last evaluated three years before death. Those patients with gaze paresis typically had vertical gaze compromised earlier and more prominently than horizontal gaze.

### Table 1 Demographic and clinical features of cases with PSP

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<th>Sex</th>
<th>Age (y)</th>
<th>At symptom onset</th>
<th>At diagnosis</th>
<th>At death</th>
<th>Symptom duration (y)</th>
<th>Clinical disease duration (y)</th>
<th>Initial symptom</th>
<th>Present at initial exam</th>
<th>Gaze paresis (any direction)</th>
<th>Present at initial exam</th>
<th>Down gaze paresis</th>
<th>Present at initial exam</th>
<th>Duration from initial exam until detected (y)</th>
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*ND = not diagnosed with certainty in life; †not detected.
Certain examination findings were invariably present, including bradykinesia, rigidity, and dysarthria (table 2). Rigidity was noted in all patients, but was slight in two (cases 3 and 10). Rigidity of the neck (axial) exceeded that in the limbs in eight of the 11 patients examined at the Mayo Clinic. Dysarthria was a presenting complaint in four patients and was characterised by combinations of hypokinetic and spastic features. In nine patients, the examiner specifically commented about the severe degree of facial masking and absence of blinking with terms such as "totally blinkless"; "does not blink"; "fixed stare".

In eight of the patients examined at the Mayo Clinic, the gait was shuffling like that of Parkinson's disease (table 2); however, the base was noted to be wide in at least four of these patients, unlike Parkinson's disease. Examiners noted that four patients sat "en bloc", characterised by the patient's feet coming high off the floor as they sat down (table 2); this is unusual in idiopathic Parkinson's disease except for patients in very advanced stages. Dystonia was identified in five patients, involving the neck in four. In one patient, antecollis was noted, by contrast with the more typical retrocollis. Although a resting tremor was documented in two patients, it was of low amplitude in each. Cognition was impaired in seven patients, but moderate or severe dementia was noted in only two (table 2). Formal psychometric evaluations were performed in five patients, and were normal in two (cases 3 and 5). Mild psychometric deficits were found in the other three, including delayed recall (case 2), impaired new learning (case 9), and right hemispheric deficits, including visual spatial learning impairment and left hemineglect (case 12).

Dyskinesiae other than dystonia and not attributable to medication were noted in four patients, including myoclonus in two and repetitive oral dyskinesiae in another. One patient displayed generalised adventitious movements described as choreiform by several neurologists. A cerebellar type upper extremity ataxia was noted in one patient. The symmetry typical of PSP was not seen in all patients and half had asymmetric signs with the asymmetry moderately pronounced in two patients.

Upper limb apraxia was noted in two patients (cases 6 and 12). In case 12, this was sufficient, in combination with asymmetry of signs, to raise a suspicion of corticobasal degeneration.10-15 The examiner (DMM) noted, however, that the apraxia was not of the extreme magnitude typical of corticobasal degeneration and, also, the asymmetry was not as striking as usually seen in that condition.

Disordered respirations during sleep led to polysomnography in a single patient (case 5), documenting recurring cycles heralded by a stuttering deep inspiratory gasp held for three to four seconds before a variably forceful exhalation. This was associated with an increase in the intrathoracic pressure with apnoea lasting for up to 60 seconds, but not associated with any significant oxygen desaturation. These events occurred primarily in the transition between wakefulness and sleep. Also noted in this patient were findings characteristic of periodic movements of sleep.

Abnormalities of somatic sensation, apart from mild to moderate vibratory loss in distal lower limbs were not documented in any patient. Clinical findings to suggest a generalised polyneuropathy were not seen. Symptomatic orthostatic hypotension was absent except for one patient who experienced this transiently during a state of severe dehydration.

Carbidopa/levodopa (Sinemet) or levodopa alone was given to 10 of the 12 patients. Seven had no or minimal response. Two patients experienced partial improvement in motor symptoms, but this was only transient, lasting less than six months in one (case 4) and about two years in the other (case 5). The response was unknown in one patient. The maximum known daily levodopa dosage ranged from 500 mg to 1500 mg (mean 807 mg) in the seven patients who were given carbidopa/levodopa. One of two patients treated with levodopa without carbidopa received a maximum of 5-5 g daily; the maximum dose was unknown in the other. Other medications—namely, amantadine, amitriptyline, and trihexyphenidyl—were tried in four patients without substantial benefit.

