Diagnosis and Management of Progressive Supranuclear Palsy

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Progressive supranuclear palsy (PSP) is a rare, fatal neurodegenerative disease with limited treatment options that is characterized by gait and postural instability and a classical vertical supranuclear gaze palsy. Initially often misdiagnosed as idiopathic Parkinson's disease (IPD), proper patient care in PSP may be delayed until late into the disease course, after dopaminergic medication fails to improve symptoms. Here, we review the diagnostic criteria that help to separate PSP from IPD and rarer forms of parkinsonian diseases to help clinicians with earlier recognition. We discuss current treatment concepts as well as ongoing experimental approaches that are derived from an emerging pathological understanding.

Key words: *progressive supranuclear palsy, clinical diagnosis, imaging, differential diagnosis, management*

Introduction

Progressive supranuclear palsy (PSP), also called Steele-Richardson-Olszewski syndrome,[1] is an uncommon neurodegenerative disorder with a prevalence rate of two to seven per 100,000 person years. Constituting one of the more common Parkinson-plus syndromes, PSP is often misdiagnosed as idiopathic Parkinson's disease (IPD). This distinction is critical, however, as symptomatic treatment in PSP is very limited and the prognosis is unfavourable, with a life expectancy of 5–10 years after disease onset. Given that PSP, on average, remains undiagnosed for 3 years (half of the natural history of the disease), a correct diagnosis early on in the disease course is important as it provides timely guidance for understanding the disease progression, coping with the disease, and initiating support services. In the future, early diagnosis will be invaluable for disease-modifying approaches. Here, we review the current understanding of PSP with the aim of facilitating timely diagnosis and appropriate management. We focus on the distinction of PSP from IPD but include other rare diseases that require consideration.

Diagnosis

Progressive supranuclear palsy shares many clinical features with IPD and other parkinsonian conditions, such as multiple system atrophy (MSA) and corticobasal degeneration (CBD), as it may present with rigidity, bradykinesia, postural instability, and, less commonly, tremor.[2] A definite diagnosis of PSP can only be made on pathological grounds that are based on a complex distribution of specific pathological changes in the brain (Table 1). Clinical recognition of probable or possible PSP requires a combination of early postural instability and vertical supranuclear (gaze) palsy in a person above the age of 40[3] (Table 2). The average age of diagnosis of PSP is typically later than that in IPD, that is, 63 years of age versus 60 years of age.

Parkinsonian Symptoms

Although parkinsonian features may present in a wide variety of diseases, it is the pattern of presentation that can provide supportive clues for the diagnosis of PSP and the distinction from IPD.[2] In the classic form of PSP (also known as Richardson's syndrome[4] or RS), postural instability is evident early. Patients tend to fall backwards and often without leg involvement, described as "falling like a log." Imbalance can be shown clinically by impaired postural reflexes on the pull test in the neurological examination. Gait is also frequently abnormal early in PSP and is a key clinical sign in helping differentiate from IPD. The gait may be wide-based and can be misdiagnosed as ataxia, in contrast to the narrow-based gait typically seen with IPD. Individuals with PSP also lack bilateral arm swing, which can give the impression of the so-called gunslinger sign. Shuffling and stooped posture may occur, similar to IPD.

Other parkinsonian features in RS are usually symmetrical, contrasting the asymmetrical onset in IPD. Tremor is commonly absent. Rigidity is more pronounced in the axial musculature than in the limbs. This can be tested by standing behind the patient and holding the patient's shoulders and twisting the body side-to-side; the neck and trunk will have resistance to movement, while the arms may swing easily. The limbs may sometimes be hypotonic (given possible involvement of cerebellar tracts), and retrocollis may indicate added dystonia. A helpful observation is the relatively preserved bradykinesia in contrast to

Table 1: Pathological Diagnostic Criteria for Definite Progressive Supranuclear Palsy

The finding of neurofibrillary tangles or neuropil threads, or both, in the basal ganglia and brainstem is mandatory for the diagnosis of PSP.
Typical PSP:
Two or more neurons with neurofibrillary tangles or neuropil threads (high density) in at least three of the following brain areas: pallidum, subthalamic nucleus, substantia nigra, and pons
and
One or more neurons with neurofibrillary tangles or neuropil threads (low density) in at least three of the following brain areas: striatum, oculomotor complex, medulla, and dentate nucleus

Source: Adapted from Hauw J-J et al., 1994.[30]

marked rigidity. Finally, the facial expression can also suggest PSP; in addition to hypomimia, contraction of the procerus, corrugator supercilii, and the orbicularis oculi muscles gives rise to the typical "frowning" expression (sometimes called "procerus sign," although this term is controversial[5,6]); alternatively, an overactive frontalis muscle may produce a "startled" expression. Clinical signs are summarized in Table 3.

