Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study

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Abstract

Objective—To analyse the natural history of progressive supranuclear palsy (PSP or Steele-Richardson-Olszewski syndrome) and clinical predictors of survival in 24 patients with PSP confirmed by necropsy, who fulfilled the NINDS criteria for a neuropathological diagnosis of typical PSP.

Methods—Patients were selected from the research and clinical files of seven medical centres involving tertiary centres of Austria, England, France, and the United States. Clinical features were analysed in detail. The patients' mean age at onset of PSP was 63 (range 45-73) years.

Results—The most frequent clinical features (occurring in at least 75% of the patients) were early postural instability and falls, vertical supranuclear palsy, akinetic-rigid predominant parkinsonian disorder characterised by symmetric bradykinesia and axial rigidity unrelieved by levodopa, pseudobulbar palsy, and frontal release signs. Occasionally, segmental dystonia or myoclonus were described, but neither aphasia nor alien limb syndrome was reported. Fractures occurred in 25% of the patients but were unrelated to the severity of the gait or to the presence of falls. Median survival time was 5.6 (range 2-16.6) years. Onset of falls during the first year, early dysphagia, and incontinence predicted a shorter survival time. Age at onset, sex, early onset of dementia, vertical supranuclear palsy, or axial rigidity had no effect on prognosis of survival. Pneumonia was the most common immediate cause of death. PSP was most often clinically misdiagnosed as Parkinson's disease. Errors in diagnosis suggest that PSP is underdiagnosed.

Conclusion—Progressive onset of early postural instability with falls or supranuclear vertical palsy in the fifth decade, should suggest the diagnosis of PSP. Onset of falls during the first year are emphasised, as they could lead to an early diagnosis and influence the prognosis of patients with PSP. Whether appropriate treatment of the dysphagia could prolong the survival of PSP patients needs to be explored.

Keywords: progressive supranuclear palsy; natural history; survival

Progressive supranuclear palsy (PSP or Steele-Richardson-Olszewski syndrome) causes postural instability, supranuclear vertical ophthalmoplegia, parkinsonism unresponsive to levodopa, pseudobulbar palsy, and mild dementia.^{1,2} However, patients with PSP without ophthalmoplegia or dementia, or presenting only with dementia or akinesia, have also been reported.³⁻⁷

In the absence of laboratory markers for the diagnosis of PSP, neuropathological examination remains the "gold standard" for its diagnosis. Neuropathologically confirmed cases of corticobasal degeneration, multiple system atrophy, diffuse Lewy body disease, cerebrovascular disease, subcortical gliosis, and prion disease have been clinically misdiagnosed as PSP.⁸⁻¹⁴ Thus PSP can be difficult to diagnose because of its increasingly recognised clinical diversity and because the topographic distribution of lesions in the basal ganglia and brainstem overlaps with what is found in other parkinsonian syndromes.^{15,16} Moreover, PSP may be associated with more than one neuropathological diagnosis, such as Alzheimer's or Parkinson's disease.¹⁷

To develop a clinically useful description of the natural history of PSP which could improve the accuracy of its *early* diagnosis,¹⁶ we reviewed the records of the first and last visits of 24 patients with neuropathologically typical PSP confirmed at necropsy,¹⁸ and compared our findings with those of other confirmed series.^{15,19-22} We also evaluated the cause of death and clinical predictors of survival in these patients because both may provide useful insights into the management of patients with PSP.

Methods

Patients were selected from the research and clinical neuropathological files of seven medical centres of four countries (Austria, England, France, and the United States) by neuropathologists who based their selection on the recently published National Institute of Neurological Disorders and Stroke (NINDS) neuropathological criteria for the diagnosis of PSP.¹⁸ Only neuropathologically typical cases of PSP, which were shown to have substantial reliability,²³ were included in the study. Briefly, neuropathologically typical PSP