The clinical diagnosis during life was progressive supranuclear palsy in eight of the 12 patients. Diagnoses in the remaining four patients were "atypical PSP" (case 6), "Parkinson's plus, perhaps PSP" (case 12), and "indeterminate extrapyramidal disease" (cases 3 and 11).

Cranial CT, performed in nine patients, showed non-specific abnormalities consisting of mild to moderate generalised cerebral atrophy, sometimes in association with mild lateral ventricular dilatation. The neuroradiologists reviewing the scans during the patients' life were not impressed by disproportionate brain stem changes in any of the patients. In two patients (cases 3 and 8), mild to moderate low attenuation changes were
noted bilaterally in the deep white matter of the cerebral hemispheres. Magnetic resonance imaging performed in two patients contributed no substantial additional information. When performed, EEG (six patients) and CSF examinations (three patients), showed only minor, non-specific changes.

The most common recognised causes of death were pneumonia (three patients) and respiratory arrests (two patients), with one patient dying from myocardial infarction and one from a massive pulmonary embolism. The cause of death was unknown in five cases.

Discussion

The demographic characteristics of our patient population were similar to previously published series. In that there was a male predominance, symptom onset after age 40, and a disease duration until death that was relatively short (5-3 years). In one third of our patients, the diagnosis was not made with certainty during life; this is consistent with the increasing recognition that the clinical characteristics of PSP extend beyond the homone
cuneous clinical presentation recorded in the initial series by Steele and colleagues. Not only are the classic clinical criteria insufficient to allow the diagnosis in some atypical cases, but also, the clinical hallmark of PSP, supranuclear ophtalmoparesis, may be present in other neurodegenerative conditions, resulting in diagnostic confusion.

Typical of postmortem series, the patient selection was biased toward the atypical; the wide clinical range, however, can serve as a basis for the development of relatively sensitive and specific clinical diagnostic criteria.

Not unexpectedly, early pronounced gait imbalance and supranuclear downgaze paresis were the two signs in this series that were “red flags” for the diagnosis of PSP. Prominent imbalance with frequent falls was a heralding symptom in half of the patients in this series and was a prominent complaint in all by the time three years had elapsed. This contrasts with idiopathic Parkinson’s disease in which prominent imbalance occurs much later; only rarely is it severe enough to cause frequent falling within the first five years.

Supranuclear vertical gaze paresis is regarded as the primary clinical hallmark of PSP. Upgaze paresis, however, may be present in normal aging and may also be a non-specific sign in other neurodegenerative conditions including idiopathic Parkinson’s disease. Supranuclear downgaze paresis, however, is more specific for PSP, although it occurs in corticobasal degeneration and, uncommonly, in other conditions. Downgaze paresis was not present in all patients in this series, being absent at the time of the initial examination in half and never detected in two cases that had been carefully examined as late as 2-5 and 3-6 years into their condition. Thus the clinician cannot rely on the presence of downgaze paresis to aid in the diagnosis in every case, as has become increasingly recognised.

Early in its course, PSP is often confused with idiopathic Parkinson’s disease, even by experienced clinicians. Corticobasal degeneration or multiple system atrophy are also alternative diagnostic considerations in a few cases. There are several distinctions among the extrapyramidal signs, however, that differentiate PSP from idiopathic Parkinson’s disease as well as corticobasal degeneration and multiple system atrophy. Firstly, whereas facial masking is seen in all these conditions, the extremely immobile facies with a wide eyed, blinkless staring expression is very distinctive of PSP. Blink rates have been shown to be substantially less in patients with PSP, compared with all but those with most advanced Parkinson’s disease. In the present series, the facies were sufficiently distinctive in nine of the 11 Mayo Clinic patients to cause the clinicians to comment specifically in terms such as “totally blinkless”, “reptilian stare”, “non-moving facies”. Perhaps the combination of extrapyramidal plus corticobasal dysfunction is the reason for the distinctive facies in PSP.

PSP also differs from idiopathic Parkinson’s disease and most other neurodegenerative disorders in that the motor deficits are more axial than appendicular. This was exemplified in the present series in which neck rigidity was given a more severe rating than limb rigidity in most patients, opposite to that typically seen in Parkinson’s disease. Axial movements of the body are also performed extremely slowly and stiffly in classic cases of PSP, prompting Steele and colleagues to characterise this in certain of their patients as “apraxia” of truncal turning and sitting.

