Postgrad Med J 1999;75:579–584

Classic diseases revisited

Progressive supranuclear palsy (Steele-Richardson-Olszewski disease)

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Summary

Progressive supranuclear palsy is a neurodegenerative disease which affects the brainstem and basal ganglia. Patients present with disturbance of balance, a disorder of downward gaze and L-DOPA-unresponsive parkinsonism and usually develop progressive dysphagia and dysarthria leading to death from the complications of immobility and aspiration. Treatment remains largely supportive but, potentially, treatments based on cholinergic therapy may be useful. As in Alzheimer's disease, the neuronal degeneration is associated with the deposition of hyperphosphorylated tau protein as neurofibrillary tangles but there are important distinctions between the two diseases. Evidence from familial fronto-temporal dementia with parkinsonism linked to chromosome 17 suggests that tau protein deposition is a primary pathogenic event in some neurodegenerative diseases. The understanding of the mechanism of tau deposition in progressive supranuclear palsy is likely to be of importance in unravelling its aetiology.

Keywords: progressive supranuclear palsy; Steele-Richardson-Olszewski disease; tau protein

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Accepted 14 May 1999

Progressive supranuclear palsy (PSP) is an important but probably underdiagnosed neurodegenerative syndrome. The anatomy of PSP overlaps with that of Parkinson's disease (PD) and its microscopic pathology is similar to that of Alzheimer's disease. The distinctive clinical features of PSP, in large part due to brainstem involvement, make the diagnosis reasonably straightforward once it has been considered by the examining physician.

Historical aspects

PSP was first described as a distinct syndrome by John Steele, J Clifford Richardson and Jerzy Olszewski in 1963 following Richardson's clinical observations on several patients with a unique syndrome in Toronto in the late 1950s.[1 2] Although experienced neurologists at that time were unable to categorize the syndrome, a number of reports from the early 20th century indicate that it is not a new disorder.[3 4] An early photograph showing the typical posture of PSP has been identified,[5] and review of the film archives of Denny-Brown have shown a number of cases which can be identified to have been early cases of PSP.[6] It is also likely that one of MacDonald Critchley's cases of 'arteriosclerotic pseudoparkinsonism', described in the 1920s, also had PSP.[7] The clinical skill of Steele and Richardson together with the expertise of Olszewski in delineating brainstem anatomy allowed this 'new' clinicopathological entity to be described and their seminal report was followed by many case reports and case series from around the world.[8] The documentation of these individual cases and case series through the 1960s, 1970s and 1980s have been followed by more recently by epidemiological studies.[9 10]

Clinical diagnosis

PSP is frequently misdiagnosed, most commonly as PD, but when PSP is considered, its distinctive features usually make it possible to make a confident diagnosis (box 1). Most patients present with gait disturbance and unsteadiness with a tendency to fall backwards. The gait has a characteristic reeling or staggering quality, due to the stiff posture of the trunk and neck with irregular large steps forwards, which allow a distinction to be made from the veering broad based gait of cerebellar ataxia.

Some patients present with early complaints of visual disturbance which are related to fixation instability and disruption of the control of saccadic eye movements. Unfortunately, as visual acuity itself is not affected by PSP, these symptoms may be initially thought to be psychogenic in origin until the typical disturbance of downward gaze emerges. The neuro-ophthalmological features of patients with established PSP are usually clear cut.[11] Frontalis overactivity and a diminution of the blink rate to less than 4/minute lead to a 'surprised' facial appearance. Eye opening may be impaired either by active involuntary contraction of orbicularis oculi (blepharospasm) or by inability to voluntarily open the eyes ('apraxia of eyelid opening') (figure 1).[12] Fixation on a stationary object may be interrupted by visible constant velocity saccadic intrusions in which the gaze is diverted briefly away and then back to the target, described as square wave jerks.[13] In the earliest stages of the disease there may be slowness of vertical saccadic eye movements which progress to limitation of downwards vertical saccadic eye movements and then to a complete vertical gaze palsy.[11] The doll's head manoeuvre may be used to generate a normal vertical vestibular-ocular response demonstrating the integrity of the third nerve nuclei and confirming that the eye movement disorder is supranuclear. Some limitation of upgaze is a frequent accompaniment of normal ageing and may be seen in PD; limitation of downgaze is a much more specific finding suggestive of PSP. In the late stages of the disease, involvement of the horizontal eye movement system may lead to a complete supranuclear gaze palsy.[11]

Diagnostic criteria for PSP[18]