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includes a high density of neurofibrillary tangles and neuropil threads in at least three of the following areas: pallidum, subthalamic nucleus, substantia nigra, and pons, and a low to high density of neurofibrillary tangles or neuropil threads in at least three of the following areas: striatum, oculomotor complex, medulla, and dentate nucleus. It also requires the exclusion of other disorders including large or numerous infarcts; profound diffuse or focal atrophy; Lewy bodies; changes diagnostic of Alzheimer's disease; oligodendroglial argyrophilic inclusions; Pick bodies; diffuse spongiosis; or prion P positive amyloid plaques. All cases met the criteria for inclusion in the study—that is, neuropathological diagnosis of PSP made with at least a 75% degree of certainty by the neuropathologists who provided the cases, and detailed neurological examinations, including neurooculomotor examination, on the first and last visits.

The patients' records were abstracted on standardised forms by eight of us (AM, MV, KJ, KRC, RKBP, LD, IL, or CAM), who followed strict instructions. Signs or symptoms were recorded as missing data if they were not mentioned in the records. However, as the data were retrospectively collected, we assumed that neurologists performed complete examinations and considered that a feature (for example, supranuclear palsy) was absent when they reported that the examination was "within normal limits" (for example, cranial nerves). For the purpose of this study, upward gaze limitation was considered abnormal when either a restriction, in pursuit, or voluntary gaze, or both, of at least 50% of the normal range was described, or the upward supranuclear palsy was rated as moderate to severe. The severity of gait disturbance was classified as follows: 0 = not affected; 1 = minimal (impaired but no assistance is needed); 2 = mild (needs the use of a stick or walker); 3 = moderate (needs the assistance of one or more persons); and 4 = severe (unable to walk even with assistance).

Survival was calculated by the Kaplan-Meier and proportional hazards (Cox) life table analysis.²⁴ Analysis of variance (ANOVA), the χ^2 test, and the Spearman r test were used for statistical analysis, as appropriate.²⁴ Results are expressed as mean (SD); statistical significance was defined as $P \leq 0.05$.

Results

DEMOGRAPHIC

Table 1 shows the main demographic characteristics of the 24 patients. There were nine

women and 15 men, a typical sex distribution for patients with PSP. The mean age at onset of PSP was 63 (SD 7) years; mean age at the first visit was 66.4 (SD 7) years; and mean age at death was 69.6 (SD 6.6) years. None of the patients had a familial parkinsonian disorder. Of the 24 patients, 21 were right handed, one was left-handed, one was ambidextrous, and one had no record of handedness.

INITIAL SYMPTOMS OF PSP

The onset of PSP symptoms was insidious and disease progression was steady. The initial symptom was most often (63%, $n = 15$) postural instability. Both postural instability and falls occurred during the first year in 58% of the patients. Dysarthria was the second most common symptom (33%, $n = 8$), followed by bradykinesia (13%, $n = 3$). Visual disturbances (diplopia, blurred vision, burning eyes, light sensitivity) were the first symptoms in 13% ($n = 3$) of the patients. Cognitive or behavioural changes generally followed these initial symptoms, but were the first symptoms in 8% ($n = 2$) of the patients.

SYMPTOMS AT FIRST VISIT

The first clinical visit occurred a mean of 3.7 years (range 1–11 years) after onset of disease. At the first visit, most of the patients with PSP had gait disorder and postural instability, a history of falls, bilateral bradykinesia, a predominant akinetic-rigid course, axial rigidity, vertical supranuclear palsy, and dysarthria (table 2). Gait was unstable ($n = 23$), small stepped ($n = 12$), or broad based ($n = 5$). Falls were backwards in eight of 11 patients for whom the direction of the falls was described.

Supranuclear gaze deficits involved initially either downward or upward gaze and, later, horizontal gaze. The patients rarely presented with vertical supranuclear palsy at onset; it usually occurred three years after onset of disease, and in three patients it never developed. Moderate to severe upward gaze palsy was more frequent than downward gaze abnormalities ($n = 19$ v $n = 16$). Pursuit and voluntary saccades were affected early in the course of the disease, and often patients had abnormalities in convergence (although such data were often missing).