This “truncal apraxia” is often most apparent when the patient with PSP is asked to sit and subsequently plops backward on to the seat “en bloc” with feet rising high off the floor; this was described in four of the patients in this series.

Although a shuffling gait in PSP may resemble that of idiopathic Parkinson’s disease, it is more typically wide based, as noted in four of the five patients in which this specific information was recorded. As already mentioned, the tendency to move “en bloc” and the prominent and early imbalance also distinguish the classic PSP gait from that of idiopathic Parkinson’s disease.

Whereas a prominent resting tremor is highly characteristic of idiopathic Parkinson’s disease, it is either absent or of slight amplitude in PSP. Although two patients in this series displayed a resting tremor, it was clear from the records that this was of low amplitude and not prominent. Thus although a mild resting tremor does not exclude PSP, a pronounced resting tremor argues against this diagnosis.

Symmetric onset of clinical signs is also characteristic of PSP, by contrast with idiopathic Parkinson’s disease and corticobasal degeneration, in which the signs typically are asymmetrical and even unilateral. Symmetry is not invariant, however, as found in the present series in which moderate asymme-
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Asymmetry was noted in two patients and mild asymmetry in an additional four. Unilateral or predominantly unilateral motor deficits, however, suggest a diagnosis other than PSP.

The response to levodopa also distinguishes PSP from idiopathic Parkinson's disease. Whereas patients with PSP occasionally fail to respond, the improvement is typically short lived and insufficient to alter major disability. Similarly, two of our cases responded to levodopa, but with no more than moderate and short lived benefit. Thus lack of an impressive sustained improvement with levodopa is an important diagnostic clue.

Dystonia is a non-specific clinical sign; however, dystonia of the neck, especially retrocollis, as well as arm dystonia, may suggest PSP in the proper clinical context. In the present series, retrocollis or arm dystonia were present in four patients. Although lower limb dystonia is common in untreated Parkinson's disease, arm dystonia or retrocollis is uncharacteristic. Whereas corticobasal degeneration is characterised by a stiff, dystonic limb, neck dystonia, particularly retrocollis, is exceptional.

Corticobulbar signs as well as corticospinal tract signs are also highly characteristic of PSP, as exemplified in the present series. The strained, harsh quality of the voice, characteristic of a spastic dysarthria, is not present in idiopathic Parkinson's disease, although it does occur in multiple system atrophy. Whereas dysphagia and a pseudobulbar affect can occur late in Parkinson's disease, these are relatively earlier signs in PSP. Babinski signs, which are unexpected in Parkinson's disease, were documented in 75% of patients in this series. Cognitive impairment was noted in most of our patients, but was severe in only two. Personality changes may herald the development of cognitive impairment. Although dementia is a frequent occurrence in certain other neurodegenerative disorders such as Parkinson's disease, it is rare in others, specifically multiple system atrophy; in certain cases this may be a useful clinical distinguishing feature.

Prominent and early dysautonomia was not seen in the present series and its absence may be a useful clinical clue. Although the autonomic nervous system is known to be compromised in PSP, it is not severely impaired. Thus although bowel and bladder dysfunction were frequent problems in end stage disease in this series, symptomatic orthostatic hypotension was not encountered except for a single transient episode in one patient due to dehydration.

Ideomotor apraxia of the limbs is thought to reflect a cortical deficit and is not an expected finding in PSP, in which the pathology is largely confined to subcortical structures. None the less, two patients from the present series displayed ideomotor limb apraxia. In one patient (case 12), the asymmetric apraxia was sufficient to raise the possibility of corticobasal degeneration. The clinician (DMM), however, noted that the apraxia was not as pronounced, nor was the asymmetry as prominent, as in typical corticobasal degeneration. Several other signs suggested PSP as a more likely diagnosis including a "fixed stare" and the early development of imbalance with frequent falls. An alien limb sign, which is frequent in corticobasal degeneration, was not noted in case 12, although sought. Whereas downgaze paresis was noted in this patient, this sign is also frequent in corticobasal degeneration.

As reported by Gibb et al., a clinical distinction between PSP and corticobasal degeneration may be extremely difficult to make in occasional patients.