Less well recognized (but equally important) are other two forms of PSP, designated as the syndrome of pure akinesia with gait freezing (PAGF)[7] and PSP-parkinsonism (PSP-P).[4] Both forms are more benign, with a longer duration of disease and less severe brain pathology, and occur in up to 30% of pathologically proven cases.[4,7] The PAGF variant presents, as implied by its name, as a primary high-level gait disorder with progressive freezing of gait and gait ignition failure. Only later do parkinsonian features develop, and cognitive and oculomotor deficiencies arise also only 2–5 years after disease onset.[7] On the other hand, PSP-P may be misdiagnosed as IPD as the presentation is asymmetrical in onset, with early bradykinesia, tremor in up to 20% of cases, nonaxial dystonia, and an initial response to levodopa treatment that can be significant.

Oculomotor Deficits

Vertical supranuclear palsy (VSP) is characterized by the inability to voluntarily perform a vertical gaze in which vertical eye movements are preserved when the head is passively moved in the same plane (doll's-eye maneuver). The slowing of vertical saccades and delayed saccadic initiation in vertical direction are considered early abnormalities in the progression to VSP, usually accompanied by saccadic smooth pursuit (well seen in the horizontal direction), a loss of convergence, and sometimes by dysmetric eye movements (over- or undershooting on saccadic gaze). The gaze may also be fixed, making the patient appear to stare. Likely a product of frontal lobe pathology, this "frontal fixation" can be broken by moving out of the patient's view and using moving targets to trigger smooth pursuit. Testing such eye movements can be performed with the use of tape, material with lines, or an optokinetic nystagmus (OKN) drum.

Other Motor Features

Eyelid-opening apraxia (and, less commonly, eyelid-closing apraxia) may be seen in PSP,[2] usually more frequently than in IPD. It presents with an inability to voluntarily open the eyes in the absence of any neuromuscular weakness. Patients frequently have to manually open the eyelids. Interestingly, this dysfunction may not be an apraxia but, instead, a form of dystonia.[8] Limb and axial dystonia can be seen in both PSP and IPD but are not usually related to levodopa use in PSP. Bulbar dysfunction, particularly dysarthria, can be early and

Table 2: NINDS-SPSP Clinical Diagnostic Criteria for Progressive Supranuclear Palsy

Diagnosis	Criteria
Definite	*All* criteria for probable or possible PSP are met *and* Histopathological confirmation is provided at autopsy
Probable*	Vertical supranuclear palsy *and* Prominent postural instability with falls within 1st year of disease onset
Possible*	*Either* vertical supranuclear palsy *or* *Both* (1) slowing of vertical saccades and (2) postural instability with falls within 1st year disease onset

NINDS-SPSP = National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy, Inc.
*For possible or probable PSP, onset of disease should be at age 40 or later and the disorder should be gradually progressive in nature.
Source: Adapted from Litvan I et al., 2003.[3]

Table 3: Other Clinical Findings That Support the Diagnosis of Progressive Supranuclear Palsy

NINDS-SPSP-Based Findings
Symmetrical akinesia or rigidity, proximal more than distal
Abnormal neck posture, especially retrocollis
Poor or absent response of parkinsonism to levodopa
Early dysphagia and dysarthria
Early onset of cognitive impairment including >2 of the following:
Apathy
Impairment in abstract thought
Decreased verbal fluency
Utilization or imitation behaviour
Frontal release signs
Non-NINDS-SPSP-Based Findings*
Parkinsonian features
Absent tremor
Rigidity more in trunk than limbs (limbs can be hypotonic)
Rigidity more marked than bradykinesia
Wide-based gait with reduced arm swing ("gunslinger sign")
Rushed micrographia (small amplitude from the beginning, no fatiguing)
Eyes and face
Eyelid opening or closing apraxia
Frontal fixation of gaze
Procerus contraction
Behaviour
Pattern of apathy, disinhibition, impulsivity and impaired judgment
"Rocket sign"

NINDS-SPSP = National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy, Inc.
*These findings are suggestive of PSP based on clinical experience in practice and literature but are not found to meet the standards for inclusion into the NINDS-SPSP criteria. We regard these findings as helpful clinical tools in the appropriate context.
Source: Adapted from Litvan I et al., 2003.[3]

prominent in PSP. Compared with IPD, micrographia in patients with PSP is classically not characterized by a decrease in amplitude (called fatiguing), where words at the beginning of a row look larger than those at the end; rather, handwriting is consistently small and rushed. We believe that this distinction is helpful in suspecting early-stage PSP; this pattern of rushed and small amplitude movements can also be seen with other hand functions (demonstrated by finger tapping or alternate hand movements on examination) and speech (fast and incomprehensible, sometimes referred to as tachyphemia).[9]

