Progressive supranuclear palsy

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Progressive supranuclear palsy, also known as Steele–Richardson–Olszewski syndrome, is an uncommon neurodegenerative parkinsonian disorder that starts in middle and late life, and is frequently misdiagnosed as Parkinson's disease. This review will cover the epidemiology, clinical picture, differential diagnosis and management of patients with progressive supranuclear palsy.

The Steele–Richardson–Olszewski syndrome was named after the three Canadian neurologists who first described it. During the 1950s, Dr Clifford Richardson used the name progressive supranuclear palsy (PSP) to describe a number of patients with unusual neurological features including supranuclear gaze palsy, parkinsonism, dystonia, dementia and pseudobulbar palsy. The characteristic neuropathological features, which are similar to postencephalitic parkinsonism, were later described by his colleagues Drs John Steele and Jerzy Olszewski. PSP was reported as a separate disease entity to Parkinson's disease (PD) in 1963 (Richardson et al, 1963).

EPIDEMIOLOGY

The exact prevalence of PSP is not known but is widely believed to be underdiagnosed. Clinicopathological studies of patients with PD indicate that PSP is commonly misdiagnosed as PD (Hughes et al, 1992). The annual incidence rate of PSP was estimated at 5.3 per 100 000 of population above the age of 50 years in the USA (Bower et al, 1997). Two epidemiological studies have examined the prevalence of PSP in the UK. Schrag et al (1999) estimated the prevalence of PSP in London at 6.4 per 100 000 of population, while Nath et al (2001) showed that the prevalence of PSP increased from 1 per 100 000 to 6.5 per 100 000 of population with more rigorous case ascertainment.

CLINICAL PICTURE

PSP has a gradual onset and a relentlessly progressive course. The disease frequently starts in the sixth decade and affects both sexes equally. The main clinical features include:

- Parkinsonism
- Ophthalmoplegia
- Postural instability
- Cognitive impairment.

Parkinsonism

Bradykinesia and rigidity of the limbs may be present but parkinsonism is mainly axial with early onset of dysarthria, dysphagia and truncal rigidity. Patients have a masked facial expression with an astonished look and a much reduced rate of blinking. Tremor is uncommon in PSP, and a pill-rolling resting tremor is rare. Neck dystonia is common with a tendency for the head to be held in retropulsion. PSP patients have a stooped posture with an unsteady gait and a tendency to fall backwards. Freezing of gait is present in approximately half of the patients, but levodopa-induced dyskinesia is very rare (Muller et al, 2002b).

Ophthalmoplegia

As PSP patients have a much reduced rate of blinking, this frequently leads to dry eyes and increased susceptibility to infections such as conjunctivitis. Eyelid opening and closure are slowed down. Blepharospasm can be a feature, and apraxia of eyelid opening has been reported in up to a third of patients with PSP (Lamberti et al, 2002). Patients experience difficulty in maintaining gaze which can be detected clinically with the demonstration of square-wave jerks. These are transverse back and forward involuntary movements when the person is asked to fixate on an object, caused by saccadic intrusions on fixation.

The first sign of ophthalmoplegia is usually slowing down of vertical saccadic eye movements. The slowing down of eye movements usually develops before the restriction in vertical gaze, which is the hallmark of the disease. As the disease progresses there is also slowing down and restriction of transverse gaze, and eventually there is complete paralysis of eye movements. Reduction of upward gaze is non-specific as it may be present in other neurodegenerative disorders, such as PD, and even with

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normal ageing. Paralysis of down-gaze, however, is very highly suggestive, but not pathognomonic, of PSP (it has been reported with fronto-temporal dementia). Paralysis of downward gaze results in patients experiencing problems with reading, eating (messy tie syndrome), walking and characteristically with descending stairs.

Postural instability

Postural reflexes become impaired very early in PSP and this is the presenting feature of the disease in over half the patients (Birdi et al, 2002). Postural reflexes are also affected in PD but usually several years after disease onset. The impairment of postural reflexes results in poor balance and increased risk of falls. A history of falls is usually present in the first year or two of disease onset. The increased risk of falling is compounded by the limitations of eye movements, the tendency for the head to be held back in retropulsion, and the limited regard for safety which is common in PSP patients as a result of impaired frontal lobe function. Impaired mobility is the most common symptom at disease onset, being present in 69% of patients in a recent report (Nath et al, 2003).