Speech was slurred ($n = 15$), dysphonic ($n = 12$), slow ($n = 9$), palilalic ($n = 2$), ataxic ($n = 1$), or unintelligible ($n = 1$). Frontal lobe type symptomatology (mainly decreased fluency, concrete thought, and difficulty with analogies, less often perseveration and imitation behaviour), and personality changes (mostly apathy and depression) was present in

Table 1 Characteristics of patients with PSP in three series confirmed by necropsy

	Present series	Collins et al ²¹	De Bruin et al ²⁰
Sex	9F/15M	3F/9M	34F/51M*
Age at onset (y) (mean (range))	63 (45–73)	66 (48–77)	62 (47–78)
Disease duration (y) (mean (range))	6.6 (2–16.6)	5.3 (2–10)	5 (1–13)
Time to first visit (mean (SD))	3.7 (2)	1.5 (0.9)	NA
Time between visits (y) (mean (SD))	2.2 (1)	NA	NA

*Sex was not specified in five cases.

No patients had history of encephalitis or familial disease; NA = data not available.

Table 2 Features of patients with PSP in three series confirmed by necropsy

Features	Present series first visit (n = 24) (%)	Present series last visit (n = 24) (%)	Collins et al ¹ last visit (n = 12) (%)	De Bruin et al ²⁰ last visit (n = 90) (%)
Disease course:				
Akinetic-rigid	15 (63)	19 (79)	NA	NA
Mixed disease	4 (17)	4 (17)	NA	NA
Tremor dominant	1 (4)	1 (4)	NA	NA
Extrapyramidal features:				
Gait disorders	23 (96)	24 (100)	NA	63 (71)
Postural instability	22 ^a (92)	24 (100)	NA	NA
Falls	20 (83)	24 (100)	12 (100)	54 (60)
Falls in first year	14 (58)	—	9 (75)	NA
Bilateral bradykinesia	21 ^a (88)	23 ^a (96)	11 ^a (100)	60 (67)
Axial rigidity	15 ^b (63)	20 ^a (83)	NA	52 (58)
Tremor, rigidity, or bradykinesia (at least two)	18 (75)	24 (100)	11 ^a (100)	NA
Tremor, rigidity, and bradykinesia	3 (13)	4 ^a (17)	2 ^a (18)	NA
Neck dystonia	5 ^a (21)	11 (46)	4 (33)	43 (48)
Rest tremor	5 (21)	3 (13)	2 ^a (18)	15 (17)
Unilateral dystonia	1 (4)	1 (4)	2 ^a (18)	18 (20)
Treatment:				
Levodopa				
None or unknown	12 (52)	9 (35)	3 (25)	NA
Pronounced response	2 (8)	4 (27)	2 ^a (18)	NA
No response	9 (39)	11 (73)	7 (64)	NA
Other features:				
Supranuclear vertical palsy	19 (79)	20 ^a (19 downward)	11 (10 downward)	61 (69)
Dysarthria	18 ^b (75)	24 (100)	11 ^a (100)	60 (67)
Frontal release signs	13 (54)	19 ^c (79)	NA	NA
Frontal lobe type symptomatology	11 ^d (46)	4 ^e (58)	NA	NA
Extensor plantar	5 (21)	9 (38)	8 ^a (66)	30 (34)
Dysphagia	4 (16)	20 (83)	6 ^a (55)	51 (58)
Anomia	1 (4)	4 (17)	NA	NA

^aData missing in one patient; ^bdata missing in two patients; ^cdata missing in three patients; ^ddata missing in four patients; ^edata missing in seven patients; NA = data not available.

11 of 20 patients. Dysphagia and neck dystonia were infrequent.

Details of treatment and initial response were known for 15 patients (table 2). Seventy three per cent of them did not benefit from levodopa treatment, and 27% (n = 2) had a good response to levodopa (50–70% benefit), but the benefit lasted less than one year in one patient, and was unknown in another.

Fractures occurred in 25% of the patients, mostly early in the course of the disease (mean, 2.9 years after onset; range 0.5–6 years). Gait severity or falls during the first year of the disease were not correlated with the number of fractures.