Nonmotor Symptoms

Progressive supranuclear palsy may present with cognitive decline and behavioural abnormalities suggestive of a frontotemporal dementia or CBD, given the overlapping pathology (all three disorders belong to the so-called tauopathies—see below).[10] Thus, behavioural neurologists, psychiatrists, or geriatricians may see such patients initially. The frontal-subcortical pattern of cognitive decline in PSP is also seen in IPD; but in PSP, it occurs earlier and is often more severe. Deficits include attention, abstraction, verbal fluency, judgment, ability to execute complex motor or cognitive tasks, working memory, and speed of cognition (bradyphrenia). Screening testing for frontal lobe deficiencies is best performed with the Montreal Cognitive Assessment (MoCA) battery (available free at www.mocatest.org). Behavioural changes in PSP, prominent over the course of disease, also reflect frontal lobe pathology and may present with imitation or utilization behaviour, impulsivity and disinhibition (orbitofrontal cortex), or apathy (often mesiofrontal cortex).[2] Hallucinations, delusions, and depression are much more typical in IPD.[11] Disinhibitory tendencies can affect movement control as patients jump out of a sitting position only to fall backwards into the chair or risk a fall onto the ground ("rocket sign"). Changing such behaviour is very difficult, given impaired judgment, and this latter feature may also make it difficult for patients to accept changes in their lives that involve loss of control (e.g., cessation of driving privileges, supervision at home, and transfer of financial affairs to family members).

Other clinical features that may occur in both PSP and CBD (but are more common in the latter condition) include the presence of unusual cortical symptoms that involve association motor cortex and nonmotor cortical areas, for example, primary progressive nonfluent aphasia, limb-kinetic and ideomotor apraxias (the inability to perform a previously learned task that cannot be explained by problems with language and elementary motor and sensory functions), the asymmetrical involvement of one limb that is out of proportion with other body regions, reflex myoclonus, and an alien limb (a limb exhibiting

involuntary complex movements, such as utilization behavior, that occur either in addition to or instead of a planned or willed movement).[2,12] Another parkinsonian syndrome that may be misdiagnosed as PSP is MSA, which may present with poor levodopa responsive parkinsonism and early falls. However, individuals with MSA tend to be younger at onset and can have a very good initial response to levodopa, although this is lost within a few years. Levodopa treatment can be associated with dyskinesia or, more characteristically, with facial dystonia. In addition, people with MSA may have early erectile dysfunction, bladder and bowel problems, red and cold distal limbs, and excessive sweating (all signs of dysautonomia); coordination deficits in limbs and gait (cerebellar signs); increased reflexes and spasticity (pyramidal tract signs); antecollis; aphonia or stridor; and tilted trunk (Pisa sign). Progressive supranuclear palsy-like presentations may also occur with ischemic changes in basal ganglia structures that can give rise to symptoms mimicking classic (idiopathic) PSP. History demonstrates stroke risk factors, onset is usually abrupt, and sometimes lower-body parkinsonism can be appreciated (rigid legs, wide-based gait, and preserved arm swing and tone).

Key Points

- Progressive supranuclear palsy (PSP) is primarily a clinical diagnosis.
- Early diagnosis of PSP is important, as it allows the patient and family time to cope with the disease, plan life events, and initiate the use of support services and resources.
- The standard of care remains symptomatic treatment, physical therapy, and speech therapy.
- Advances in diagnostics and management await a better pathogenic and molecular understanding of the disease. Early diagnosis will become crucial for disease-modifying therapies in the future.

Imaging and Other Diagnostic Tests

Imaging may independently assist in the diagnosis of PSP. While magnetic resonance imaging (MRI) in IPD lacks definable criteria, pathological changes in the midbrain may be identified as atrophy in PSP. On sagittal sections, the midbrain resembles the bill of a hummingbird ("hummingbird sign"; Figure 1). The pattern of atrophy affects the rostral tegmentum, which may explain the supranuclear oculomotor findings.[13] On axial sections, this pattern of midbrain atrophy has been termed the "morning glory sign."[14] On T2 MRI, structural pathology is sometimes noted as midbrain hyperintensity that usually does not subscribe to vascular boundaries. In contrast, in vascular PSP, small-vessel ischemia can be seen in basal ganglia and the midbrain, and lower-body parkinsonism, if present, may be indicated by significant periventricular white matter changes.