Cognitive impairment

Approximately 15% of patients present with cognitive problems varying from memory problems and personality change to apathy, depression and anxiety (Nath et al, 2003). Cognitive impairment in PSP is frequently of a frontal nature and there seem to be a correlation with frontal lobe volume loss (Cordato et al, 2002). Patients frequently experience problems with planning, decision making and logical thinking. Uninhibited and unsocial behaviour may be a feature, but more likely patients are apathetic (Aarsland et al, 2001). Repetitive behaviour and emotional lability is common, but frank dementia is rare.

TABLE 1.
National Institute of Neurological Disorders and Stroke – Symposium on PSP (NINDS – SPSP) diagnostic criteria

Probable PSP	Gradually progressive disorder
	Onset at 40 years of age or younger
	Vertical supranuclear palsy and prominent postural instability with falls in the first year of disease onset
	No evidence of other disease to explain the above features
Possible PSP	Gradually progressive disorder
	Onset at 40 years of age or younger
	Vertical supranuclear palsy or prominent postural instability with falls in the first year of disease onset
	No evidence of other disease to explain the above features
Definite PSP	Clinical probable or possible PSP and histopathological evidence of typical PSP
Supportive criteria	Symmetrical akinesia more axial than peripheral
	Abnormal neck posture, especially retrocollis
	Poor or absent response to levodopa
	Early dysphagia and dysarthria
	Early onset of cognitive impairment including at least two of the following; apathy, impaired abstract thinking, decreased verbal fluency, utilization or imitation behaviour or frontal release signs

From Litvan et al (1996). PSP = progressive supranuclear palsy

Other clinical features

Extensor planter responses and cerebellar signs may be present although upper motor neuron weakness is usually absent.

NEUROIMAGING

Structural neuroimaging with brain computed tomography (CT) or magnetic resonance imaging (MRI) are usually normal in early disease. In more advanced cases of PSP atrophy may be demonstrated in the brainstem, particularly midbrain, globus pallidus and cerebral cortex (Yekhlef et al, 2003). The changes detected on neuroimaging correlate with the density of the underlying pathology (Aiba et al, 1997). A recent report claimed that diffusion-weighted MRI was able to differentiate PSP from PD but not from other parkinsonian disorders such as multiple system atrophy (Seppi et al, 2003). Functional imaging with iodobenzamine single photon emission tomography may show reduced dopamine receptor binding in the striatum (Arnold et al, 2002). Although the diagnosis of PSP is a clinical one, neuroimaging may play an important part in reaching the diagnosis in future.

CLINICAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A number of diagnostic criteria have been proposed, the most recent of which being that of the National Institute of Neurological Disorders and Stroke – Symposium on PSP (NINDS – SPSP) international workshop criteria (Litvan et al, 1996). The primary diagnostic indicators include the early onset of postural instability and vertical gaze palsy. Although the NINDS – SPSP criteria for probable PSP have a 100% specificity they have been criticized for being too rigid, missing too many patients with early disease (sensitivity is only 50%). *Table 1* lists the NINDS - SPSP diagnostic criteria of PSP, while *Table 2* lists the differential diagnosis.

PATHOLOGY AND PATHOGENESIS

The distribution of neurodegeneration in PSP is much more widespread than in PD and mainly includes the brainstem, basal ganglia and cerebellar nuclei (Hauw et al, 1994). There is deposition of tau positive neurofilaments in the cytoplasm of affected neurons and glial cells. The exact function of the microtubule-associated protein tau is not fully understood, but it is probably important for the assembly and stabilization of the microtubule. The microtubular system acts as an extensive transport network for the neuron. PSP is not the only neurodegenerative disease that is characterized by the deposition of tau positive inclusions. Other examples include frontotemporal dementia and corticobasal degeneration. These neurodegenerative disorders, including PSP, are now referred to as the 'tauopathies'.

Tau protein itself is coded for by a single gene on chromosome 17, and exists in six different isoforms, according to how the gene is spliced. It was discovered that being homozygous for a certain tau gene haplotype (H1/H1) represents a risk factor for PSP (Baker et al, 1999). It is also claimed that PSP patients who are homozygous for the H1 haplotype have typical clinical and pathological features of the disease, compared to those that are heterozygous who have less typical features (Morris et al, 2002).