Age at onset of symptoms was significantly correlated with the onset of falls during the first year of disease (Spearman $r = 0.82$; $P < 0.0001$). Patients who had recurrent falls during the first year of disease were significantly older (67 (1.1) years) than those who did not (56.4 (1.3) years; ANOVA, $P < 0.0001$). Patients with PSP who had begun falling during the first year of disease sought medical

attention earlier (33.8 (7) months) than those who did not (59 (9) months; ANOVA, $P < 0.04$).

SYMPTOMS AT LAST VISIT

The last clinical visit occurred a mean of 5.9 (range, 1.6–16) years after onset of disease. In general, symptoms and signs that were apparent early in the course of PSP progressed steadily up to the last visit. The gait was abnormal with postural instability and bradykinesia in all of our patients (table 2); 67% (n = 16) of the patients used a wheelchair. Axial rigidity was more common (83%, n = 20) than retrocollis (46%, n = 11). Speech was always impaired: it was slurred (n = 22), dysphonic (n = 19), slow (n = 15), unintelligible (n = 10), palilalic (n = 3), mute (n = 3), echolalic (n = 2), ataxic (n = 2), or tachypneic (n = 1). Few patients had what could be considered unusual motor features: one patient had unilateral dystonia, one myoclonus, three asymmetric parkinsonian signs, one motor neuron disease in the lower limbs, and one both tremor dominant disorder and resting tremor at onset of disease. A few patients had anomia, but aphasia or alien limb syndrome was never reported.

SURVIVAL

The median survival from onset of PSP was 5.6 (95% confidence interval 4.8–7.1 years; figure), and after the first clinical visit it was 2.7 years. The onset of falls during the first year together with dysphagia and incontinence at the first visit predicted a shorter survival ($\chi^2 = 13.5$, $P < 0.003$). The median survival of patients who had begun to fall during the first year of disease was shorter (5.2 years) than those who did not (6.8 years; $P < 0.05$). Survival of two patients with PSP with early incontinence (3.2 and 3.3 years), and of one

Kaplan-Meier life table analysis of patients with PSP after onset of symptoms.

with early dystonia (two years) was brief. The only patient with tremor at onset and tremor dominant disease had the longest survival (16.6 years). Although patients with early dysphagia had a shorter survival (3.9 years) than those without (5.8 years), early dysphagia did not independently predict survival. Age at onset, sex, early onset of dementia, vertical supranuclear palsy, or axial rigidity had no effect on prognosis of survival.

CLINICAL DIAGNOSIS AND CAUSE OF DEATH

The neurologists who clinically followed up these patients made a diagnosis of PSP in 58% of the patients at the first visit (11 typical, three atypical); Parkinson's disease in 21% ($n = 5$); corticobasal degeneration in 4% ($n = 1$); multiple system atrophy in 4% ($n = 1$); Alzheimer's disease in 4% ($n = 1$); and other disease in 8% ($n = 2$). At the last visit, a diagnosis of PSP was made in 88% of the patients (14 typical, seven atypical). False negative misdiagnosis occurred with Parkinson's disease ($n = 1$), corticobasal degeneration ($n = 1$), and other disorders ($n = 1$).

Thirteen of the 20 patients in whom the cause of death was known died of pneumonia (two with aspiration pneumonia), four of cardiovascular disorders (pulmonary emboli, myocardial infarct, congestive heart failure), and three of renal infections.

LABORATORY TESTS

Eighteen of the 24 patients had CT, MRI, or both. Eight patients had diffuse atrophy; one had atrophy of the tectum of the brainstem at a later stage; one had ventricular dilation compatible with normal pressure hydrocephalus; one had right temporal opercular infarct without a clinical history of stroke, which was not confirmed at necropsy; one had multiple foci of prolonged T2 in the white matter and putamen; and six were reported to be normal.

