

Progressive supranuclear palsy

New concepts

Orlando Graziani Povoas Barsottini, André Carvalho Felício,
Camila Catherine Henriques de Aquino, José Luiz Pedroso

ABSTRACT

Progressive supranuclear palsy (PSP) is a distinctive form of neurodegenerative disease which affects the brainstem and basal ganglia. Patients present supranuclear ophthalmoplegia, postural instability and mild dementia. PSP is defined neuropathologically by the accumulation of neurofibrillary tangles in the subthalamic nucleus, pallidum, red nucleus, substantia nigra, striatum, pontine tegmentum, oculomotor nucleus, medulla and dentate nucleus. Over the last decade many lines of investigations have helped refine PSP in many aspects and it is the purpose of this review to help neurologists identify PSP, to better understand its pathophysiology and to provide a more focused, symptom-based treatment approach.

Key words: progressive supranuclear palsy, atypical parkinsonism, tauopathy.

Paralisia supranuclear progressiva: conceitos atuais

RESUMO

A paralisia supranuclear progressiva (PSP) é uma doença neurodegenerativa, que afeta principalmente o tronco cerebral e os núcleos da base. O quadro clínico se caracteriza por oftalmoparesia supranuclear, instabilidade postural e demência. Do ponto de vista anátomo-patológico, a PSP se caracteriza por acúmulo de emaranhados neurofibrilares no núcleo subtalâmico, globo pálido, núcleo rubro, substância negra, estriado, tegumento da ponte, núcleos oculomotores, bulbo e núcleo denteado. Nas últimas décadas, muitas linhas de pesquisa têm colaborado para redefinir a PSP em muitos aspectos. Os objetivos dessa revisão são auxiliar o neurologista geral na identificação da doença, compreensão da sua fisiopatologia, além de apresentar alternativas para seu tratamento sintomático.

Palavras-chave: paralisia supranuclear progressiva, parkinsonismo atípico, taupatias.

Progressive supranuclear palsy (PSP), also called Steele-Richardson-Olszewski syndrome, is a distinctive and probably under diagnosed neurodegenerative syndrome. It is the most common cause of degenerative parkinsonism after Parkinson's disease (PD) in most series^{1,2}. The "classic" PSP syndrome is characterized by gait disorder, ophthalmoparesis (down gaze palsy), cognitive dysfunction and parkinsonism, but a number of PSP phenotypic variants have been described recently^{1,2}. The prevalence of PSP is age-dependent and estimated at 6% to 10% that of PD, or 6-7 cases per 100.000. The disease has a peak onset at age 63 and no reported cases before

the age of 40. The correct diagnosis is usually made 3.6 to 4.9 years after the onset of clinical signs².

In the last few years, we have learned much about clinical, neuroimaging, molecular pathology and genetic of PSP. This syndrome is a tauopathy, with deposits of neurofibrillary tangles in the brain, which are mainly composed of hyperphosphorylated microtubule-associated protein tau. Tauopathies refers generally to neurodegenerative disorders with prominent tau pathology in the neuronal or glial cells. Tau is a microtubule-associated protein expressed in neurons, which in tauopathies forms abnormal, fibrillar structures of ag-

Correspondence

Orlando G.P. Barsottini
Av. Brigadeiro Luiz Antonio 4454
01402-002 São Paulo SP - Brasil
E-mail: orlandobarsottini@gmail.com

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Federal University of São Paulo, Department of Neurology and Neurosurgery, São Paulo SP, Brazil.

gregated, hyperphosphorylated and ubiquitinated tau^{3,4}. There are an increasing number of tauopathies described, including Alzheimer's disease, corticobasal degeneration, postencephalitic parkinsonism, Parkinson-dementia complex of Guam, Guadeloupien parkinsonism, frontotemporal dementia with parkinsonism linked to chromosome 17, Pick disease and Niemann-Pick disease type C²⁻⁴.

PSP is pathologically defined by the accumulation of tau protein and neuropil threads in the subthalamic nucleus, pallidum, red nucleus, substantia nigra, striatum, pontine tegmentum, oculomotor nucleus, medulla and dentate nucleus. Similar histopathological findings can be seen in other forms of tauopathies (ex. Guadeloupien parkinsonism), complicating the pathological diagnosis of PSP. The most specific features are star-shaped astrocytic tufts and neurofibrillary tangles that can be seen with light microscopy and that immunostain strongly with antibodies to tau^{3,4}.

In adult human brain tau has six alternatively spliced isoforms that are derived from a single gene. Disordered regulation of exon 10 splicing may therefore explain tau aggregation into neurofibrillary tangles in PSP and other tauopathies. The microtubule-binding domain contains either three 31 amino acids repeats (3R) or four 31 amino acids repeats (4R) and in normal adults brains the proportion of 3R and 4R tau are similar. In PSP the ratio of human brain tau isoforms is at least 3:1 in favor of 4R tau⁴.

PSP has traditionally been considered a sporadic disease, but its consistent genetic association with markers in chromosome 17q21 and reports of familial PSP cases suggest a familial aggregation. A linkage study on a large Spanish family with typical autosomal dominant PSP mapped a candidate gene in a 3.4-cM region in chromosome 1q31.1. Several families with PSP-like presentation have been described. MAPT (microtubule-associated protein tau) and PARK-2 mutations may cause a PSP-like phenotype. Mutations in the LRRK2 gene cause an autosomal dominant parkinsonism and may present as a PSP-like parkinsonism. Rajput and coworkers described a family, with parkinsonism and LRRK2 (G2019S mutation), where the affected proband had tau-immunopositive neurofibrillary tangles at autopsy rather than Lewy body disease⁵. Santos-Rebouças and colleagues reported the co-occurrence of sporadic parkinsonism and late-onset Alzheimer's disease in a Brazilian male with mutations in the LRRK2 gene⁶. The MAPT H1 haplotype is probably a genetic risk locus for PSP, but the haplotype H2 plays a protective role⁷⁻⁹.

Clinical subtypes

PSP is frequently misdiagnosed, most commonly as PD, and less than a half of patients with pathologically-proven PSP will have received the diagnosis of PSP at pre-



Fig 1. An illustrative image of a patient with progressive supranuclear palsy with 5 years of disease duration and retrocollis. Note that the patient is already in wheelchairs.

sentation. The National Institute of Neurological Disorders and Stroke/ Society for PSP (NINDS/SPSP) criteria detect only 50-70% of patients within 3 years of disease onset². Several clinical variants have recently been identified and a new nosology is emerging. These clinic-pathological variants can be separated by differences in their severity, regions of pathology involvement and clinical features.

Richardson's syndrome (RS): Starting after the age 40, this is the "classical" and more common picture of PSP. A lurching gait and unexplained fall backwards without loss of consciousness are the commonest presentations of PSP. Patients have more axial than appendicular rigidity and retrocollis is a common form of dystonia (Fig 1). Early ocular symptoms include blurred vision, slow saccades, photophobia, slowing of vertical saccades and involuntary eyelid closure due to blepharospasm. Vertical supranuclear gaze palsy is the definitive diagnostic feature but this commonly develops many years after disease onset. In RS, apathy, intellectual slowing and impairment of executive functions are also consistent findings, and may include the "applause sign", a test of impaired motor control leading to perseveration due to frontal dysfunction. Apraxia of eyelid opening, a slow and slurred speech and difficulties in swallowing are other typical features. Limb-kinetic apraxia, or difficulty performing simple gesture and the fine movements, although most often associated with corticobasal syndrome, also occurs in PSP. Most patients become dependent on others for care within 3 to 4 years of diagnosis and the common causes of death are aspiration pneumonia, primary neurogenic respiratory failure and pulmonary emboli. RS consists of diffuse tau pathology and the most severely affected regions are subthalamic nucleus and substantia nigra^{3,4,7,10}.

PSP-parkinsonism (PSP-P): The PSP-P phenotype

comprises about one-third of the cases and is a more indolent form with a PD-like presentation. The features include bradykinesia and rigidity, tremor, asymmetric onset, normal eye movements and a clear, but transient levodopa response. Parkinsonism dominates the early clinical picture and a jerky postural tremor and even a 4-6 HZ rest tremor are common in PSP-P patients. Falls and cognitive impairment occur later in PSP-P than in RS. These syndromes can be distinguished by their clinical pictures in the first 2 years but there is a clinical overlap, and after 6 years of follow up, the clinical phenomenology might become similar. The patients with PSP-P have less severe tau pathology than those with RS^{3,7,10}.

PSP-pure akinesia with gait freezing (PSP-PAGF):

This PSP-phenotype is highly predictive of PSP-tau pathology. The clinical picture is a syndrome with progressive gait disturbance with start hesitation and subsequent freezing of gait, speech or writing, without tremor, rigidity, dementia or eye movement abnormality during the first 5 years of the disease. The classical PSP features may be delayed or even absent. The isolated gait freezing may also appear in several other diseases including subcortical white matter ischemia, PD and dementia with Lewy bodies. The tau-pathology in these individuals is described as pallido-nigro-lusial. The restricted distribution of pathology in PAGF is thought to be the cause of clinical differences and better prognosis^{3,10}.

PSP-progressive non-fluent aphasia (PSP-PNFA):

The clinical presentation is consistent with non-fluent spontaneous speech, hesitancy, phonemic errors and agrammatism. The neuropsychological profile in these cases is similar to other patients with PNFA. However, patients with PSP-PNFA have more marked reduction in propositional speech, fewer speech errors and less marked impairment of literacy skills. Moreover, there are more severe associated deficits of episodic memory and praxis. These PSP-PNFA cases have less prominent midbrain atrophy but more marked prefrontal atrophy. PNFA fits within the spectrum of frontotemporal dementia but in a small case series patients with PNFA had underlying PSP-tau pathology^{10,11}.

PSP-cerebellar: Kanazawa and coworkers recently described the cerebellar involvement in PSP. They analyzed 22 consecutive Japanese patients with pathologically proven PSP and 3 patients developed cerebellar ataxia as the initial and main symptom. All the patients with cerebellar ataxia exhibited more neuronal loss with gliosis and higher densities of coiled bodies in the cerebellar dentate nucleus than those without cerebellar ataxia¹².

PSP-corticobasal syndrome (PSP-CBS): Is characterized by progressive, asymmetric dyspraxia, cortical sensory loss, including an alien limb, jerky dystonia of the limb and bradykinesia that is unresponsive to levodopa. Several studies showed that only 50% of patients with

CBS have pathology that is typical of corticobasal degeneration and the PSP-CBS seems to be a rare presentation of PSP-tau pathology. For instance, in neuropathologically studied cases, a "corticobasal syndrome" was observed in PSP, Pick disease, Alzheimer's disease, frontotemporal dementia with parkinsonism and frontotemporal lobar degeneration with ubiquitin-positive inclusions^{3,7,10}.

Clinical criteria for the diagnosis of PSP

There are many proposed clinical criteria for PSP and the majority of them have a similar characteristic: high specificity and low sensitivity. Although the classic PSP syndrome presents with clear clinical signs in later stages, the clinical variants recently described are less distinctive, and many patients with PSP are initially thought to have PD, multiple system atrophy, Lewy body disease and other sporadic primary tauopathies. Maybe this fact explains the high specificity and low sensibility of clinical criteria for PSP¹⁰.

The NINDS/SPSP clinical diagnostic criterion (Table 1) was compiled to reliably identify patients for clinical research who had underlying PSP-tau pathology¹³. This specific criteria state that early falls due to postural instability and supranuclear gaze palsy or slowed vertical saccades are the most helpful defining clinical features. When these two physical signs are present, it is extremely useful in differentiating between PSP and PD. In spite of this, the absence of falls and gaze palsies in many patients do not exclude the diagnosis of PSP¹⁰.

In accord to some studies, the application of current available operational criteria, including those proposed by the NINDS/SPSP, fails to improve the accuracy of final diagnosis by neurologists. Although supranuclear gaze palsy, prominent early postural instability with falls, and frontal behavioral or cognitive deficits are the cardinal features of PSP, all may occur in other neurodegenerative disorders, potentially leading to some false-positive diagnoses. Early differentiation between PSP and other neurodegenerative movement disorder syndromes or dementias can be important for a number of reasons, including foreseeing differences in the natural course, choosing appropriate pharmacologic approaches, and avoiding inclusion of misdiagnosed patients in treatment trials¹⁴⁻¹⁶.

Biomarkers for the diagnosis of PSP

One of the key issues in the management of neurodegenerative disorders is the requirement for reliable biomarkers to increase diagnostic accuracy. In the last few years, several biologic markers have been tested, but no specific biologic tool for early PSP detection is available. Actually, all the proposed biomarkers showed an individually considerable overlap between PSP and other neurodegenerative disorders. Several studies aimed at evaluat-

Table. NINDS-SPSP clinical criteria for the diagnosis of PSP.

PSP	Mandatory inclusion criteria	Mandatory exclusion criteria	Supportive criteria
Possible	<p>Gradually progressive disorder</p> <p>Onset at age 40 or later</p> <p>Either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset</p> <p>No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria</p>	<p>Recent history of encephalitis</p> <p>Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy</p> <p>Hallucinations or delusions unrelated to dopaminergic therapy</p> <p>Cortical dementia of Alzheimer's type (severe amnesia and aphasia or agnosia, according to NINCDS-ADRA criteria)</p> <p>Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances)</p>	<p>Symmetric akinesia or rigidity, proximal more than distal</p> <p>Abnormal neck posture, especially retrocollis</p> <p>Poor or absent response of parkinsonism to levodopa therapy</p> <p>Early dysphagia and dysarthria</p> <p>Early onset cognitive impairment including at least two of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs</p>
Probable	<p>Gradually progressive disorder</p> <p>Onset at age 40 or later</p> <p>Vertical (upward or downward gaze) supranuclear palsy and prominent postural instability with falls in the first year of disease onset</p> <p>No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria</p>	<p>Severe, asymmetric parkinsonian signs (i.e., bradykinesia)</p> <p>Neuroradiologic evidence of relevant structural abnormality (i.e. basal ganglia or brainstem infarcts, lobar atrophy)</p> <p>Whipple's disease, confirmed by polymerase chain reaction, if indicated</p>	
Definite	<p>Clinically probable or possible PSP and histopathology evidence of typical PSP</p>		

PSP: Progressive Supra Nuclear Palsy; NINDS-SPSP: National Institute of Neurological Disorders and Stroke Society for Progressive Supra Nuclear Palsy; NINCDS-ADRA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

ing tau levels in cerebral spinal fluid (CSF) in PSP compared with patients affected by either other tau-related disorders or other neurodegenerative extrapyramidal syndromes, such as synucleinopathies^{14,17}. In CSF, extended (55 kDa) and truncated (33 kDa) tau forms have been previously recognized, and the tau 33 kDa/55 kDa ratio has been found significantly reduced in PSP in comparison with other neurodegenerative disorders¹⁴.

Moreover, recent data have shown that tau protein burden, type and ultrastructure in CSF and in pathological analyses are different between the various subtypes of PSP described above, contributing not only to separate the PSP phenotypes clinically, but also affecting the severity and distribution of the histopathological lesions¹⁷.

Brain imaging

As aforementioned, the diagnosis of PSP relies mainly on clinical data, and misdiagnosis can be frequent, especially in the early disease stages¹⁸. According to a recent study it is estimated that at least 1 in every 20 patients taking medication for PD is misdiagnosed¹⁹, and these data may be even worse taking into account PSP, which is much less frequent than PD, and under diagnosed.

Nevertheless, conventional structural and functional brain imaging may help not only in the differential diagnosis of PSP between PD and other atypical forms of parkinsonism [multiple system atrophy (MSA) and CBD], but also aid to understand the neurobiological basis of this neurodegenerative disorder²⁰.

Conventional structural brain MRI

Conventional structural brain MRI can help on the differentiation between PSP and PD, and other atypical parkinsonian subtypes. Using an automated computer differential classification in parkinsonian syndromes via pattern analysis on MRI, Dushesne and coworkers obtained 91% accuracy (agreement with long-term clinical follow-up), 88% specificity, and 93% sensitivity in the diagnosis of PSP²¹. In the paper by Cosottini and coworkers, assessing midbrain atrophy through morphometric measurements in patients with clinically diagnosed PSP they found that the midbrain area had the highest diagnostic accuracy in distinguishing between PSP and other conditions, with a sensitivity of 100% and specificity of 90.5%²².

The following brain MRI regions should be carefully analyzed in the evaluation of patients with suspected PSP, and further details on the measurement procedures can be found elsewhere²³: [1] Presence or not of enlargement of the third ventricle; [2] Anteroposterior diameter of the midbrain; [3] Quadrigeminal plate thickness; [4] Interpeduncular angles; [5] Brainstem volumetry; [6] Volumetry of the caudate nucleus and putamen; [7] Presence or not of hypersignal in the periaqueductal region.

We make available illustrative brain MRI images of a patient with PSP (Fig 2).

Functional neuroimaging

Functional neuroimaging provides a unique *in vivo* opportunity to study the neurobiological abnormalities that takes place in neurodegenerative disorders assessing cerebral blood flow, patterns of regional glucose metabolism and dopaminergic binding sites. The rationale of functional neuroimaging consists of the radioligand with high affinity to a particular binding site. Further details on this methodology can also be found elsewhere²⁴.

Regional cerebral blood flow (rCBF)

SPECT imaging techniques using the technetium-based radioligand ECD showed hypoperfusion of the anterior cingulate and medial frontal cortex in PSP patients as compared to controls and PD. In PSP patients the rCBF impairment extended to the pre-supplementary motor area and prefrontal cortex, areas involved in executive function and motor networks. Compared with PSP patients, PD patients showed a mild rCBF decrease in associative visual areas which could be related to the known impairment of visuospatial function. Therefore, the anterior cingulate hypoperfusion seems to be an early, distinct brain abnormality in PSP as compared with PD²⁵.

Glucose metabolism

Using PET with [¹⁸F]-FDG, a characteristic feature among the PSP group is brain glucose hypometabolism along the midline of the frontal regions and in the brainstem, notably midbrain. Decreased metabolism was also noted in the superior frontal and insular areas, and in the caudate nucleus²⁶. Interestingly, these abnormalities seen in PSP also occur, but to a lesser extent, in PSP-PAGE, suggesting that both diseases are actually part of the same spectrum²⁷.

Molecular imaging (dopaminergic binding sites)

Dopaminergic binding sites can be evaluated using SPECT and PET radiotracers that selectively bind to pre and postsynaptic targets. Pre-synaptic binding sites that are studied in degenerative parkinsonisms consist of the dopamine transporter (DAT; SPECT [^{99m}Tc]-TRODAT-1, [¹²³I]-β-CIT, [¹²³I]-FP-CIT or PET [¹¹C]-MP), vesicular monoamine transporter (VMAT2; PET [¹¹C]-DTBZ), and dopa-decarboxylase activity (PET [¹⁸F]-FDOPA). Overall, they point toward the integrity of pre-synaptic



Fig 2. Brain MRI illustrative images of a patient with progressive supranuclear palsy [A] Enlargement of the third ventricle (coronal plan; T2-weighted); [B] Internal-1 and external-2 interpeduncular angles showing midbrain atrophy (axial plan; T1-weighted); [C] Quadrigeminal thickness showing atrophy (sagittal plan; T1-weighted); [D] Periaqueductal hypersignal (sagittal plan; FLAIR).

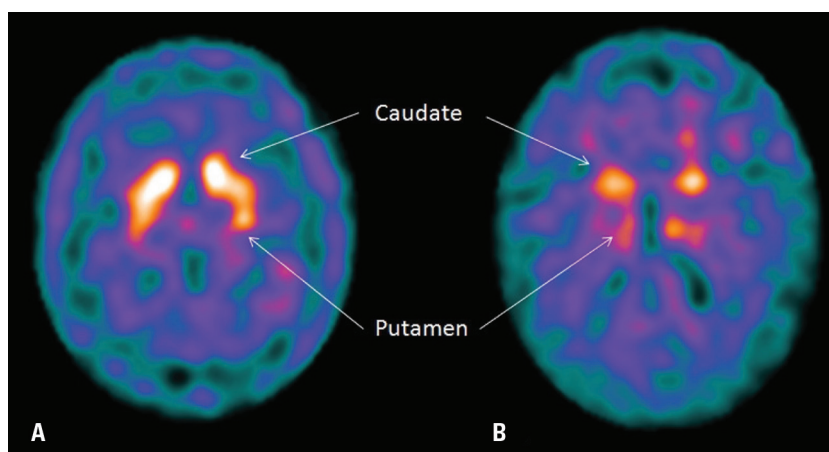


Fig 3. An illustrative brain SPECT imaging (axial plane) using a dopamine transporter ligand (TRODAT-1) of a 65-year-old male healthy subject [A] matched with a 61-year-old male patient with progressive supranuclear palsy with 5 years of disease duration [B]. The Figure shows a marked decreased uptake of the radioligand in both caudate and putamen (arrows) as compared to the control.

dopaminergic terminals. On the other hand, we can also study post-synaptic receptors (D2 receptors) using specific radioligands either for SPECT ($[^{123}\text{I}]$ -IBZM or IBF) or PET ($[^{11}\text{C}]$ -Raclopride)²⁴.

In general, the posterior putamen is useful in differentiating parkinsonism from controls but is not helpful in further discriminating between PD, multiple system atrophy, and PSP. However, D2 receptors may help further differentiate between parkinsonian disorders, since drug-naïve PD and PSP patients have normal D2 receptor availability, while MSA patients show reduced D2 receptor availability. Therefore, posterior putamen D2 binding above the normal range of healthy controls in a parkinsonian patient before dopaminergic treatment suggests a diagnosis of PD or PSP, whereas a result below the normal range suggests an alternative diagnosis, such as MSA²⁸.

In PD a distinctive neurodegenerative pattern of dopamine cell loss can be assessed using *in vivo* molecular imaging, with more pronounced involvement of the posterior part of the putamen contralateral to the most affected side, and lesser involvement of the caudate ipsilateral to the most affected limb²⁴. On the contrary, in PSP DAT imaging (putamen-to-caudate ratio) suggests a more uniform involvement of dopamine nerve terminals in both caudate nucleus and putamen²⁹. In Fig 3 we highlight an illustrative brain SPECT imaging using TRODAT-1 as the radiopharmaceutical in a PSP-P subject matched for age and gender to a healthy control subject.

Treatment of PSP

The “multisystem” pathology of this degenerative disease, as mentioned above, predicts the challenge of treatment⁷. The scope of this section is reviewing pharmaco-

logical therapies, future disease modifying strategies, surgical implants and palliative methods.

Symptomatic treatment

Although parkinsonism is a characteristic feature in PSP, it is often distinct from that typically seen in PD, not only in clinical picture, but also in levodopa (LD) responsiveness. This is explained by the pathology distribution of PSP, involving subthalamic nucleus, pallidum, substantia nigra, striatum, and other regions in brainstem^{3,4}.

Poor or absent response to LD has been considered one of the diagnostic criteria for PSP, while marked or prolonged LD benefit has been included as an exclusion criteria³⁰. Most studies shows that LD benefit, if exists, is minimal and transient. A review of the literature identified an approximate response rate of 26 percent³¹, and the average dosage administrated on different trials is around 500 mg-1 g/day of LD with a dopa decarboxylase inhibitor.

Responsiveness to LD is probable different between subtypes of PSP, being poor in classical RS, and initially moderate in PSP-P³². Considering side effects, LD-induced dyskinesias seems to be rare, however, some can develop worsening of motor features and dystonia³³. A retrospective study involving 12 autopsy-confirmed cases of PSP, found a positive response in four of 11 patients using LD, and in two of 6 using dopamine agonist. LD-induced dyskinesia was present in only one LD responsive patient³⁴.

The absence of benefit with pramipexole therapy has been showed in a study involving six patients, in which none responded significantly, and three presented adverse effects as hallucinations and worsening of motor symptoms³⁵.

Drugs directed to systems other than dopaminergic, such as serotonergic, noradrenergic, and cholinergic, were also tried in PSP. Serotonergic drugs, such as selective serotonin reuptake inhibitors, 5-hydroxytryptophan, and methysergide have no confirmed benefit in PSP^{31,33}, neither have cholinergic drugs, such as AChE inhibitors, and muscarinic agonists³⁶. Concerning cognitive deficit in PSP, rivastigmine lead to a slight improvement in specific function in a small series with five cases³⁷. Concerning noradrenergic drugs, idazoxan, a α -2 antagonist was found to improve four of seven patients, however efaroxan, a more potent α -2 antagonist did not lead any improvement of symptoms in a placebo controlled trial^{38,39}.

Tricyclic antidepressants improved gait and rigidity in three of four patients in a small double-blind trial⁴⁰, on the other hand, these drugs have a high risk/benefit ratio in population with PSP, according to a published review⁴¹. In spite of this, nortryptiline seems to be useful as an option for depression in this population, but it lacks randomized controlled data that support this observation⁴².

Following the hypothesis that GABA (gamma amino butyric acid) is involved in the pathogenesis of PSP, due to loss of interneurons containing benzodiazepine/GABA receptors, zolpidem, a GABA agonist of the benzodiazepine subtype receptor BZ1, was administered to isolated cases and small groups of patients with PSP. These works showed a motor benefit, including in eye movements during therapy. Further studies with this drug are necessary, to elucidate if this benefit is transient or sustained, as the ones already done found different outcomes^{43,44}. Another GABAergic drug, gabapentin has failed in ameliorating parkinsonism in PSP, however it caused some effect in oculomotor reflex⁴⁵.

As presented here, until this time, there is no evidence enough to recommend a specific symptomatic treatment in PSP. In practice, physicians prescribe symptomatic drugs empirically and individualized in each patient.

Botulinum toxin

According to our previous published experience the overall frequency of dystonia in Brazilian patients with atypical parkinsonian syndromes is of 50%⁴⁶. Therefore, botulinum toxin may be helpful in PSP for treating dystonia, such as retrocollis (Fig 1), and apraxia of eyelid opening, reducing disability provoked by these symptoms³⁶. This must be used with cautions to avoid worsening of dysphagia.

Disease modifying therapies

The Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study randomized PSP and MSA patients for receiving riluzole, evaluating survival as primary outcome. This drug did not have a sig-

nificant effect on survival neither in the rate of functional deterioration⁴⁷.

Development of future therapies will come from a greater understanding of PSP and other tauopathies pathophysiology. Glycogen synthase kinase 3 (GSK-3) may play a role in tau diseases because it can phosphorylate tau *in vivo*, and inhibition of this enzyme in transgenic mice and in drosophila leads to functional improvement^{48,49}. Lithium seems to be a GSK-3 inhibitor in mice with increased activity of this enzyme, preventing neuropathologic changes⁵⁰.

Several studies point toward: manipulation of splicing regulation by RNA stem-loops reducing 4-repeat tau production; inhibition of tissue transglutaminase (TGase), an enzyme that cross-links substrate proteins into insoluble form potentially initiating neurofibrillary tangles formation; and use of trophic factors³⁶, in order to find a disease modify therapy.

Surgical treatment

As deep brain stimulation (DBS) surgery for PD requires response to LD most patients with PSP do not fulfill this criterion. A published case that was initially diagnosed as PD responsive to LD, but later developed atypical signs compatible with PSP-P, presented benefit with subthalamic nucleus DBS in ameliorating parkinsonism⁵¹.

Palliative methods

There are no evidence-based data for palliative treatment in PSP, however these recommendations are based on good practice and clinical experience. A multidisciplinary team is essential in management of PSP³⁶. Physiotherapist, speech, language, and occupational therapists, and dietitians should be involved in management of treatment.

According to development of symptoms, different palliative methods should be recommended. Physicians must be aware to predict complications before their occurrence. To prevent falls, when postural instability is present, weighted walkers and physiotherapist may be necessary. For patients with dysphagia, thickeners, speech therapist and/or percutaneous endoscopic gastrostomy will be useful to avoid nutrition deterioration and aspiration pneumonia. To ocular phenomena such as decreased rate of blinking, vertical palsy and apraxia of eyelid opening, it can be used artificial tears, prism glasses and botulinum toxin can be used. In the case of excessive drooling, topical or systemic anticholinergic drugs may be used with caution, or either botulinum toxin⁵².

CONCLUSIONS

Recently, an emerging knowledge in PSP physiopa-

thology, diagnosis and treatment has become available to physicians, but despite all these information PSP still remain an under diagnosed disorder. Therefore, we should always be careful in the evaluation of patients with parkinsonian disorders and keep in mind the most important “red flags” that may point out to PSP or other atypical forms of parkinsonism. These main “red flags” that we should take into consideration in clinical practice are: supranuclear gaze palsy, early falls, and unresponsiveness to LD. We should also notice that different PSP-phenotypes other than the “classic” and PSP-P may lead to misdiagnosis, and recently we have also been challenged with a PSP-cerebellar phenotype, adding more difficulty to PSP diagnosis.

Conventional structural MRI is very helpful, improving diagnosis accuracy, and some particular areas especially of the cerebellum-brain stem region should be thoroughly assessed. Caution, however, should be considered in patients with recent disease onset since these characteristic brain MRI alterations may not be evident.

Functional neuroimaging may also help, but yet its main role is much more in elucidating *in vivo* PSP-pathology, for instance, demonstrating regional cerebral glucose hypometabolism in the midline region of the frontal lobe and brainstem, particularly midbrain. Of note, molecular imaging target to dopaminergic binding sites demonstrate a more extensive dopamine cell loss than in PD. Finally, promising new therapies are emerging to at least improve survival rates in PSP, but we are still far from a more effective treatment strategy. Therefore, symptomatic therapy and palliative support is advocated. In the meanwhile, we take the opportunity to reinforce PSP diagnosis, which is the first step for future, evidence-based, disease-modifying therapies.

REFERENCES

- Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* 1964;10:333-359.
- Santacruz P, Uttl B, Litvan I, Grafman J. Progressive supranuclear palsy: a survey of the disease course. *Neurology* 1998;50:1637-1647.
- Lubarsky M, Juncos JL. Progressive supranuclear palsy: a current review. *The Neurologist* 2008;14:79-88.
- Morris HR, Wood NW, Lees AJ. Progressive supranuclear palsy (Steele-Richardson-Olszewski disease). *Postgrad Med J* 1999;75:579-584.
- Rajput A, Dickson DW, Robinson CA, et al. Parkinsonism, Lrrk2 G2019S, and tau neuropathology. *Neurology* 2006;67:1506-1508.
- Santos-Rebouças CB, Abdalla CB, Baldi FJR, et al. Co-occurrence of sporadic parkinsonism and late-onset Alzheimer's disease in a Brazilian male with the LRRK2 p.G2019S mutation. *Genet Test* 2008;2:471-473.
- Ludolph AC, Kassubek J, Landwehrmeyer BG, et al. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers and treatment options. *Eur J Neurol* 2009;16:297-309.
- Pastor P. Familial neurodegeneration in progressive supranuclear palsy. More frequent than expected? *Neurology* 2009;73:86-87.
- Ros R, Gomez Garre P, Hirano M, et al. Genetic linkage of autosomal dominant progressive supranuclear palsy to 1q31.1. *Ann Neurol* 2005;57:634-641.
- Williams D, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol* 2009;8:270-279.
- Rohrer JD, Paviour D, Bronstein AM, et al. Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis. *Mov Disord* 2010; in press.
- Kanazawa M, Shimohata T, Toyoshima Y, et al. Cerebellar involvement in progressive supranuclear palsy: a clinicopathological study. *Mov Disord* 2009;24:1312-1218.
- Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. *Neurology* 1996;47:1-9.
- Borroni B, Malinverno M, Gardoni F, et al. Tau forms in CSF as a reliable biomarker for progressive supranuclear palsy. *Neurology* 2008;71:1796-1803.
- Osaki Y, Ben-Shlomo Y, Lees AJ, et al. Accuracy of clinical diagnosis of progressive supranuclear palsy. *Mov Disord* 2004;19:181-189.
- Sakamoto R, Tsuchiya K, Mimura M. Clinical heterogeneity in progressive supranuclear palsy: problems of clinical diagnostic criteria of NINDS-SPSP in a retrospective study of seven Japanese autopsy cases. *Neuropathology* 2009;29:1-12.
- Williams DR, Holton JL, Strand C, et al. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. *Brain* 2007;130:1566-1576.
- Seppi K, Schocke MF. An update on conventional and advanced magnetic resonance imaging techniques in the differential diagnosis of neurodegenerative parkinsonism. *Curr Opin Neurol* 2005;18:370-375.
- Newman EJ, Breen K, Patterson J, et al. Accuracy of Parkinson's disease diagnosis in 610 general practice patients in the West of Scotland. *Mov Disord* 2009;24:2379-2385.
- Seppi K. MRI for the differential diagnosis of neurodegenerative parkinsonism in clinical practice. *Parkinsonism Relat Disord* 2007;3(Suppl):S400-S405.
- Duchesne S, Rolland Y, Vêrin M. Automated computer differential classification in Parkinsonian syndromes via pattern analysis on MRI. *Acad Radiol* 2009;16:61-70.
- Cosottini M, Ceravolo R, Faggioni L, et al. Assessment of midbrain atrophy in patients with progressive supranuclear palsy with routine magnetic resonance imaging. *Acta Neurol Scand* 2007;116:37-42.
- Barsottini OG, Ferraz HB, Maia AC Jr, et al. Differentiation of Parkinson's disease and progressive supranuclear palsy with magnetic resonance imaging: the first Brazilian experience. *Parkinsonism Relat Disord* 2007;13:389-393.
- Felicio AC, Shih MC, Godeiro-Junior C, et al. Molecular imaging studies in Parkinson disease: reducing diagnostic uncertainty. *Neurologist* 2009;15:6-16.
- Varrone A, Pagani M, Salvatore E, et al. Identification by [^{99m}Tc]ECD SPECT of anterior cingulate hypoperfusion in progressive supranuclear palsy, in comparison with Parkinson's disease. *Eur J Nucl Med Mol Imaging* 2007;34:1071-1081.
- Eckert T, Barnes A, Dhawan V, et al. FDG PET in the differential diagnosis of parkinsonian disorders. *Neuroimage* 2005;26:912-21.
- Park HK, Kim JS, Im KC, et al. Functional brain imaging in pure akinesia with gait freezing: [¹⁸F] FDG PET and [¹⁸F] FP-CIT PET analyses. *Mov Disord* 2009;24:237-245.
- Kim YJ, Ichise M, Ballinger JR, et al. Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP. *Mov Disord* 2002;17:303-312.
- Antonini A, Benti R, De Notaris R, et al. [¹²³I]-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Neurol Sci* 2003;24:149-50.
- Litvan I, Bhatia KA, Burn DJ, et al. Movement Disorder Society Scientific Issues Committee Report. SIC task force appraisal of clinical diagnostic criteria for parkinsonian disorders. *Mov Disord* 2003;18:467-486.
- Lang AE. Treatment of progressive supranuclear palsy and corticobasal degeneration. *Mov Disord* 2005;20:583-591.
- Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain* 2005;128:1247-1258.
- Constantinescu R, Richard I, Kurlan R. Levodopa responsiveness in disorders with parkinsonism: a review of literature. *Mov Disord* 2007;22:2141-2148.
- Kompoliti K, Goetz CG, Litvan I. Pharmacological therapy in progressive supranuclear palsy. *Arch Neurol* 1998;55:1099-1102.

35. Weiner WJ, Minagar A, Shulman LM. Pramipexole in progressive supranuclear palsy. *Neurology* 1999;52:873-874.
36. Burn DJ, Warren NM. Toward future therapies in progressive supranuclear palsy. *Mov Disord* 2005;20:S92-S98.
37. Liepelt I, Gaenslen A, Godau J, et al. Rivastigmine for the treatment of dementia in patients with progressive supranuclear palsy: clinical observations as a basis for power calculations and safety analysis. *Alzheimers Dement* 2010;6:70-74.
38. Ghika J, Tennis M, Hoffman E, et al. Idazoxan treatment in progressive supranuclear palsy. *Neurology* 1991;41:986-991.
39. Rascol O, Sieradzan K, Peyro SP, et al. Efaroxan, an alpha-2 antagonist, in the treatment of progressive supranuclear palsy. *Mov Disord* 1998;13: 673-676.
40. Newman GC. Treatment of progressive supranuclear palsy with tricyclic antidepressants. *Neurology* 1985;35:1189-1193.
41. Nieforth KA, Golbe LI. Retrospective study of drug response in 87 patients with progressive supranuclear palsy. *Clin Neuropharmacol* 1993;16: 338-346.
42. Tamai S, Almeida OP. Nortriptyline for the treatment of depression in progressive supranuclear palsy. *J Am Geriatr Soc* 1997;45:1033-1034.
43. Cotter C, Armytage T, Crimmins D. The use of zolpidem in the treatment of progressive supranuclear palsy. *J Clin Neurosci* 2010; in press.
44. Mayr B, Bonelli RM, Niederwieser G, et al. Zolpidem in progressive supranuclear palsy. *Eur J Neurol* 2002;9:184-185.
45. Poujois A, Vidailhet M, Trocetto JM, Bourdain F, Gaymard B, Rivaud-Péchéux S. Effect of gabapentin on oculomotor control and parkinsonism in patients with progressive supranuclear palsy. *Eur J Neurol* 2007;14:1060-1062.
46. Godeiro-Junior C, Felício AC, Barsottini OG, et al. Clinical features of dystonia in atypical parkinsonism. *Arq Neuropsiquiatr* 2008;66:800-804.
47. Bensimon G, Ludolph A, Agid Y. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain* 2009;132: 156-171.
48. Mudher A, Shepherd D, Newman TA, et al. GSK-3beta inhibition reverses axonal transport defects and behavioural phenotypes in *Drosophila*. *Mol Psychiatry* 2004;9:522-530.
49. Engel T, Hernandez F, Avila J, Lucas JJ. Full reversal of Alzheimer's disease-like phenotype in a mouse model with conditional overexpression of glycogen synthase kinase-3. *J Neurosci* 2006;26:5083-5090.
50. Engel T, Goni-Oliver P, Lucas JJ, Avila J, Hernandez F. Chronic lithium administration to FTDP-17 tau and GSK-3b overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but preformed neurofibrillary tangles do not revert. *J Neurochem* 2006;99:1445-1455.
51. Bergmann KJ, Salak VL. Subthalamic stimulation improves levodopa responsive symptoms in a case of progressive supranuclear palsy. *Parkinsonism Relat Disord* 2008;14:348-352.
52. Litvan I. Diagnosis and management of progressive supranuclear palsy. *Semin Neurol* 2001;21:41-48.