Historical review

Although the earlier literature contained several accounts of progressive supranuclear palsy (PSP) [1], including the famous case reported by Charcot in the nineteenth century [2], the first detailed description of this condition came from John Clifford Richardson, John Steele, and Jerzy Olszewski in the early 1960s [3]. The term PSP was introduced by the same Canadian investigators in 1964 [4]. They described a pre-senile sporadic neurodegenerative disease characterized clinically by a combination of supranuclear vertical ophthalmoplegia, pseudobulbar palsy, nuchal dystonia, and dementia. In their report they described the clinical features of nine patients and reported the neuropathological changes in seven of them. The predominant pathological changes were cell loss and gliosis in the brainstem, basal ganglia, and cerebellum.

In 1986, Pollock and colleagues first reported that the filamentous aggregates found in the brains of patients with PSP shared antigenic determinants with microtubule-associated protein tau [5]. Histopathological studies then confirmed that PSP is a tauopathy characterized by hyperphosphorylated tau protein deposition forming fibrillary aggregates (globose neurofibrillary tangles) in neurons and glia of numerous cerebral areas including the cerebral neocortex, pallidum, subthalamic nucleus, substantia nigra, periaqueductal gray matter, superior collicula, and dentate nucleus [6]. The abundant presence of these aggregates in all clinical PSP subtypes suggested that PSP should be considered a tauopathy along with corticobasal degeneration (CBD), frontotemporal dementia (FTD), and Alzheimer’s disease (AD) [7].

The introduction of clinical diagnostic criteria, first proposed by Lees in 1987, made it easier to identify these patients clinically [8]. Others subsequently proposed different sets of diagnostic criteria, mainly based on personal experience [9–11]. New clinical diagnostic criteria were developed in 1996 during a workshop held under the auspices of the National Institute for Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) [12]. This time the criteria were also validated on a clinical data set from autopsy-confirmed cases of PSP. Although the NINDS-SPSP criteria (Table 4.1) have gained wide acceptance in the research community, in movement disorder clinics, they remain to be validated prospectively.

Morphological features

Macroscopic examination of the brain in PSP usually shows midbrain atrophy and substantia nigra depigmentation, sometimes with mild frontal lobe atrophy. Microscopic examination
invariably discloses neuronal loss, gliosis, neurofibrillary tangles (NFTs), and neuropil threads (NTs) in the basal ganglia and brainstem. PSP is now considered a tauopathy, characterized by hyperphosphorylated tau protein aggregates. Tau protein binds to microtubules, and plays an important role in neuronal cytoskeletal stability. Alternative splicing of exons 2, 3, and 10 of the tau gene generates six tau isoforms. The inclusion or exclusion of exon 10 produces isoforms with four (4R) or three (3R) microtubule binding sites. Normal brains have similar levels of 4R and 3R, but in some neurodegenerative disorders this ratio is changed. The revised neuropathological criteria for PSP require high NFT and NT densities in at least three of the following brain areas: striatum, oculomotor complex, medulla, or dentate nucleus [13]. The pathological changes often involve the neocortex, especially the

<table>
<thead>
<tr>
<th>Table 4.1 NINDS/SPS criteria</th>
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<tbody>
<tr>
<td><strong>Basic features</strong></td>
</tr>
<tr>
<td>• gradually progressive disorder</td>
</tr>
<tr>
<td>• onset age &gt;40 yr</td>
</tr>
<tr>
<td>• no evidence of other diseases that could explain the clinical features as indicated by exclusion criteria*</td>
</tr>
<tr>
<td><strong>Diagnosis of clinically possible PSP</strong></td>
</tr>
<tr>
<td>• vertical supranuclear palsy#</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>• slowing of vertical saccades</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>• postural instability with falls within a year of disease onset</td>
</tr>
<tr>
<td><strong>Diagnosis of clinically probable PSP</strong></td>
</tr>
<tr>
<td>• vertical supranuclear palsy</td>
</tr>
<tr>
<td><strong>AND</strong></td>
</tr>
<tr>
<td>• prominent postural instability with falls within a year of disease onset</td>
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#Upward gaze is considered abnormal when pursuit or voluntary gaze, or both, have a restriction of ≥50% of the normal range

**Supportive features**
- 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 two or more of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs

**Exclusion criteria**
- recent history of encephalitis
- alien limb syndrome
- cortical sensory deficits
- focal frontal or temporoparietal atrophy
- hallucinations or delusions unrelated to dopaminergic therapy
- cortical dementia of Alzheimer type
- prominent, early cerebellar symptoms
- unexplained dysautonomia
- neuroradiological evidence of relevant structural abnormality
- Whipple's disease, confirmed by polymerase chain reaction

Reproduced with kind permission from Litvan et al. [12]
primary motor area of the frontal lobe, and severe cell loss in this area has been indicated as a possible contributor of the early falls [14].