Six of the 24 patients had a single-photon emission computed tomography (SPECT). The iodoamphetamine SPECT showed varied results: one patient had bilateral frontal and basal ganglia hypoperfusion; one had bilateral orbitofrontal and left thalamic hypoperfusion; one had left basal ganglia, and left temporo-parietal hypoperfusion; one had left parieto-occipital and left frontal hypoperfusion; and one had right frontal, right basal ganglia and left cerebellum hypoperfusion; one scan was read as within normal limits. One patient had a PET with 18 fluorodeoxyglucose, which showed bilateral frontal hypometabolism. Only one patient had a barium swallowing study, which showed difficulty initiating the swallow, lingual propulsion difficulties, delayed pharyngeal transit, and slow oral transit.

Fourteen patients with PSP had an EEG; 11 had diffuse, frontal or bimodal slowing and three were normal.

Discussion

NATURAL HISTORY OF PSP

The patients with PSP usually presented in the seventh decade, and never before the age of

45, with rapidly progressive postural instability and falls, followed by dysarthria and supranuclear vertical palsy, affecting either upward or downward gaze. Similar symptoms often occurred in other series confirmed by necropsy.^{19–22} Although falls often occur in elderly people secondary to various causes,^{25–26} the diagnosis of PSP should be considered when falls are associated with postural instability. Vertical supranuclear palsy, considered to be the hallmark of the disease, was present at disease onset in only a few patients. Much more commonly, vertical supranuclear palsy occurred several years after disease onset, or rarely, never developed, as previously reported.^{3–15–22–27–28} Downward gaze palsy is considered to be more specific for the diagnosis of PSP than is upward gaze palsy primarily because of age related restrictions in upward gaze.^{29–30} In our patients, however, moderate to severe upward gaze palsy was more frequent than downward gaze abnormalities. Our findings suggest that downward gaze palsy might not be a requirement for the diagnosis of early PSP, and that upward gaze palsy in association with early gait instability and postural falls may be a better predictor of the disease.

Our patients with PSP also showed (as in other series; table 2) impaired behaviour consistent with frontal lobe dysfunction. In addition, they developed non-levodopa responsive parkinsonism that was typically manifested as a predominantly axial, symmetric akinetic-rigid syndrome, and occasionally with extensor neck dystonia. Despite its emphasis in the medical literature,²⁹ neck dystonia was an infrequent early feature in our patients. Rest tremor and segmental dystonia were rarely seen, as in other series.²¹ A study²² which evaluated 16 pathologically confirmed PSP cases within three years of onset found that the symptoms progressed rapidly in 94%; in 81% onset was symmetric; 50% had vertical supranuclear palsy; 56% had axial dystonia; and 50% cognitive impairment. Likewise, symptoms in our series progressed rapidly and steadily for an average of six years.

Although clinical series based on cases of PSP confirmed by necropsy may have more atypical cases, the demographics from our 24 patients with PSP confirmed by necropsy are similar to those of other clinicopathological and clinical series.^{15–19–22–31} The heterogeneity of patients with PSP is also increasingly recognised.¹⁵ Patients with PSP without ophthalmoplegia may have fewer falls and less axial dystonia, dysarthria, dysphagia, and rigidity.¹⁵ In our series, patients with PSP without early downward gaze palsy also had less axial rigidity. Interestingly, survival was longest in one of our three patients with PSP who never developed ophthalmoplegia and had other features suggestive of Parkinson's disease, such as asymmetric resting tremor at onset, tremor dominant disease, and late onset of dysarthria, dysphagia, and postural instability.

Differences in the occurrence of clinical features among the published series^{19–20} may be partially explained by incomplete records. Even though we chose only records that were

complete and participating centres are dedicated to the study of parkinsonian disorders, this is a retrospective study. Thus there may have been inconsistent recording of symptoms and signs. Moreover, there are always problems of reliability of recollection of data, particularly as the first visit occurred a mean of 3.7 years after the onset of symptoms. Patients may have not recalled the events and physicians may not have recorded patients' complaints or may not have probed them sufficiently. However, as these are tertiary centres, it is possible that patients would have come to their first visit with records from other primary centres. Only prospective population studies in which patient information is recorded in a standardised manner can provide us with the information for a definite natural history of PSP.