Mandatory inclusion criteria
- postural instability with falls in the first year of symptoms
- slowing of vertical saccadic eye movements (clinically possible); vertical supranuclear gaze palsy (clinically probable)

Supportive criteria
- frontal/sub-cortical cognitive dysfunction
- axial rigidity
- pseudobulbar dysphagia and dysarthria
- blepharospasm/apraxia of eyelid opening

Box 1

Table Clinical features differentiating Parkinson's disease (PD) and progressive supranuclear palsy (PSP)

	PSP	*PD*
Balance	Early postural instability	Initially well preserved gait and balance
Speech	Growling dysarthria	Hypophonic dysarthria
Facial appearance	Taut	Loose
Extrapyramidal features	Axial rigidity; relatively well preserved fine finger movements; tremor in <10%	Distal rigidity and bradykinesia; decrement in amplitude and speed of fine finger movements; tremor in 95% through disease course
Symmetry	Symmetry of symptoms and signs	Asymmetry of onset and persistent asymmetrical signs
L-DOPA	Little response to L-DOPA	Excellent response to L-DOPA

The extrapyramidal features of PSP are distinctive and should be separable from PD (table). Lack of spontaneous and associative movements, dysarthria and facial immobility may suggest the diagnosis of PD during conversation and history taking. However, careful observation and examination often reveals a taut spastic face, a growling dysarthria, neck held in extension with axial rigidity, and a symmetrical relatively mild distal bradykinesia, often in the presence of normal muscle tone and in the absence of rest tremor. PSP rarely responds to L-DOPA therapy and it should be considered in the differential diagnosis of L-DOPA unresponsive Parkinson's syndrome along with vascular pseudo-parkinsonism, corticobasal degeneration, and multiple system atrophy.

While amnesia resulting from mesial temporal damage is not a feature of PSP, history from relatives and carers and specific bedside tests may reveal more subtle cognitive impairment. Functional imaging and clinical psychological studies show frontal hypometabolism and a deficit in frontal psychological tasks, respectively.[14] There may be a prodromal history of personality change or difficulty in carrying out day-to-day tasks which reflect frontal/subcortical disinhibition, apathy or difficulties in planning or judgement. Emotional lability and aggressive outbursts are common. Bedside testing may reveal difficulty in performing a three-stage command and markedly impaired verbal fluency in initial or category naming tests. Neuropsychological testing is often characterised by profound slowing of responses, with correct replies eventually being produced when sufficient time is allowed.[15]

The final stages of PSP are usually dominated by an increasingly severe dysarthria and dysphagia. These features are usually described as being part of a pseudo-bulbar palsy, as brisk jaw and facial jerks may be present. However, the aetiology of these bulbar features is probably multifactorial with a contribution from damage to extrapyramidal, pyramidal and brainstem reticular structures.

Figure 1 Facies of a patient with PSP showing asymmetric blepharospasm, frontalis overactivity and taut dystonic facial expression (reproduced with the patient's permission)

Differential diagnosis

In addition to PD, a number of other conditions may be misdiagnosed as PSP, usually on the basis of a parkinsonian syndrome with gaze abnormalities (box 2). These conditions include corticobasal degeneration, multiple system atrophy, progressive subcortical gliosis due to prion disease, some forms of autosomal dominant cerebellar ataxia (particularly SCA-7 and SCA-2), and vascular pseudo-parkinsonism. Whipple's disease is also important to consider since, although rare, it is a treatable cause of progressive neurological disease with a gaze palsy and may be diagnosed by small bowel biopsy or cerebrospinal fluid polymerase chain reaction for *Tropheryma whippeli*. In younger patients, Niemann-Pick disease type C and occasionally other storage disorders may present in a similar way to PSP. In the elderly population, vascular pseudo-parkinsonism is common and worth considering, particularly in view of the potential to identify modifiable risk factors. Vascular pseudo-parkinsonism may be identified by a shuffling small-stepped gait with a good arm swing ('lower body parkinsonism'; 'marche à petit pas'),[16] and relative sparing of axial and upper limb function. Rarely, neurosyphilis and compressive midbrain lesions may produce a midbrain neuro-ophthalmologic disorder and these conditions should be excluded with syphilis serology and neuroimaging.[17]

Operational criteria for the research diagnosis of PSP have recently been formulated (box 1).[1] These criteria focus on postural instability and evidence of damage to the vertical gaze system as the two core features of the disease together with the absence of clinical or investigative features suggesting an alternative diagnosis. These criteria have been reported to have an 80% sensitivity

Causes of a vertical supranuclear gaze palsy

- progressive supranuclear palsy
- corticobasal degeneration
- fronto-temporal dementia with parkinsonism linked to chromosome 17
- prion diseases (Creutzfeld-Jakob disease, progressive subcortical gliosis)
- autosomal dominant cerebellar ataxias (particularly SCA-2 and SCA-7)
- Whipple's disease
- Niemann-Pick disease type C
- vascular pseudo-parkinsonism
- compressive midbrain syndromes (Parinaud syndrome), eg, pinealoma, glioma
- neurosyphilis

Box 2

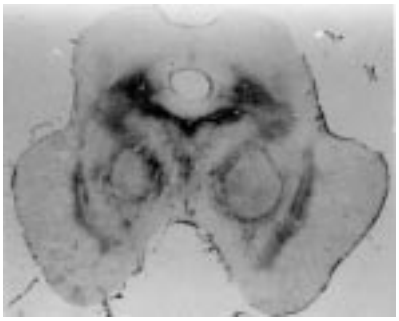

Figure 2 Glial stained section through the midbrain of a patient with PSP showing midbrain atrophy with dilation of the cerebral aqueduct and gliosis of the substantia nigra and peri-aqueductal region. Courtesy of Dr T Revesz, Institute of Neurology, London

and specificity but potentially may exclude patients with PSP who develop behavioural or personality change significantly before the occurrence of a gait disorder and those who have atypical disease without a supranuclear gaze palsy.[19 20]

Epidemiology

A prevalence of 1.4/100 000 has been reported from New Jersey, but this is likely to be an underestimate because of the exclusion of 'atypical parkinsonism', misdiagnosed as PD.[9 21] The median life expectancy from symptom onset to death is 9 years.[9] The 1991 UK Parkinson's Disease Society brain bank study showed that 25% of clinically diagnosed PD cases, had alternative pathological diagnoses; atypical PSP was the commonest misdiagnosis accounting for around 6% of the cases in this series.[21] Studies of this type suggest that PSP may be substantially under-diagnosed and that the true population prevalence of PSP may be much greater than has been reported. Case-control studies have not demonstrated any definite risk factors for the disease,[22 23] but there is increasing interest in the role of genetic susceptibility.

Pathology

PSP has a distinctive topographical and molecular pathology. The cellular hallmark of the disease is neurofibrillary degeneration; and the distribution and intensity of damage to the brainstem and basal ganglia is used to pathologically define the syndrome.[24] The main lesions are in the substantia nigra pars compacta and reticulata, the globus pallidus, the subthalamic nucleus, and the midbrain and pontine reticular formation. This destruction of midbrain and pontine structures leads to identifiable changes of brainstem atrophy on neuroimaging with dilatation of the cerebral aqueduct, thinning of the midbrain tegmentum and dilatation of the fourth ventricle (figure 2).[25] A recent blinded study indicates that dilatation of the third ventricle and a midbrain diameter of less than 17 mm are useful in distinguishing PSP from other atypical parkinsonian syndromes (A Schrag, personal communication).

The renaissance of neurosurgical approaches to PD and the study of primate models of extrapyramidal dysfunction have led to reconsideration of the functional pathology of the basal ganglia. Current models are inconsistent in their explanation of the symptomatology of potentially the simplest disease, PD,[26] and the functional anatomy of PSP is even more complex and poorly understood. PSP involves damage to both the putaminal and caudate striatal projections of the substantia nigra pars compacta (SNpc), the ventrolateral and dorsomedial areas, respectively.[27] This homogenous depletion of the SNpc is in contrast to the ventrolateral nigral selectivity of PD, which preferentially damages the putaminal nigrostriatal projection. This anatomical difference can be visualised *in vivo* with PET imaging of loss of ^{18}F-DOPA uptake by both caudate and putaminal nigrostriatal nerve terminals in PSP as opposed to preferential loss of putaminal uptake in PD,[28] (figure 3). The treatment of PD with L-DOPA is thought to lead to a restoration of normal output from the basal ganglia with attenuation of pallidothalamic GABAergic inhibition, but in PSP the major output centres of the basal ganglia, the substantia nigra pars reticulata and the globus pallidus internus, are already severely damaged by the underlying disease process.[29] The subthalamic nucleus has been shown to be overactive in PD and lesioning or high frequency stimulation (producing suppression) of the subthalamic nucleus is proving to be a highly successful manoeuvre in ameliorating the tremor, bradykinesia and rigidity of PD.[30] The subthalamic nucleus is also damaged in patients with PSP.[31] This destruction of the major basal ganglia output areas and the subthalamic nucleus, which are intact and overactive in PD, presumably partly contributes to the clinical differences between PSP and PD (figure 4).