In early disease, when midbrain pathology may not be seen on MRI, other test modalities might be helpful (although these are usually performed in research settings). Glucose-based positron emission tomography, for example, has demonstrated decreased uptake in the brainstem, striatum, and mesiofrontal cortex in PSP, which represents a pattern that is distinct from those seen in early IPD, MSA, and CBD.[15,16] Recently, transcranial brain sonography and cerebrospinal fluid studies have also shown promise in their ability to distinguish between PSP and IPD, MSA, and other related disorders.[17,18] Although these tests require substantial development to gain clinical acceptance, they bear the hope for diagnosing PSP at an earlier disease stage.

Pathology

Progressive supranuclear palsy is a "tauopathy," characterized by deposition of the microtubule-associated protein tau, mostly in nerve and glial cells of the substantia nigra, subthalamic nucleus, globus pallidus, and brainstem.[4,19,20] Recent evidence suggests that the three clinical subtypes of PSP might have distinct pathology to some degree, raising the notion that PSP may be composed of discrete nosological entities.[2,4] Compared with RS, PSP-P and PAGF have a different composition of deposited tau protein (a higher proportion of the three-repeat tau isoform) and a weaker H1/H1 PSP susceptibility genotype. Both factors may explain the milder brainstem tau pathology in PSP-P and PAGF, which correlates with the more benign clinical course; for example, it has been speculated that the four-repeat tau isoform is important in promoting PSP brainstem pathology.[21]

Management

Good options for symptomatic treatment are not currently available.[20] The cornerstones of therapy remain physical and speech therapies. A levodopa trial can be tried to improve parkinsonian features, but success is limited, even at high doses (>1,000 mg). In fact, a failed levodopa trial is commonly used as a clinical tool

Figure 1: Hummingbird Sign



The "hummingbird sign" is a radiological finding describing midbrain atrophy on sagittal magnetic resonance images. In this T1 image of a 68-year-old patient with PSP, the marked midbrain atrophy (arrow) makes the rostral brainstem resemble the outlines of a hummingbird.

Clinical Pearl

The pattern and timing of parkinsonian symptoms and oculomotor abnormalities should be carefully assessed to avoid misdiagnosis of Parkinson's disease.

A reasonable treatment approach is to use levodopa for parkinsonian symptoms and titrate it up to 1.0–1.5gm, as long as a response is noted and the patient is able to tolerate such high doses. Also try amantadine, 100–300 mg per day, for postural instability.

to consider PSP rather than IPD. When speech therapy fails, voice amplifier devices may be used, but these are usually helpful if the main problem is hypophonia, not dysarthria. When dysphagia becomes a major problem, dietary adjustments are needed, and a percutaneous endoscopic gastrostomy tube for nutritional support is eventually required. We refer patients for tube placement only if they retain reasonable cognition; otherwise, palliative care is preferred to respect dignity and quality of life. Eyelid-opening apraxia may respond well to botulinum toxin into the pretarsal part of the orbicularis oculi muscle.

Other treatment options are more experimentally based. Given that gamma-aminobutyric acid (GABA)ergic neurons are decreased in PSP, the GABAergic agonist zolpidem was shown to improve both oculomotor and parkinsonian findings, but the effects were very transient.[22,23] Amantadine had mild effects in very small studies.[20] However, in clinical practice, amantadine 100–300mg/d is worth a try as PSP patients may get a transient benefit in postural stability. Experimental surgical targets include deep brain stimulation surgery of the pedunculopontine nucleus, which has been found to play an important role in the control of postural stability and motor control.[24,25]

Curing Progressive Supranuclear Palsy?

The prospect of disease-modifying therapy is far from becoming a reality, but the pathogenic understanding has advanced enough for initial approaches to be studied. These have focused on inhibiting tau aggregation, given that this process appears to be disease promoting (which is not conclusively proven). Riluzole, an antiexcitotoxicity agent with aggregation-inhibiting properties,[26] was recently tested in a large, multicentre prospective trial of PSP patients[27]; however, it failed to show any benefit on survival or rate of disease progression after a three-year follow-up. This approach was based on noted improvements in a mouse model of MSA and in amyotrophic lateral sclerosis, another neurodegenerative disease with aggregation pathology. Similarly, the protein glycogen synthase kinase 3b (GSK3b) has become a target of investigation as it abnormally phosphorylates tau to promote protein aggregation.[28] Valproic acid and lithium, two agents that inhibit GSK3b, are currently being studied in PSP patients for safety assessment [29] (www.clinicaltrials.gov). Future investigations that expand disease-modifying approaches beyond aggregation inhibition are needed, and these will depend on progress in our understanding of the molecular and pathological aspects of this disease.

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