In addition to their clinical similarities, PSP and CBD share certain pathological features. This clinicopathological overlap led some to consider the two diseases as different ends of the same disease spectrum. A neuropathological finding of tau-positive tufted astrocytes is considered highly characteristic of PSP and differentiates it from CBD. These astrocytic alterations probably reflect the main degenerative process rather than a change secondary to gliosis. The ballooned neurons typically found in CBD are rarely observed in PSP. The tau aggregates in PSP and CBD contain mainly 4R isoforms and accumulate in neuronal and glial cells. How these aggregates form and how they affect different regions of the brain remain unclear. Ultrastructural examination shows that PSP NFTs consist of mainly straight filaments, whereas AD NFTs contain paired helical filaments [15].

**Genetics**

The importance of tau aggregates in causing PSP receives further support from genetic findings. PSP is strongly associated with a specific haplotype in the tau gene (denoted as H1). Several reports from different populations show that patients with PSP (like those with CBD) show the H1 haplotype and the H1/H1 genotype significantly more frequently than controls [16]. Fine-mapping of this region detected a variation in a single intron regulating tau expression on the H1 background [17]. A genome-wide association study subsequently discovered a second major susceptibility locus on chromosome 11 that contains several interesting candidate genes [18].

Although PSP is usually a sporadic disease, some studies describe familial clustering. One pedigree with autosomal dominant PSP has been described and linked to a locus on chromosome 1q31, but the gene responsible for the disease in this family still has to be identified [19]. Although mutations in the tau gene may occasionally give rise to a clinical and pathological picture similar to PSP [20,21], screening of large cohorts of sporadic and familial PSP cases has failed to identify tau gene mutations to date.

**Clinical picture**

**Presenting features**

The most frequently reported symptom at disease onset is balance problems, followed by personality changes, bulbar symptoms, and visual problems. PSP patients present with a peculiar akinetic-rigid motor disorder that in most cases differs from that observed in Parkinson’s disease (PD). Symptoms are more prominent in the axial segments whereas the limbs are relatively preserved [8]. Unlike the onset symptoms in PD, postural stability is compromised early on. In the classic PSP phenotype (recently re-named Richardson’s Syndrome, RS), the motor disorder usually responds poorly to levodopa. The poor motor response to dopaminergic drugs is helpful in differentiating between the classic PSP phenotype and PD [22]. A subgroup of PSP patients may nevertheless show a good, but usually short-lived, response to levodopa (PSP-Parkinsonism [PSP-P]) [22]. In some patients, behavioral (apathy, disinhibition) and cognitive (progressive aphasia, apraxia of speech, memory loss) disorders may also be the presenting feature or accompany the motor disorder at disease onset.
Core characteristics of the disease

Patients with PSP generally manifest parkinsonian signs characterized by bradykinesia, rigidity, and disequilibrium with severe gait unsteadiness. The marked axial rigidity influences the posture, which may be characteristically erect like the original cases described by Richardson and colleagues (who described it as “nuchal dystonia,” Figure 4.1) or more closely resembles the flexed posture typical of PD. Progressive imbalance leads to repeated and frequent falls (usually backward). Postural tremor and less commonly tremor at rest may be superimposed occasionally. Even so, a classical pill-rolling resting tremor has been reported in less than 20% of the subjects [23]. Patients with PSP frequently have dysphagia and a characteristic growling high-pitched severe dysarthria, with mixed spastic and parkinsonian features [4]. PSP patients also manifest eyelid movement disorders, including blepharospasm and eyelid opening-and-closing apraxia. Although neurological examination in patients with PSP sometimes shows pyramidal signs, obvious spastic paraparetic gait or significant pyramidal weakness should cast doubt on the clinical diagnosis of PSP.

The most specific diagnostic feature of PSP is a limitation of vertical gaze with preserved oculocephalic reflexes (Figure 4.2), and many specialists consider frank gaze limitations indispensable for a diagnosis of PSP. Abnormalities of vertical gaze may be absent in up to 50% of the cases, however, and are not often the presenting symptom of PSP [12]. Because some limitation of upgaze is a frequent accompaniment of normal ageing and may be seen in a number of neurodegenerative disorders, limitation of downgaze is a much more specific finding suggestive of PSP. Patients with PSP may also present with other oculomotor disorders (Table 4.2) [24]. The oculomotor disorders are the main component of the peculiar facial expression (often described as worried or astonished) found

![Figure 4.1](image_url)
in patients with PSP, together with the characteristic dystonic features of the frontalis, procerus, and corrugator muscles [25]. The physician needs to differentiate PSP from the numerous other neurological conditions that can initially manifest with oculomotor dysfunction [26–29] (Table 4.3).

**Clinical variants**

In addition to RS, other clinical syndromes known to accompany PSP-tau pathology include PSP-P (the second most frequent after RS), corticobasal syndrome (CBS) [30], and pure akinesia with gait freezing (PAGF) [31]. These syndromes differ in their clinical features at disease onset and with disease duration. Patients with RD also have a shorter disease course than those with PSP-P and PAGF.
The concept of PSP-P has evolved notably over the past 40 years. The literature repeatedly refers to occasional cases of pathologically definite PSP whose neurological signs and disease course resemble that of PD. Only in recent years, however, did the large clinicopathological series reported by Williams et al. [22] underline that this clinical presentation of PSP

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**Table 4.2** Oculomotor abnormalities in progressive supranuclear palsy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Abnormalities</th>
</tr>
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<tbody>
<tr>
<td><strong>Early stages</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Slowness of vertical saccadic movements</td>
</tr>
<tr>
<td></td>
<td>• Hypometric saccades</td>
</tr>
<tr>
<td></td>
<td>• Reduced blinking</td>
</tr>
<tr>
<td></td>
<td>• Square wave jerks</td>
</tr>
<tr>
<td><strong>Middle stages</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Supranuclear vertical gaze palsy</td>
</tr>
<tr>
<td></td>
<td>• Lid retraction with very rare blinking (&lt;3)</td>
</tr>
<tr>
<td></td>
<td>• Impaired convergence</td>
</tr>
<tr>
<td></td>
<td>• Apraxia of eyelid opening or closing</td>
</tr>
<tr>
<td><strong>Late stages</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Supranuclear horizontal gaze palsy</td>
</tr>
<tr>
<td></td>
<td>• Loss of oculocephalic reflexes</td>
</tr>
<tr>
<td></td>
<td>• Blepharospasm</td>
</tr>
<tr>
<td></td>
<td>• Disconjugate gaze</td>
</tr>
</tbody>
</table>

Modified from Golbe [24]

**Table 4.3** Other causes of supranuclear ophthalomoplegia associated with parkinsonism

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
</tr>
<tr>
<td>MSA-P</td>
</tr>
<tr>
<td>CBD</td>
</tr>
<tr>
<td>DLB</td>
</tr>
<tr>
<td>FTD and parkinsonism linked to chromosome 17</td>
</tr>
<tr>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>Genetic cerebellar ataxias (SCA 2, SCA 3, SCA 7, SCA 17)</td>
</tr>
<tr>
<td>Postencephalitic parkinsonism</td>
</tr>
<tr>
<td>Prion diseases</td>
</tr>
<tr>
<td>Progressive external ophthalmoplegia</td>
</tr>
<tr>
<td>Tumors compressing the brainstem (pinealoma, glioma)</td>
</tr>
<tr>
<td>Multi-infarct state</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>CNS lymphoma</td>
</tr>
<tr>
<td>Niemann–Pick type C disease</td>
</tr>
<tr>
<td>Drug-induced</td>
</tr>
<tr>
<td>Whipple’s disease</td>
</tr>
<tr>
<td>Calcification of the basal ganglia</td>
</tr>
</tbody>
</table>

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is far more common than previously recognized. These authors first proposed designating this clinical disease phenotype PSP-P; this form may account for up to one-third of all cases of PSP. Patients with PSP-P typically present with tremor at rest, unilateral or asymmetrical bradykinesia, and a discrete or good response to levodopa. The initial clinical features are difficult to distinguish from those of PD. Multiple system atrophy of the parkinsonian type (MSA-P), particularly in patients without signs of full-blown dysautonomia, may be quite difficult to differentiate clinically from PSP-P [32].

Clinical diagnostic criteria

In 1996, an International Consensus Workshop under the auspices of NINDS and SPSP was convened to develop optimized criteria for a clinical diagnosis of PSP [12]. These diagnostic criteria have since been widely used in the research community and in movement disorder clinics. They define three diagnostic categories of increasing certainty: possible, probable, and definite. The diagnosis of possible and probable PSP depends primarily on the presence of specific clinical features (Table 4.1) and also on exclusion criteria. A definite diagnosis requires a typical PSP neuropathological lesion pattern with tau-positive inclusions.

A retrospective evaluation of the NINDS-SPSP criteria and of the other existing sets of clinical diagnostic criteria for PSP was conducted by Osaki et al. [33] on 60 pathologically proven cases from the Queen Square Brain Bank for Neurological Disorders in London. The main features of these diagnostic criteria are summarized in Table 4.4. The diagnosis was made by 40 different physicians on 60 cases clinically diagnosed as PSP when last assessed in life. In 47 cases (78%), the diagnosis of PSP was confirmed pathologically. The findings from this study showed that most cases of PSP were correctly diagnosed by neurologists at the final assessment. Although applying the category “possible,” NINDS-SPSP marginally improved the accuracy of the initial clinical diagnosis; none of the existing operational criteria could significantly improve the accuracy of the final clinical diagnosis. All published criteria have good positive predictive values whereas sensitivity is relatively poor [33]. In conclusion, although these formal diagnostic criteria are important for certain clinical

| Table 4.4 Outline of features required by different sets of diagnostic criteria for progressive supranuclear palsy |
|---------------------------------|-----------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|
| **Gaze abnormalities** | **Falls** | **Axial rigidity** | **Pseudobulbar palsy** | **Parkinsonism** | **Frontal lobe signs** | **LD response** |
| NINDS-SPSP Vertical | <1 yr | – | – | – | – | – |
| Lees Down | Backward | + | + | Brady/rigidity | + | – |
| Golbe Down | Not specified | + | + | Brady | – | – |
| Tolosa Down | Not specified | + | + | Brady | + | + |
| Blin Vertical | Not specified | – | + | Brady/rigidity | – | + |

NINDS-SPSP, National Institute for Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy; LD, levodopa; brady, bradykinesia. + or – means that these features are/are not required for diagnosing PSP. Reproduced with kind permission from Osaki et al. [33]
research fields, they add little to the problem of detecting early cases and screening tools need improving.

**Time course of the disease**

PSP affects both genders, despite a slight male predominance. The disease progresses relentlessly and has a significantly shorter mean survival than PD [24]. The clinical symptoms commonly begin in the seventh decade, although occasionally as early as the fifth decade. Pooling several PSP case series yielded a median onset age of 63 years, with rare cases beginning as early as 40 years of age.

PSP is a chronically progressive disease characterized by the gradual onset of neurological symptoms with increasing disability. In a comparative clinicopathological study, latencies to onset of falls were short in patients with PSP, intermediate in MSA, dementia with Lewy bodies (DLB), and CBD, and long in PD [34]. Recurrent falls within the first year after disease onset predicted PSP in 68% of the patients. Conversely, latency to onset, but not duration, of recurrent falls differentiates PD from other examples of parkinsonism. In another study, the progression to different Hoehn and Yahr (HY) stages was evaluated in 81 pathologically confirmed patients with parkinsonism. Latencies to each HY stage were longer in patients with PD than in those with atypical parkinsonism (AP). Development of a HY-III within one year of motor onset accurately predicted AP. The progression to each HY stage was unhelpful in distinguishing the various disorders with AP from each other. Once patients with PD and AP became wheelchair-bound, both had equally short survival times [35].

The prognosis of PSP remains poor. This is a progressive disorder associated with a shortened life span, often leading to death within ten years after symptom onset. Mean survival ranges from 5.9 to 9.7 years according to the different series.

**Epidemiology**

The dearth of published epidemiological studies makes it difficult to determine incidence and prevalence rates for PSP. The estimated prevalence of PSP (per 100,000 in the population) in the various studies ranged from 1.3 to 4.9 [36,37]. The estimated annual incidence of PSP was about 0.3–1.1 cases per 100,000 persons or 5.3/100,000 people over the age of 50 years [38]. These figures match those for other well-known neurodegenerative disorders such as Huntington’s disease or motor neuron disease. The analytical epidemiology of PSP is even poorer and more controversial. Although a retrospective study conducted in Switzerland showed an increased risk of PSP associated with arterial hypertension [39] other independent series failed to confirm the finding [40]. Smoking habits seem to be similar to those in healthy controls. The fact that the inverse association with smoking found previously in PD is shared by MSA but not by PSP lends epidemiological support to the notion that different smoking habits are associated with different groups of neurodegenerative disease [41].

**Investigations**

**Introduction**

The clinical diagnosis of PSP depends primarily on history and physical examination. Recent evidence, however, shows that additional investigations may be useful in differentiating PSP from other parkinsonian syndromes.
Computerized tomography
Although CT scans sometimes disclose pathological changes including generalized or brainstem atrophy in patients with PSP, current data suggest that this diagnostic tool is of limited use in routine clinical practice [8].

Routine magnetic resonance imaging
Several studies have sought to improve the diagnostic accuracy of PSP by using various MRI techniques [42]. Routine and volumetric MRI imaging may show midbrain atrophy, a finding that helps in differentiating patients with PSP from healthy controls and those with PD and other disorders with AP. A study designed to provide a quantitative assessment of atrophy by measuring midbrain diameter or area found that a diameter of <17 mm on axial MRIs differentiates patients with PSP from healthy controls [43]. Other studies suggest that atrophy is better evaluated on mid-sagittal slices because they are not subject to variation in the scanning angle. The midbrain atrophy seen on these slices typically resembles a penguin or hummingbird silhouette [44]. In a study designed to measure the midbrain area in patients with PSP, Japanese investigators found a significant area reduction in PSP versus PD and controls [45]. The relationship between the midbrain/pons areas was also significantly lower in patients with PSP than that observed in PD patients and controls. Although these measurements were helpful in differentiating PSP, MSA, and PD as groups, the data obtained overlapped among the groups of patients investigated, and therefore were not helpful for an individual diagnosis.

In a study investigating morphometric MRI in PSP, MSA, PD, and controls using volumetric T1-weighted sequences [46], Quattrone and colleagues measured the midbrain and pons areas, together with the medial cerebellar peduncle (MCP) and superior cerebellar peduncle (SCP) width. They found that atrophy in PSP involves the midbrain and SCP whereas atrophy in MSA involves the pons and the MCP. In patients with PD all brain areas measured had dimensions similar to those in control subjects. Single structure measurements did not discriminate among the different diseases on an individual basis, because of substantial overlap. The investigators therefore proposed a new index calculated with a specific formula (area of pons/area of midbrain x MCP diameter/SCP diameter) obtained by combining the single measurements obtained in the various cerebral structures. The ‘magnetic resonance parkinsonism index’ (MRPI) was significantly higher in PSP than in the other conditions, and could differentiate individual patients with PSP from those with MSA and PD. The promising results obtained with morphometric MRI should be confirmed in studies conducted by other groups before proposing its use in routine clinical practice.

Diffusion-weighted imaging
Diffusion-weighted imaging (DWI) is a useful diagnostic tool that can provide additional support for a diagnosis of AP, and especially for PSP. In their study, Seppi and coworkers found significantly higher rADC (regional apparent diffusion coefficient) values in both the putamen and globus pallidus in patients with PSP than in those with PD [47]. The increased putaminal rADC values in PSP probably reflect ongoing striatal degeneration, whereas most neuropathological studies reveal an intact striatum in PD. Despite these differences, increased putaminal rADC values are not able to discriminate PSP from MSA-P.
Magnetic resonance volumetry

Whether magnetic resonance volumetry will help in differentiating PSP from other disorders with AP remains to be confirmed. Patients with PSP, MSA-P, and MSA-C had significantly lower mean striatal and brainstem volumes than patients with PD, and patients with MSA-P and MSA-C also showed a reduction in cerebellar volume [48]. Total intracranial volume-normalized MRI-based volumetric measurements provide a sensitive marker to discriminate PD from AP.

Voxel-based morphometry is an observer-unbiased volumetric procedure that can be used to investigate the entire brain. A study comparing patients with probable PSP and healthy controls showed that in patients with PSP several cortical areas in the frontal, temporal, and insular lobes were decreased in volume [49]. White matter comparisons also disclosed a volume reduction in the frontotemporal regions and the mesencephalon. This brain atrophy pattern probably accounts for the cardinal PSP-associated behavioral deficits.

Functional imaging

Functional imaging methods for differential diagnosis in AP are techniques designed to investigate receptor binding and glucose metabolism. Studies of brain receptor binding in parkinsonism, by evaluating dopa-decarboxylase activity and the dopamine transporter (DAT) examine the presynaptic nigrostriatal neurons, and by evaluating the dopamine D2-receptors examine postsynaptic dopaminergic function. More recently, SPECT and PET ligands have become available to study cardiac sympathetic innervation.

Using PET, the Hammersmith group found that putaminal uptake of the presynaptic dopaminergic marker 18F-fluorodopa was reduced to a similar extent in PD and PSP [50]; in some patients with PSP, caudate uptake was also markedly reduced, as opposed to only a moderate reduction in PD [51]. Measurements of striatal dopamine D2-receptor densities using raclopride and PET also failed to differentiate between PD and AP, demonstrating a similar loss of densities in patients with advanced PD, PSP, and MSA [52].

SPECT evaluation of DAT using 123I-β-CIT may be useful in differentiating true parkinsonism from patients with essential tremor and patients with parkinsonism owing to a subcortical vascular encephalopathy. Although PSP cannot be distinguished from PD with this method alone [53], patients with PSP may show a more symmetrical DAT loss, consistent with the more symmetrical clinical motor dysfunction observed in this condition. SPECT imaging studies of patients with dopa-naïve parkinsonism have used 123I-IBZM as a D2-receptor ligand [54]. Subjects with normal IBZM binding responded well to apomorphine and benefitted from subsequent chronic dopaminergic therapy, whereas subjects with reduced binding failed to respond. In some of these patients, other clinical features atypical for PD developed during follow-up [55]. Despite these interesting findings, because striatal IBZM binding is also reduced in other disorders with AP such as MSA, IBZM binding has limited predictive value for an early diagnosis of PSP [56].

Scintigraphic visualization of postganglionic sympathetic cardiac neurons was found to differentiate patients with PD from patients with AP [57]. Considering all reports published so far, standard scintigraphy with 123I-metaiodobenzylguanidine (MIBG), a technique used for years to detect pheochromocytoma cells, correctly distinguished most patients with PD, all of whom had severely reduced cardiac MIBG uptake. This radioactive ligand method appears to be a highly sensitive and specific tool to discriminate between PD and AP within
two years after the onset of symptoms but it cannot distinguish PSP from other forms of AP such as MSA [58].

Neurophysiology

Among the standard neurophysiological tests used in patients with abnormal eye movements, electro-oculographic recording may help in distinguishing patients with PSP from those with CBD at an early stage [59]. Patients with PSP have decreased horizontal saccadic amplitude and velocity but normal latency, whereas those with CBD show normal saccadic velocity and increased latency. The antisaccadic task (looking in the direction opposite to a visual stimulus), which correlates well with frontal lobe dysfunction, is markedly impaired in patients with PSP, although it may also be impaired in AD. Conversely, patients with PD or MSA-P have no or only slight saccadic impairment [60].

In a recent study by our group, when we recorded blink movements in patients with PSP we found that voluntary, spontaneous, and reflex blinking all show abnormal kinematic features, and there was a correlation between abnormal kinematic variables and patients’ clinical features [61]. Our findings suggest that abnormal blinking in patients with PSP reflects the widespread cortical, subcortical, and brainstem degenerative changes related to this disease.

Other neurophysiological measures of brainstem function are abnormal, reflecting the pathological alterations in the midbrain and pons typical of PSP. An absent or a severely reduced startle reaction has been described in patients with PSP, whereas it was only mildly affected in PD patients [62]. The orbicularis oculi response to an electrical stimulus is abnormal in patients with PSP in whom electrical median-nerve stimulation elicits a normal mentalis response [59]. These findings differentiate patients with PSP from those with PD, MSA, and CBD, in whom peripheral nerve stimulation invariably elicits simultaneous responses in the orbicularis oculi and mentalis muscles.

In patients with parkinsonism, diagnostic neurophysiological studies now commonly include external anal or urethral sphincter EMG. Owing to degeneration of Onuf’s nucleus, the anal and urethral external sphincter muscles both undergo denervation and re-innervation [63]. Neurogenic changes in the sphincter muscles can be present in patients with PSP [64]. Sphincter EMG recordings nevertheless have limited diagnostic value in PSP because they almost invariably disclose similar abnormalities in patients with MSA as well [65]. Another disadvantage of sphincter-EMG recordings is confounding from nonspecific abnormalities such as chronic constipation, previous pelvic surgery, or vaginal deliveries [66].

Finally, although somatosensory, visual, and brainstem evoked potentials are usually normal in PSP, the presence of abnormal motor potentials evoked by transcranial magnetic stimulation and a prolonged central motor conduction time suggests the involvement of pyramidal tracts. In addition, PSP patients show an increased cortical excitability as demonstrated by an abnormal input–output curve [67].

Other investigations

Although several studies over the past 15 years have sought PSP biomarkers in cerebrospinal fluid (CSF), none of them has provided findings that can be applied in clinical practice. For example, Holmberg and colleagues [68] first showed that the CSF neurofilament (NFL)
content was significantly higher in patients with PSP and MSA than in those with PD, reflecting the degree of ongoing neuronal degeneration affecting mainly the axonal compartment. They also proposed that combining CSF-NFL dosing and a levodopa test may improve the differential diagnosis of parkinsonian syndromes [69]. Whereas the CSF-NFL test predicted 79% and levodopa tests predicted 85% correct diagnoses (PD vs. non-PD [MSA and PSP]), the combined test predicted 90% correct diagnoses.

CSF levels of total tau protein in patients with PSP were found to be similar to those in controls and patients with AD [70], but significantly increased in patients with CBD. In contrast, a recent study found that patterns of proteolytic tau fragments in CSF from patients with PSP differed from those in patients with other neurodegenerative conditions such as AD, FTD, CBD, and PD [71]. These results using qualitative tau-measures are promising, and if confirmed by other groups may indicate a possible biomarker for diagnosing patients with PSP early in the disease course.

**Treatment**

Given the few randomized controlled studies so far conducted, the symptomatic management of PSP is based largely on empirical evidence.

**General approach**

A number of therapeutical approaches, other than pharmacological, are important in PSP: for example, physical therapy, speech therapy, occupational therapy, and psychological support for patients and carers; macrogol-water solution [72] for constipation; and food thickeners, feeding via a nasogastric tube, or percutaneous endoscopic gastrostomy for dysphagia. (See also Chapter 8). These management decisions should be based on careful clinical judgment, taking into account the patient’s and caregivers’ expectations.

**Treatment of parkinsonism**

Most patients with PSP have parkinsonian features and these should be a major target for therapeutic intervention. Unfortunately, dopaminergic treatment provides only modest results. Open-label or retrospective studies suggest that up to 30% of patients with PSP may benefit from levodopa at least transiently [22]. Occasionally, a beneficial effect is evident only when seemingly unresponsive patients deteriorate after levodopa withdrawal. Results with dopamine agonists have been even more disappointing [24]. Anti-parkinsonian effects have been reported in a few patients with PSP treated with amantadine but an open study including subjects with PSP reported no significant improvement [73].

**Treatment of other clinical features**

PSP involves the dopaminergic and also the cholinergic systems [74]. Unfortunately, studies with the cholinesterase inhibitor donepezil found no improvement in the cognitive dysfunction associated with this disease [75]. Blepharospasm, apraxia of eyelid opening, salivary, as well as limb and nuchal dystonia may respond well to local injections of botulinum toxin A [76].
Neuroprotection trials

Despite the disappointing results from the first trials with coenzyme Q10 [77] and riluzole [78], several international groups are conducting multicenter intervention trials with possible disease-modifying agents in PSP. These trials should change our approach to PSP. For example, they will provide previously unavailable prospective data concerning disease progression that can be used to identify reliable predictors of survival.

In addition, a specific rating instrument has recently been developed to standardize severity assessments in specialized clinics and research programs worldwide [79]. The PSP rating scale (PSPRS) is a prospectively validated clinical tool that represents a convenient global measure of disability and disease progression in PSP. The score on this disease-specific scale increases at a rate of around 10 points per year in patients with clinically probable PSP, up to a maximum of 100 points. This new tool will be helpful for planning future phase III intervention trials more effectively during the next decade.

Conclusions

The recently obtained molecular information along with findings from clinical trials of disease-modifying agents hopefully should bring about a major change in our therapeutic approach to this devastating illness.

References

11. Tolosa E, Valdeoriola F, Marti MJ. Clinical diagnosis and diagnostic criteria of progressive supranuclear palsy
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randomized, placebo-controlled trial. 