The brainstem reticular pathology in PSP includes the midbrain and pontine nuclei involved in the supranuclear control of gaze: the rostral interstitial nucleus of the medial longitudinal fasciculus, the interstitial nucleus of Cajal, the nucleus of Darkschewitsch, and the raphé nucleus interpositus.[32 33] Additionally, the cholinergic pedunculopontine nucleus is damaged, which is thought to have a role in the control of sleep and balance.[34] Contrary to the earliest reports, cortical pathology does occur in PSP and is most marked in the deepest cortical layers of the precentral gyrus, occurring to a lesser extent in pre-frontal areas.[35] However, clinical and functional imaging data suggest that the major cognitive deficit in PSP is in frontal function and given the distribution of cortical

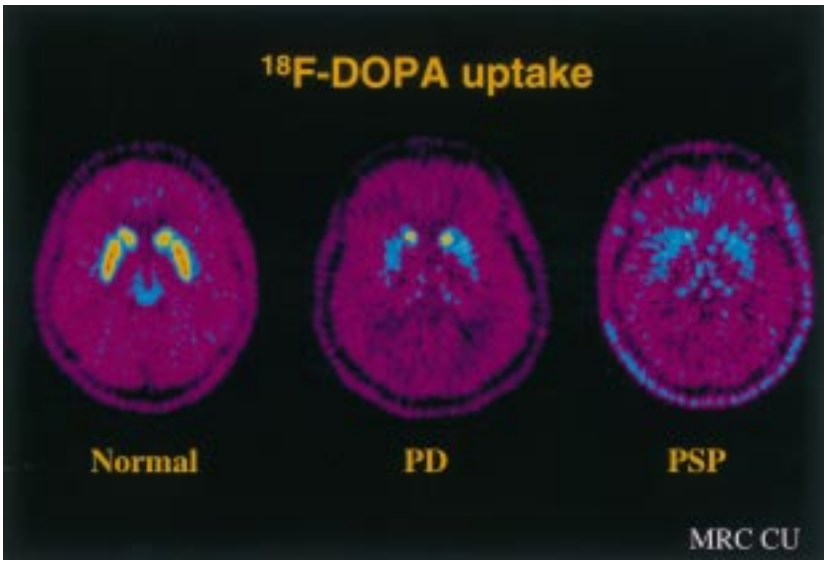

Figure 3 18-FDOPA uptake scan showing loss of uptake in the putamen in PD and both caudate and putamen in PSP. Courtesy of Dr P Piccini and Prof D Brooks, MRC Cyclotron Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London

neurofibrillary tangle formation, this presumably relates in part to a disturbance of reciprocal thalamocortical connections.[14 15]

Molecular pathology

PSP is one of a group of neurofibrillary tangle disorders.[36] Corticobasal degeneration, post-encephalitic parkinsonism, post-traumatic parkinsonism, some forms of frontotemporal dementia and the parkinsonism dementia complex of Guam, all involve the deposition of hyperphosphorylated tau protein as neurofibrillary tangles.[36] The discovery of autosomal dominant mutations in the *tau* gene causing some forms of frontotemporal dementia has focused interest on the possibility that primary abnormalities in tau protein are responsible for neuronal degeneration in these conditions.[37] This suggests that therapies which alter the deposition of tau protein may be the most effective way to modify the underlying disease process. The neurofibrillary tangles deposited in PSP can be distinguished from those seen in Alzheimer's disease in a number of ways. Tau neurofibrillary tangles appear most commonly as globose tangles under the light microscope, in contrast to the flame-shaped tangles of Alzheimer's disease. Under the electron microscope, the tangles in PSP appear as straight filaments with a diameter of 15–18 nm.[38] *In vitro* work suggests that these straight filaments are preferentially formed by isoforms of the alternatively spliced *tau* gene containing four microtubule binding domains,[39] and this theory is supported by recent work confirming that *tau* protein in PSP has four repeat isoforms.[40] In Alzheimer's disease, tau is identified on immunoblotting to have three abnormal major protein bands, at 55, 64 and 68 kDa, whereas the major bands in PSP are at 64 and 68 kDa. This has also been shown to be consistent with the expression of four repeat isoforms of the *tau* gene in PSP, as opposed to expression of all six isoforms of the *tau* gene in Alzheimer's disease.[40] The link between a genetic predisposition to PSP and the differential isoform expression of the *tau* gene may be the key to explaining the pathogenesis of PSP.