Although upper limb ideomotor apraxia is classically attributed to cortical dysfunction, no distinctive neuropathological abnormalities sufficient to account for this sign were identified in the cortex of our two apractic patients. This is analogous to the findings of Davis et al. in two patients with PSP with severe dementia suggesting cortical involvement, but without cortical pathology. Positron emission tomography studies in patients with PSP have shown functional (hypometabolic) compromise of the cortex, especially frontal, but sometimes including the parietal cortex, presumably secondary to loss of subcortical activation.

Various dyskinesiae can occasionally be seen in patients with PSP. Myoclonus was noted in two patients in the present series, whereas chorea and oral dyskinesiae, unrelated to medications, were found in additional single patients.

Pure akinesia unresponsive to levodopa (akinesia without rigidity or tremor) has been described as a presenting and sometimes persisting manifestation of PSP in certain Japanese patients. Two patients in the present series were a close fit with the dopa unresponsive pure akinesia syndrome (cases 3 and 10); although rigidity was noted in these two patients, it was graded as mild and distinctly dropped in the earlier motor manifestations, as well as being anatomically limited to one arm (case 3) or the neck (case 10).

Although not found in the present series, other authors have noted several additional signs in patients clinically diagnosed with PSP, including dysphasia, and internuclear ophthalmoplegia, as well as various other oculomotor disorders.

Head scanning is an appropriate diagnostic procedure in patients with suspected PSP. The primary utility is to exclude structural lesions that might be contributing to the clinical picture as well as multi-infarct states or hydrocephalus, which have been reported to produce clinical findings similar to PSP. Whether these studies can provide PSP specific clues is debatable; various signs of brain stem atrophy have been shown by MRI in some patients with PSP. Signal hypointensity within the putamen has also been documented via MRI in PSP, as well as other parkinsonian syndromes. In the present series, hypointensity was not identified as specific to PSP.
Algorithm for the clinical diagnosis of PSP, based on the present neuropathologically confirmed series. Although not seen in our patients, dysphasia and internuclear ophthalmoplegia have also been reported in PSP.1112

Prerequisites

- Age of onset >40 years
- No family history
- Insidious onset and progressive
- Neuroimaging reveals no relevant structural abnormalities
- No exclusionary criteria

Supranuclear downgaze paresis

Both

Prominent early postural instability and frequent falls

*Exclusionary criteria

- Prominent and early dysautonomia, especially orthostatic hypotension
- Prominent polyneuropathy
- Pronounced rest tremor
- Cortical sensory loss
- Alien limb sign
- Unilateral presentation or pronounced asymmetry

Supranuclear downgaze paresis

- Bradykinesia
- Rigid neck > limbs
- Staring, non-blinking facies
- Wide based, shuffling gait
- Retrocollis or dystonic arm
- Sitting "en bloc"
- Pseudobulbar signs (two of dysarthria, dysphagia, affect)
- Babinski signs
- Dementia or personality change

Verification: minimal or unsustained (<two years) levodopa response

Progressive supranuclear palsy

Less common findings that do not exclude the diagnosis

- Limb rigidity > axial
- Narrow based gait
- Mild rest tremor
- Upper limb apraxia
- Upper limb ataxia
- Myoclonus
- Chorea
- Respiratory disturbance

Reviewed the head CT (n = 9) or MRI (n = 1). Of clinical utility, however, was the absence of lesions suggesting other conditions. One patient had rather profound white matter low attenuation changes on head CT that were sufficiently pronounced to raise a question of leukoencephalopathy during life. The neuropathological examination, however, showed only minimal changes in white matter, with the subcortical grey matter lesions typical of PSP being the paramount abnormality.

The experience from the present series permitted the development of a neuropathologically based set of diagnostic clinical criteria that would have led to the diagnosis of PSP during life in all 12 of these patients. These criteria, illustrated in the figure, emphasise some of the unique clinical features of PSP and also allow for some of the rarer and atypical features encountered in occasional patients. The algorithm was designed to exclude cases of multiple system atrophy or corticobasal degeneration, which may share some of the clinical features of PSP. Unfortunately, a diagnostic strategy for a neurodegenerative disorder based solely on clinical criteria will not be 100% sensitive or specific. The case reports of PSP-like disorders harbouring different neuropathologies are illustrative.17 18 None the less, we believe that the vast majority of patients with PSP, including most of the clinically diverse, can be correctly diagnosed in life and we offer the algorithm shown in the figure as a means of making the correct diagnosis. Ultimately, the specificity and sensitivity of this diagnostic algorithm must be tested in subsequent series of pathologically confirmed PSP and other akinetic-rigid syndromes.

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Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria