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Update on the Diagnosis and Management of Progressive Supranuclear Palsy

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Abstract Progressive supranuclear palsy (PSP) is an adult-onset neurodegenerative disease clinically characterized by a variable combination of symmetrical parkinsonism, early postural instability and falls, vertical supranuclear ophthalmoparesis, and cognitive decline. PSP is a disorder of 4-repeat tau protein aggregation, belonging to the family of tauopathies. A broad phenotypic variability has been recognized, and specific clinical diagnostic criteria are available. Several ancillary tests are helpful for diagnosis; however, there are no diagnostic biomarkers, and definite diagnosis still requires histopathological confirmation. Symptomatic management of PSP patients is limited, but recent advances in the understanding of its pathophysiology might lead us to disease-modifying treatments. A multidisciplinary approach is essential in managing the symptom complexity of a progressive condition such as PSP.

Keywords Progressive supranuclear palsy · PSP · Update · Tauopathy · Atypical parkinsonism

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Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disease with an overall prevalence in the Caucasian population of 5–6 per 100,000 [1–3]. It was first described as a distinct clinicopathological entity by John Steele, J. Clifford Richardson, and Jerzy Olszewski in 1964 [4], and since then important discoveries related to its pathophysiology have been achieved. However, its etiology is still unknown and no effective treatments are presently available.

Several lines of research point to an important contribution of both genetic [5, 6] and environmental factors to the etiology of PSP that lead to mitochondrial dysfunction and oxidative injury [7]. Although PSP has been historically recognized as a sporadic disorder, some mutations particularly affecting MAPT gene [5] have been identified in families with PSP consistent with an autosomal-dominant pattern of inheritance. Besides these few cases with a mendelian inheritance, the best established risk factor for sporadic PSP in the Caucasian population is the H1 haplotype of the *MAPT* gene [6•]. The way in which these genetic and environmental factors interact to mediate increased levels of 4-repeat tau protein (4R-tau) [8], the histopathological hallmark of PSP, its aggregation, and the eventual cell death are still uncertain.

Clinical Features

Overview

The clinical presentation of PSP is quite variable. First symptoms frequently develop in the sixth decade of life, affecting both sexes equally. The classical syndrome, pictured in the seminal paper by Steele-Richardson-Olszewski, now termed Richardson syndrome (RS) based on the similar clinical characteristics to those first described by Richardson [9] includes prominent balance impairment with falls, supranuclear gaze palsy, frequent bradykinesia, mild dementia, and progressive axial rigidity and bulbar palsy [4]. Apart from RS, other clinical presentations with different predominant symptoms at disease onset and progression have long been recognized [10, 11]. More recently, some clinicopathological studies have confirmed this and suggested that different topography of brain lesions may underlie the varied symptoms of PSP [12••]. Among the different phenotypes of PSP, there are cases with predominant asymmetric parkinsonism [13], others with prominent freezing of gait without oculomotor disturbances [14] or even with only cognitive decline resembling a frontotemporal dementia [15]. All these phenotypes may eventually present clinical overlap and evolve with disease progression to a more typical clinical picture resembling RS.

The variable clinical presentation together with the fact that the characteristic supranuclear palsy may develop years after onset of symptoms, along with the lack of reliable diagnostic markers, makes early diagnosis difficult [16••]. Table 1 lists the different presentations of PSP and compares them with Parkinson's disease (PD) clinical features.

Unsteadiness, clumsiness, and nonspecific visual symptoms are the most frequent initial patient's complaints. The patient's relatives may also have concerns about personality changes such as apathy, irritability, or depression and cognitive features like difficulty in concentration or subtle language problems. Symptoms might rapidly evolve with the appearance of the more disabling features of the disease, such as falls backwards, prominent difficulties with downward vertical gaze, or frontal lobe signs in 2 to 3 years [17]. In RS, survival time from symptom onset is around 7 years [16••, 17], ranging from 5 to 9 years, whereas atypical phenotypes may have a more benign course with a better response to the treatment and an overall better prognosis [13, 16••].

A PSP rating scale has been validated as a tool for clinical practice and research trials and is intended for use in patients with RS [18]. This scale comprise 28 items including daily activities and cognitive, motor, bulbar, oculomotor, and gait symptoms with a score ranging from 0 to 100, 100 being the worst score. The mean progression rate is 11.3(±11) points per year [18].

Richardson Syndrome (RS)

This clinical presentation has been recognized as the most characteristic phenotype of PSP accounting for almost half of cases. If the full clinical picture is present; diagnosis is straightforward [16••].

Motor Symptoms

The extent and severity of motor features in RS is variable. Parkinsonism in RS is not always obvious; Steele et al. in their original description emphasized that none of their cases had been considered as having parkinsonism by any of the numerous neurologists that had examined them. It is now agreed, though, that frequently patients develop symmetrical limb bradykinesia and prominent rigidity involving the neck and trunk. Balance is severely affected with falls, usually backwards, occurring very frequently within the first year of disease onset. Gait is slightly broad based and with the trunk and neck in hyperextension presenting the typical "drunken sailor" appearance [1, 4, 16••]. Parkinsonian-type rest tremor is present in around 5–10 % of cases whereas postural tremor of the hands is more frequent. Cervical dystonia in antero- or

Table 1 Predominant presenting features of PSP phenotypes vs. Parkinson's disease

	RS	PSP-P	PSP-GF	PSP-CBS	Parkinson's disease
Bradykinesia	absent or mild; symmetric	mild to moderate; may be asymmetric	small amplitude with no decrement	mild to moderate; asymmetric	mild to moderate; asymmetric
Rigidity	Axial > Limbs	Limbs > axial	Axial > Limbs	Limbs > axial asymmetric	Limbs > Axial
Tremor	No	Yes (jerky postural and rest)	No	No	Yes (rest)
Falls	Yes	No	No	Sometimes	No
Eye movement abnormalities	Yes	No	No	No	No
Cognitive decline	absent or mild	No	No	No	No
Response to levodopa	No	~50 % of improvement	No	No	Yes

RS Richardson syndrome, *PSP-P* progressive supranuclear palsy-parkinsonism, *PSP-GF* progressive supranuclear palsy-with prominent freezing of gait, *PSP-CBS* progressive supranuclear palsy-corticobasal syndrome, *PSP-PNFA* progressive supranuclear palsy-behavior variant of fronto-temporal dementia (non-fluent aphasia)

retrocollis is a characteristic finding of the disease although it appears only in approximately 10 % of cases, and other locations of focal dystonia affecting predominantly the eyelids or limbs are less frequent although clinically disabling [1, 11, 16••]. Patients may experience dysarthria early in the disease, characteristically slow, hypophonic, and strangled voice. In more advanced stages, dysphagia can cause aspiration pneumonia and has a dramatic impact in the quality of life of patients [11, 16••].

Neuro-Ophtalmologic Symptoms

Photophobia, blurred vision, and difficulty focusing on objects are frequent and early problems. Some patients may report more difficulties when walking down and upstairs or eating, highlighting the abnormalities of vertical eye movements. Clinicians may detect subtle ophthalmologic signs even before patient's visual complaints such as impersistence of gaze or hesitancy when initiating a voluntary movement, slow and hypometric vertical saccades, and presence of square-wave jerks (brief involuntary horizontal conjugate saccadic eye movements observed during gaze fixation) [11, 19]. At times, the trajectory of vertical saccades is affected, showing a slightly curved "round the houses" path [20]. When established, the most characteristic neuro-ophtalmologic findings are the supranuclear gaze palsy with a complete restriction of range of vertical pursuit particularly downwards and the lid retraction (the so-called Collier's sign) [21] with prominent frontalis overactivity, giving the typical "surprised" or "astonished" facial expression [1, 4, 11]. Other eyelid symptoms such as inhibition of levator palpebrae and apraxia of eyelid opening or closing can occur [21]. Vestibulo-ocular reflexes are usually preserved until the terminal stages, but its evaluation may be difficult to elicit due to the prominent neck rigidity [19].