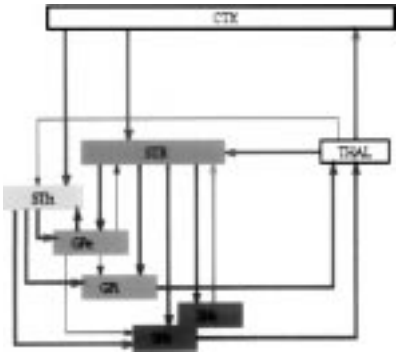

Figure 4 Connectivity in the basal ganglia. While in PD the substantia nigra pars compacta (SNc) is preferentially affected, in PSP the major outputs to the thalamus (THAL), the substantia nigra pars reticulata (SNr) and globus pallidus internus (GPi) are also affected in addition to the subthalamic nucleus (STh) which is overactive in PD. Other abbreviations: cerebral cortex (CTX), striatum (STR), globus pallidus externus (Gpe). Courtesy of Dr Andrew Gillies, Institute for Adaptive & Neural Computation, Division of Informatics, University of Edinburgh, Edinburgh

Genetics

A number of families have been described with autosomal dominant PSP,[41–46] although to date neither a linked chromosomal locus nor a causative gene mutation have been identified. Analysis of sporadic PSP cases have demonstrated that one form (the A0 allele) of a variable non-protein coding site (intronic polymorphism) within the *tau* gene occurs more frequently in patients with PSP than controls.[47] This may be a predisposing factor to PSP which, similarly to the apolipoprotein E ε4 allele in Alzheimer's disease, increases the risk of developing PSP but is in itself neither necessary nor sufficient to cause the disease. Although this polymorphism lies before an alternatively spliced protein coding exon of the *tau* gene, it is unknown whether this polymorphism or an adjacent

linked area has an effect on the alternative splicing of tau and whether this is important in the pathogenesis of the disease.

Treatment

Supportive treatment is the mainstay of management as the disease is relentlessly progressive. Explanation of the diagnosis and contact with patient support groups may be of benefit, particularly as patients may have been misdiagnosed as having PD or other disorders earlier in their illness. Physiotherapy and occupational therapy are of importance in helping with aids for balance and avoidance of falls. The early identification of problems with swallowing is important and this should prompt referral to speech therapy services for swallowing assessment and advice on appropriate measures to avoid the complications of aspiration.[48] Some patients and their families benefit from the insertion of a percutaneous gastrostomy tube but decisions on invasive interventions of this type should take into account the patient's and families' wishes in the context of the overall quality of life. Additional communication aids such as light-writers are usually not of benefit because of the concurrent eye movement disorder.

Patients usually do not derive great benefit from dopaminergic medication due to widespread damage to structures in the basal ganglia.[49] Early reports suggested that amantadine may be of more benefit in improving the motor deficits in PSP, but this has not been subject to a formal randomised trial and the response is at best modest. Most interest in PSP has centred on the use of cholinergic treatments, particularly because of the suggestion that cholinergic nuclei may be responsible for the problems with balance.[50] However, although oral physostigmine and cholinergic agonists do not produce a useful symptomatic benefit in PSP,[51 52] intravenous physostigime has been shown to improve cerebral metabolism,[53] and some measures of neuropsychometric and oculomotor performance.[54] These data suggest that, if significant enhancement of central nervous system cholinergic transmission can be achieved, some symptomatic improvement might be attained. Adrenergic agents have also been used in PSP because of the adrenergic deficit resulting in part from damage to the locus coeruleus.[55] Although these agents were initially thought to improve motor performance, this has not been replicated and their use has been limited by the occurrence of cardiovascular side-effects.[55 56]

Conclusions

PSP is a distinctive syndrome both clinically and pathologically and should be relatively easily diagnosed once considered by the clinician. The greater understanding of the tau gene and tau protein suggests that in the next few years there will be a much clearer understanding of the pathology and aetiology of this condition, which should lead to new potential disease-modifying agents. In the shorter term, cholinergic agents may emerge as useful symptomatic treatments for this disease. Currently, accurate diagnosis and the sympathetic provision of supportive care are the most important issues for the practising physician.

We are grateful to Dr JC Steele for helpful discussion. HRM is an MRC Clinical Training Fellow and supported by the PSP (Europe) Association. The PSP (Europe) Association provides support and advice for PSP patients and carers, and can be reached at The Old Rectory, Wappenham, Nr Towcester, Northamptonshire NN12 8SQ, UK.

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