TREATMENT

There is no effective treatment of PSP and treatment is therefore largely supportive and palliative. Patients need to be informed about the diagnosis so that they understand why what was thought to be PD is not responding to treatment. Informed patients can also make adequate plans for the future. Information on PSP is available from the European PSP Association (www.pspeur.org).

Parkinsonism in PSP rarely responds to antiparkinsonian drugs such as levodopa and dopamine agonists, although a few patients derive minimal benefit. Other treatments such as tricyclic antidepressants, amantadine and anticholinergics have been tried with very limited success (Kompoliti et al, 1998). Treatment with anticholinesterase inhibitors, such as donepezil, was also of little benefit (Fabbrini et al, 2001). The use of antiglutamate drugs, such as riluzole, in order to reduce neuronal damage caused by excessive glutamate receptor stimulation is still under investigation.

Dry eyes are common and can be helped by artificial tears, while prism spectacles can also be useful for gaze limitation. Troublesome blepharospasm and apraxia of eyelid opening can be helped with botulinum toxin injections (Muller et al, 2002a).

Assessment of swallowing and speech by a speech therapist is often necessary at an early stage in order to reduce the risk of aspiration, which is a common cause of early mortality. Strategies to reduce the risk of aspiration include drinking with a straw, thickening of fluids and avoiding mixing food of different consistencies. When swallowing becomes totally unsafe, the use of percutaneous endoscopic gastrostomy feeding needs to be considered. This is often a difficult decision that needs to be carefully considered according to each individual case, taking into account the patient's wishes.

Strategies to reduce the risk of falls and therefore serious injuries are equally important. Early assessment by physiotherapists and occupational therapists is advisable. Such strategies include educating the patient and carers to use safer practices, reducing environmental hazards, using appropriate walking aids, and considering the need for wearing hip protectors.

DISEASE COURSE AND PROGNOSIS

Compared to PD, PSP has a rapidly progressive course. In a recently reported cohort of 50 PSP patients, Goetz et al (2003) reported that mean time from symptoms onset to wheelchair dependence and unintelligible speech were 57 months

TABLE 2.
Differential diagnosis of progressive supranuclear palsy

Idiopathic Parkinson's disease	Asymmetrical parkinsonism
	Tremor is common
	Responsive to levodopa
	No vertical gaze palsy
	Postural instability a late feature
	Better prognosis
Multiple system atrophy	Early autonomic failure
	May be cerebellar features
	Suboptimal response to levodopa
	No cognitive impairment
Dementia with Lewy bodies	Early and progressive cognitive impairment
	Early visual hallucinations/delusions
	Marked fluctuations in attention and cognition
	No ophthalmoplegia
	Neuroleptic sensitivity
Cerebrovascular parkinsonism	Mainly lower body parkinsonism
	Cognitive impairment is common
	Poor response to levodopa

and 71 months respectively. PSP has a reported mean survival of approximately 7 years from the onset of symptoms (Nath et al, 2003). Early mortality is a result of increased risk of aspiration pneumonia, the sequelae of immobility such as pulmonary embolism and pressure ulcers, as well as injuries caused by falls. Early onset of falls, speech and swallowing problems, and diplopia all predicted poor survival (Nath et al, 2003).

CONCLUSIONS

PSP is a devastating neurodegenerative illness that is commonly misdiagnosed as PD, and responds poorly to drug treatment. Clinicians need to have a high index of suspicion, especially in patients presenting with repeated falls without loss of consciousness. PSP should be suspected in possible PD patients who have early postural instability, ophthalmoplegia, or in those who appear to have a rapidly progressive course and are not responding to antiparkinsonian medication. Early assessment by the multidisciplinary team, particularly a physiotherapist and a speech therapist, is advisable in order to reduce the risk of falls and aspiration pneumonia. **HM**

Conflict of interest: none.

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KEY POINTS

- Progressive supranuclear palsy is an underdiagnosed neurodegenerative parkinsonian disorder which is commonly misdiagnosed as Parkinson's disease.
- Compared to Parkinson's disease, progressive supranuclear palsy has a more rapidly progressive course and hardly responds to dopaminergic drugs.
- Clinically patients frequently present with recurrent falls as a result of early onset of postural instability.
- Slow saccadic eye movements followed by vertical, and later transverse, gaze palsy usually develops in the first few years of disease onset.
- Frontal type cognitive impairment is common but frank dementia is rare.
- The management of progressive supranuclear palsy patients requires all the skills of the multidisciplinary team.