MISDIAGNOSIS

Errors in the diagnosis of our cases of PSP by the primary neurologists suggest that PSP is underdiagnosed—especially early in the course of the disease—as previously suggested.^{15 16 32 33} The diagnosis of PSP is often confounded because several of its classic symptoms also occur in related disorders. For instance, supranuclear vertical gaze palsy occurs in other parkinsonian disorders, such as corticobasal degeneration, diffuse Lewy body disease, Creutzfeldt-Jakob disease, subcortical gliosis, or less commonly, multiple system atrophy.^{10 12 16 22 34–37} In addition, supranuclear vertical palsy occurs in other treatable conditions, such as Whipple's disease³⁸ or arteriosclerotic pseudoparkinsonism. In the early stages of the disease, PSP was most often confused with Parkinson's disease by the primary neurologists, whereas experienced neurologists (specialists in movement disorders) were most likely to confuse PSP with corticobasal degeneration.¹⁶

Features such as supranuclear vertical gaze palsy, rapid disease progression, early postural instability with falls, symmetric onset of akinetic-rigid parkinsonism that is unrelieved by levodopa, or pyramidal signs, help differentiate PSP from Parkinson's disease.³⁹ Alien limb syndrome, severe asymmetric parkinsonism, cortical sensory deficits, severe ideomotor apraxia, myoclonus, or late onset of postural instability may help to differentiate corticobasal degeneration from PSP.^{36 39 40} The confounding symptomatology points to the necessity of finding biological markers that will help make an earlier and definitive diagnosis of PSP.

CLINICAL PREDICTORS OF SURVIVAL AND MANAGEMENT ISSUES

Onset of falls during the first year and early dysphagia and incontinence were useful predictors of shorter survival of patients with PSP. It is unclear whether these features indicate an unusually aggressive course of the disease or alternatively, promote secondary, life threatening complications. Other studies are also needed to determine whether tremor dominant disease could be a predictor of

longer survival or whether early dystonia may shorten survival time.

Patients are not often questioned about symptoms suggestive of dysphagia (coughing or choking during meals) or silent aspiration (fever of an unknown origin),^{41 42} and barium swallowing studies are rarely requested, even though patients with PSP are often aware of their difficulty in swallowing.⁴³ In our series, a barium swallow test was requested in only one patient, although the chance of detecting aspiration on clinical examinations is poor.⁴⁴ Indeed, this is similar to what we find in our own clinical practices. Evaluation of patients with PSP by speech therapists specialising in swallowing disturbances may prevent complications such as silent aspiration pneumonia—probably one of the most frequent causes of death in this disorder. Patients may benefit from changes in the consistency of the diet or from the low morbidity and mortality of current techniques such as percutaneous endoscopic gastrostomy.

The single highest cause of death in our patients with PSP was pneumonia, whereas it is ischaemic heart disease in normal controls and patients with Parkinson's disease.⁴⁵ In our study, the cause of death cannot be explained by a certification artifact,⁴⁶ because the events were recorded from findings at necropsy. Case-control studies with larger samples are needed to determine whether early management of dysphagia or other common complications prolong the survival of patients with PSP.

LABORATORY TESTS

The diagnosis of PSP was often not supported by MRI, principally because brainstem atrophy was not routinely evaluated,^{47–49} although the MRIs did exclude other diagnoses. The SPECT scans were not useful because they did not show the typical pattern of bilateral frontal hypometabolism disclosed by ¹⁸fluorodeoxyglucose PET.^{50–53} Although iodoamphetamine SPECT⁵⁴ and imaging of dopamine D2 receptors with ¹²³I-IBZM SPECT⁵⁵ may be preferable, studies are needed to determine the role and cost effectiveness of SPECT in diagnosing PSP. An EEG was only helpful in excluding other rare disorders such as Creutzfeldt-Jakob disease.

In summary, better knowledge of the presenting symptoms, natural history of the disease, and features that predict survival will be helpful for making an earlier and more accurate diagnosis and prognosis of patients with PSP.

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