Cognition and Behavior

Cognitive and behavioral problems are nowadays better recognized and characterized. Most of the findings are related to frontal lobe dysfunction and include either apathy or disinhibition with emotional lability, irritability, and inappropriate sexual or social behavior. Executive dysfunction manifests with difficulties in planning, abstract thinking, and problem solving [22]. Motor impersistance and perseverative behavior will be recognized in a number of characteristic signs of the disease, i.e., the "pen sign" (inability to release a pen when trying to throw it), or tendency to interact with surrounding objects without an explicit order for it [23], or the "applause sign" (to initiate a repetitive and automatic applause when asked to repeat only three claps) [11, 15, 24]. Another characteristic sign demonstrating the lack of motor inhibition is the "rocket sign" observed when patient stands up from a chair too fast conditioning falls or injuries. Language alterations such as reduced spontaneous verbal output, diminished semantic and lexical verbal fluency, and other language problems such the presence of palilalia are also characteristic of PSP [16••].

Other Symptoms

Sleep abnormalities have been described as part of the clinical spectrum of the disease including an overall reduced sleep efficiency and REM sleep behavior disorder, occurring in 35 % of the patients [25] but much less intense than in Parkinson disease. Dysautonomic symptoms such as urinary urgency or incontinence, constipation, or erectile dysfunction are not uncommon in final stages of PSP, although these symptoms are more frequent and characteristic of other parkinsonisms like multiple system atrophy. Abnormal anal sphincter denervation though occurs in both MSA and PSP [26].

Progressive Supranuclear Palsy—Parkinsonism (PSP-P)

Some cases of PSP that initially resembled PD have long been recognized. Williams et al. demonstrated in a cohort of pathologically confirmed PSP patients that 32 % of them presented with an asymmetric Parkinson syndrome, that was difficult to distinguish from PD, and named these cases PSP-parkinsonism [13]. These patients can present asymmetrical bradykinesia and rigidity, jerky postural or rest tremor in 40 % of cases, and limb dystonia [13]. Neurophthalmologic symptoms may appear in the last stages of the disease, making the diagnosis difficult until the gaze problems occur. Positive response to levodopa is frequently present in these cases, and their survival is longer [13, 16••].

Progressive Supranuclear Palsy—With Prominent Freezing of Gait (PSP-GF)

Freezing of gait is a very common symptom in PSP. In some patients, though, it constitutes the most prominent sign since the illness onset and within the first 2 years of progression [14, 27].

Patients with the freezing variant of PSP present with start hesitation and freezing when turning. Other symptoms may accompany these gait problems such as hypophonia, hypomimia, and typically fast micrographia resembling "pure akinesia syndrome" [28]. The other characteristic oculomotor, bulbar, axial, or behavioral signs are not characteristic of this phenotype although can occur later in the evolution. No improvement in the disabling gait problem occurs with levodopa in such cases [27, 29].

Progressive Supranuclear Palsy—Corticobasal Syndrome (PSP-CBS)

Corticobasal degeneration (CBD) and PSP, considered two different entities, share multiple pathologic similarities and

increasing clinical overlap between both diseases has been recognized [30]. Classical symptoms of CBD include unilateral parkinsonian signs without response to levodopa therapy, supranuclear ophthalmoplegia, limb dystonia, parietal sensory dysfunction and alien limb phenomenon, ideomotor apraxia and stimulus-sensitive myoclonus, followed by prominent cognitive decline including language disturbances like progressive non-fluent aphasia and speech apraxia. Only a small proportion of PSP definite cases presents with this phenotype [31].

Progressive Supranuclear Palsy—Behavior Variant of Fronto-Temporal Dementia (PSP-FT)

Behavioral changes described in RS may appear without any motor abnormalities and be the predominant symptom throughout the disease course [15, 32].

Other phenotypes presenting with progressive non-fluent aphasia (PSP-PNFA) [33], predominant oculomotor symptoms (PSP-OM) [12••], or postural instability (PSP-PI) have been also recognized [12••].

Diagnosis

Clinical Diagnosis

The diagnosis of PSP may be challenging, especially in the earlier stages of the disease, and several pathologies may share its clinical presentation (Table 2). Secondary parkinsonisms must be considered, especially those in which a specific treatment can be implemented. Cerebrovascular disease [34], normal pressure hydrocephalus, and midbrain structural abnormalities can sometimes mimic PSP. Other neurodegenerative parkinsonisms like PD, multiple system atrophy (MSA), CBD, and diffuse Lewy body disease might resemble PSP in the early disease stages, leading to misdiagnosis [11, 35]. More rarely, Creutzfeldt-Jakob disease, Whipple disease, or post-encephalitic parkinsonism may mimic PSP. Some of these conditions can also present with supranuclear gaze palsy, which can make differential diagnosis even more difficult (Table 2). In the absence of reliably validated diagnostic biomarkers, diagnosis is still based on clinical observations. Several diagnostic clinical criteria for PSP have been proposed [11, 36–39]. The National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) criteria [37] are the most widely used criteria for research purposes. These offer a set for "possible" and "probable" PSP with high specificity and positive predictive value for the classical Richardson Syndrome. The variability and symptomatic overlap between phenotypes that do not fit NINDS-SPSP criteria demonstrates its low sensitivity [12••, 40, 41]. Prospective studies are needed in order to improve the patient's selection for clinical trials considering also the inclusion of all the clinical spectrum of PSP cases.

Table 2 List of PSP mimics

	May present with gaze palsy
Neurodegenerative disorders	
Parkinson's disease with dementia	No
Diffuse Lewy body disease	No
Multiple system atrophy	No
Corticobasal degeneration	Yes
Fronto-temporal dementia	Yes
Prion disease (Creutzfeldt-Jakob disease)	Yes
Other neurological disorders	
Wilson's disease	No
Niemann-Pick disease type	Yes
CADASIL	Yes
Cerebrovascular disease	Yes
Normal pressure hydrocephalus	No
Midbrain tumors (e.g., pinealoma, glioma)	Yes
Neurosyphilis	Yes
Antiphospholipid syndrome	No
Bulbar forms of motor neuron disease	No
Ocular myasthenia gravis	Yes

PSP progressive supranuclear palsy, *CADASIL* cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Neuropathology

The definite diagnosis of PSP is based on the neuropathological diagnostic criteria [42]. The histopathological hallmarks of PSP are abnormal aggregates of 4-repeat tau protein [8] conforming pre-tangles and neurofibrillary tangles in neurons, neuropil threads in neural processes, coiled bodies in oligodendrocytes and tufted astrocytes (Fig. 1).

Tau aggregates in PSP may be widely spread but are consistently present in subcortical structures including the globus pallidus, substantia nigra, thalamus, subthalamic nucleus, locus coeruleus, superior colliculi, pretectal regions, periaqueductal gray matter, cerebellum, tegmentum, pontine nuclei and spinal cord, and occasionally on cortical regions, mainly the frontal lobe and variably on ocular-motor visual association areas. Atrophy of the midbrain and periaqueductal gray matter, associated with enlargement of periaqueductal space, third and forth ventricles are common features [42–44].

A correlation between the extent of the pathological abnormalities and the clinical phenotype has been observed, with PSP-P cases presenting less severe tau pathology than RS patients [45]. Pathological heterogeneity has been also found in other phenotypes such as PSP-PAFG, PSP-PNFA, and PSP-CBS [30, 45, 46].

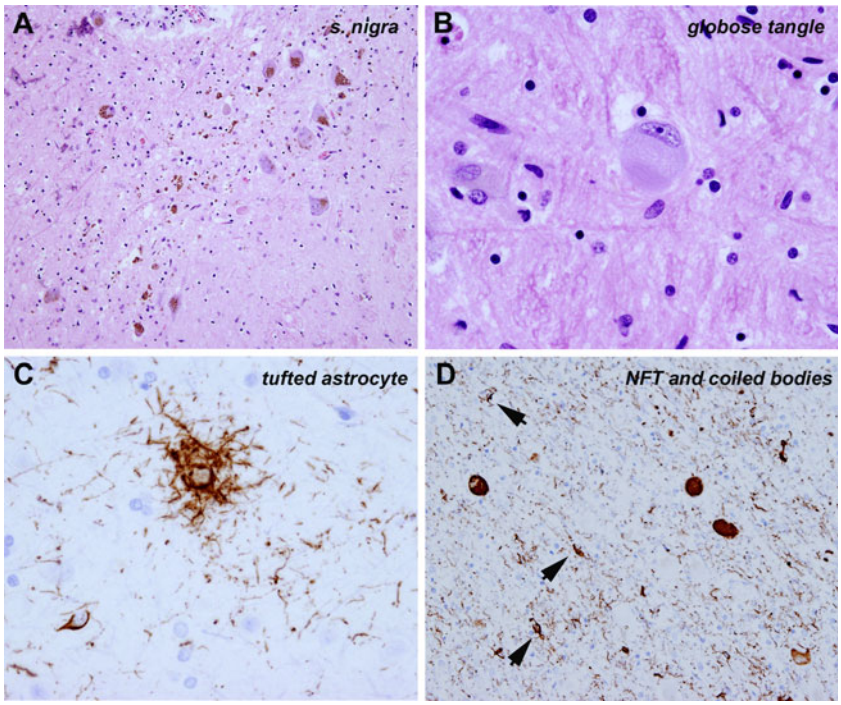

Fig. 1 Characteristic neuropathological features of PSP. **a** Prominent loss of pigmented neurons of the substantia nigra with abundant extracellular pigment in the *center* of the image. **b** Large globose tangle displacing the nucleus to the periphery of the neuron. **c** Tau positive tufted astrocyte and **d** tau positive globose neurofibrillary tangles (*NFT*) in the subthalamic nucleus with abundant tau positive oligodendroglial cytoplasmic inclusions in form of coiled bodies (*arrows*). Courtesy of Dr. Ellen Gelpí, Banc de Teixits Neurològics, Biobanc de l'Hospital Clínic i Provincial de Barcelona (IDIBAPS)

Ancillary Tests

Neuroimaging

Magnetic Resonance Imaging (MRI) MRI techniques, both routine and advanced, may play a role in the differential diagnosis between PSP and other entities. The performance of a conventional MRI is essential in order to exclude other secondary causes of parkinsonism that can clinically resemble PSP, particularly cerebrovascular disease, normal pressure hydrocephalus, Wilson's disease, hepatocellular degeneration, or other structural abnormalities of the basal ganglia, such as tumors or cysts. But MRI is not only useful to exclude these PSP mimics. It also allows detecting some characteristic findings of PSP. The most consistent radiological features are atrophy of the midbrain and superior cerebellar peduncles with secondary third ventricle dilatation [47], T2-hyperintensities in periaqueductal areas and superior cerebellar peduncles, and atrophy of the frontal and temporal lobes [48]. Midbrain atrophy is particularly specific differentiating PSP from other atypical parkinsonisms like multiple system atrophy [48, 49] and can be identified in the typical "hummingbird" or "king penguin shape" appearance in sagittal sequences [50] (Fig. 2) and in the "morning glory flower" sign (concavity of the lateral margin of the midbrain tegmentum) in axial images [51]. Also, a high midbrain to pons ratio measured on midsagittal images has demonstrated to be a simple and reliable measurement with high sensitivity and specificity that may be a useful tool in the clinic [50, 52–55].

Novel MRI techniques like volumetry, spectroscopy, and diffusion tensor imaging have been used for research purposes to identify early brain abnormalities in patients with PSP [56, 57••]. The diffusion weighted and diffusion tensor MRI techniques (DWI/DTI) might have a role in clinical practice helping to discriminate between early atypical parkinsonisms. An increased regional apparent diffusion coefficient in the caudate, pallidus, midbrain, and SCP has been observed in PSP compared to PD or MSA [56, 58]. However, further research

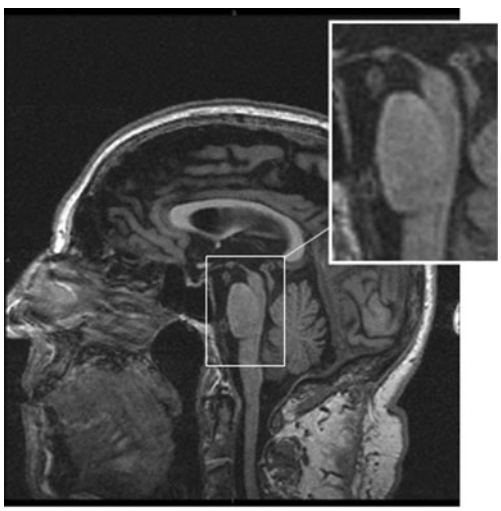

Fig. 2 Magnetic resonance imaging in PSP. Atrophy of the midbrain, the "hummingbird sign" (shape of the midbrain tegmentum as the bird's head and shape of the pons as the bird's body). Courtesy of Dr. Nuria Bargalló, CDIC Hospital Clínic i Provincial de Barcelona (IDIBAPS)

is needed to determine the usefulness of these techniques in the differential diagnosis of PSP.

Radiotracer Imaging Both positron emission tomography (PET) and single photon emission computed tomography (SPECT) using a variety of radioactive tracers (e.g., 18F-fluorodopa [FDOPA], 123 I-B -CIT, and ^{123}I-FP- CIT [FPCIT]) have been used to investigate brain function in PSP and other parkinsonian syndromes. Loss of presynaptic striatal dopaminergic function is consistently observed in PSP as well as in PD or other parkinsonisms. It has been suggested that the anterior caudate to anterior striatum uptake ratio distinguishes PD from PSP patients [59], but these findings have not been confirmed. The additional use of postsynaptic dopaminergic tracers (e.g., ^{11}C-raclopride [RAC] and ^{123}I-IBZM) might supplement the differential diagnosis between parkinsonisms. Indeed, postsynaptic dopaminergic function is usually unaltered in PD, whereas reduced tracer uptake is commonly observed in PSP [60–62]. However, normal postsynaptic function does not rule out atypical parkinsonisms. In summary, imaging of presynaptic dopaminergic function is not useful to differentiate PD from atypical parkinsonisms and postsynaptic dopaminergic imaging might have some value in this regard, but sensitivity is still low and normal postsynaptic tracer uptake does not exclude PSP.

More recently, several new tau radiotracers that can selectively bind to specific isoforms of tau have been developed [63••, 64••]. An increased uptake of [F18] AV-1451 (T807), a highly selective phosphorylated-tau ligand, has been demonstrated in the striatum, pallidum, thalamus and frontal cortex of PSP patients [64••]. Once validated, PET tau imaging may provide an objective marker of in vivo tau aggregation, which could play a role in the differential diagnosis of parkinsonisms as well as improve the understanding of the disease mechanisms [63••].

Other Tests

Neurophysiological Tests The diagnostic potential of neurophysiological tests in atypical parkinsonian syndromes has been also investigated. The simultaneous application of acoustic startle reflex (ASR), acoustic blink reflex (ABR), and electro-oculography (EOG) have provided a high sensitivity, specificity, and positive predictive value in early stages of PSP [65]. Abnormal voluntary, spontaneous, and reflex blinking in patients with PSP had been also described, probably reflecting the widespread cortical, subcortical, and brainstem degeneration related to this disease [66].

Transcranial Sonography (TCS) Over the past 15 years, the use of TCS to assess the brainstem and subcortical brain structures has become an important tool for the differential diagnosis of movement disorders. Results from studies that used TCS in patients who already had been given a definite clinical diagnosis of PSP have shown that hyperechogenicity of the substantia nigra was found only in up to a third of patients [67–69]. This echofeature is characteristic of PD and observed in more than 90 % of cases, and its identification would be more suggestive of this entity. Hyperechogenicity of the lentiform nucleus is an abnormality that can often be seen in PSP but only seldom seen in PD [68, 69]. The combination of normal echogenicity of the substantia nigra and hyperecogenicity of the lenticular nucleus in one study had a predictive value of at least 96 % for PSP [68].

Cerebral Spinal Fluid (CSF) CSF is a promising source of biomarkers for neurodegenerative disorders, and growing evidence shows their potential for the differential diagnosis between parkinsonisms. However, specific diagnostic CSF biomarkers have yet to be identified for PSP [70•]. Lower CSF total-tau and phosphorylated-tau concentrations have been recently found in PSP compared to Alzheimer's disease patients and healthy controls [71], although other studies did not confirm these findings [70•, 71, 72, 73•, 74]. A recent study using a panel including different protein determinations showed a good diagnostic accuracy for different atypical parkinsonian disorders [73•]. An important limitation of the studies assessing CSF biomarkers is the lack of a pathologic confirmation or prospective longitudinal data. Further prospective investigations should be done to validate these results.

Management

Current Treatments (Table 3)

In PSP, pharmacological symptomatic therapy is limited. Up to 30 % of patients improve motor symptoms in response to dopamine replacement therapy (up to 1–2 g of levodopa per day combined with dopa decaboxylase) [16••, 75]. For this

Table 3 List of most useful interventions in PSP

Symptom	Intervention
• Bradykinesia and rigidity	Levodopa Physiotherapy
• Dystonia, blepharospasm and sialorrhea	Botulinum toxin
• Behavioral problems	Quetiapine
• Depression	Serotonin reuptake inhibitors
• Dysphagia	Dietary modifications Percutaneous endoscopically placed gastrostomy
• Gait and balance problems	Gait retraining Walking aids

PSP progressive supranuclear palsy

reason, a therapeutic trial with oral levodopa should be performed as a first choice. Patients with a PSP-P phenotype may respond up to 50 %, probably due to a lesser extent of the postsynaptic striatal neurons loss, whereas RS show less clinical benefit. In most cases in whom a positive response is observed, this is usually insufficient and transient.

Amantadine (up to 200 mg/day) has been suggested to have a minor benefit on gait, dysphagia, and apathy in a retrospective study [76]; however, in our experience, it has not been useful. Amitriptyline showed similar benefits in a clinical trial but also presented paradoxical worsening of gait in some cases [16••]. The possible benefit of gabapentin for oculomotor dysfunction was assessed in a clinical trial but failed to demonstrate efficacy [77]. Donepezil showed mild benefit for cognitive symptoms but worsened motor symptoms [78].

The management of cognitive and behavioral symptoms relies on clinical opinion and expertise. It has been suggested that rivastigmine may play a role for the treatment of cognitive decline, and that serotonin reuptake inhibitors and antipsychotics like quetiapine (up to 300 mg/day) could be the first-choice treatment for behavioral and mood disturbances [16••, 75].

Dystonic postures, blepharospasm, eyelid apraxia, and sialorrhea do not show a response to systemic therapies but can substantially improve with local injections of botulinum toxin [16••]. This might be of special importance in those patients in whom these symptoms are annoying and disabling.

A Multidisciplinary Approach

It is essential to have a good understanding of the clinical picture that usually presents PSP and how they cause disability to plan the patient's care. A wide range of professionals may need to be involved in managing a patient with PSP and an integrated multidisciplinary approach is mandatory. Non-pharmacological treatment like physical, speech, and occupational therapy can be helpful, although little scientific evidence is available to support its application [79].

Physiotherapy

Physical therapy provides practical solutions to the principal mobility concerns of PSP patients, such as major balance problems, postural abnormalities of the trunk, and rigidity. These interventions are included in the following areas:

Mobility Physical support to prevent falls with grab bars or walkers and gait retraining [80] can be useful for delaying balance problems and improving safety. Physiotherapists provide also counseling about the appropriate footwear, the orthotics tools if needed, and general recommendations to carers in each case and situation over time.

Exercise Exercise can alleviate pain and stiffness that appears throughout the disease due to postural abnormalities, rigidity, and slowness of movement. Maintaining flexibility and strength with low impact aerobic and balance exercises and stretches can contribute to improve the general situation of patients.

Speech and Swallowing Therapy

It is important to refer patients to speech and swallowing specialists even in the early phases of the disease.

Speech Hypophonic and slurred voice, coupled with the difficulties of eye contact and forgetfulness, can make communication difficult. Appropriate exercises and communication aids addressing these problems may help in that regard [79].

Swallowing Early detection and management of eating and swallowing difficulties is crucial to decrease the risk of aspiration pneumonia. The main factors contributing to dysphagia in PSP are the patients' tendency to overfill the mouth due to their impulsivity together with the slowness of movements and a weakened coughing reflex. Ancillary tests like videofluoroscopy will provide a formal evaluation of the principal problems and will monitor the risks. Making dietary and feeding modifications improve eating in most of cases during disease evolution. More invasive interventions like the decision to recommend percutaneous endoscopically placed gastrostomy should be made considering the general patient's context [16••].

Occupational Therapy

Occupational therapy provides an individualized assessment of patient's physical and cognitive difficulties and offers an adapted intervention according the family context and the patient's needs in each step along disease progression. Areas of particular importance include home safety (such as good lighting provided to compensate for visual difficulties) and assistance with bathing or transfers. Social workers have an invaluable role recognizing patient and carer necessities and giving advice for tackling daily living tasks [79].

Current and Future Trials

Disease-modifying drugs and neuroprotective interventions are the main objectives of ongoing PSP treatment research. According to current knowledge on PSP physiopathology, tau phosphorylation and aggregation, and microtubule and mitochondrial dysfunction are the principal targets of clinical trials [81]. Recently, tideglusib, an inhibitor of tau phosphorylation, was tested in a randomized double-blind, placebo-controlled trial with 146 PSP patients over a 1-year study period and

prove to be safe but ineffective over any motor, cognitive, daily activity, or quality of life outcome [82•]. However, a reduction in the progression of cortical atrophy evaluated by MRI volumetry was detected [82•]. Therapies directed to compensate the mitochondrial dysfunction and oxidative stress in PSP, such as coenzyme Q10, have already been studied showing modest benefit [83]. Despite the lack of clinically relevant efficacy of the previous studies, increasing knowledge on pathophysiology of the disease has generated a scientific rationale to keep developing new treatments that are currently under investigation [84].

Conclusions

PSP is a primary tauopathy that should be considered in the differential diagnosis of any parkinsonian syndrome affecting an adult individual, particularly when neurophthalmologic problems and imbalance and falls are prominent and early symptoms. The diagnosis of PSP is primarily based on clinical assessment and should be suspected when both the classical features and a broader spectrum of symptoms, including early freezing of gait, behavior, or language problems, are present.

Currently, there are no available reliable diagnostic markers for PSP but novel techniques especially tau PET imaging might have a central role in the diagnosis of this disease in the future.

The understanding of the etiological and pathophysiological mechanisms underlying tau deposition and cell loss will contribute to an earlier and better selection of patients for clinical trials and hopefully lead to the identification of effective disease-modifying drugs.

Authors' Contributions All authors contributed equally to the preparation and review of the manuscript and approved the version submitted to the journal.

Compliance with Ethical Standards

Conflict of Interest Alicia Garrido, Dolores Vilas, and Eduardo Tolosa declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors.

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- •• Of major importance

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