



Progressive Supranuclear Palsy: New Diagnostic and Therapeutic Strategies

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Abstract

Progressive Supranuclear Palsy (PSP) is a Parkinson-plus syndrome associated with a variety of different clinical presentations. We describe the clinical and pathological features of the 7 major phenotypes of PSP in addition to new information about the genetic causes of PSP. We also discuss useful imaging tools, and review various management strategies. The classic form of PSP (PSP-Richardson syndrome) is more likely to be associated with postural instability, vertical gaze palsy, akinesia and cognitive changes, compared to the milder variants of PSP. There are 6 other variants of PSP besides PSP-RS, including PSP-parkinsonism, which can imitate Parkinson disease and can respond to levodopa for the first 2-3 years. The Microtubular Associated Protein Tau (MAPT) gene has a larger influence in PSP-RS than in PSP-parkinsonism. The rarer cortical variants of PSP (PSP-progressive non-fluent aphasia, PSP-frontal temporal dementia and PSP-cortical basal syndrome) can be mistaken for other neurodegenerative diseases, since the classic PSP signs may not appear for months to years after the cortical signs present themselves. MRI and Diffusion Tensor Imaging (DTI) scans are useful tools in assessing patients with signs of PSP. There is currently no disease modifying therapy available for PSP, but many signs of PSP can be managed with symptomatic treatments and various non-pharmacologic approaches.

History of PSP

In 1964, Steele, Richardson and Olszewski described a clinical syndrome in 8 patients, which involved supranuclear gaze palsy, slowed dysarthric speech, bradykinesia, pseudobulbar palsy and progressive axial rigidity [1]. It was characterized pathologically by neuronal degeneration of the basal ganglia, brainstem and cerebellum. They named it "Progressive Supranuclear Palsy" (PSP). Multiple studies have since established PSP as a separate entity that can be differentiated from similar neurodegenerative disorders, such as Parkinson Disease (PD), Frontotemporal Dementia (FTD), Dementia with Lewy Bodies (DLB), Corticobasal Syndrome (CBS), and Multiple System Atrophy (MSA).

Clinical Phenotypes of PSP

According to Williams and colleagues [2], most of the 8 PSP cases originally described in 1964 would probably be defined today as having the "PSP-Richardson Syndrome" (PSP-RS). According to the new revised diagnostic criteria of Hoglinger and others [3], most of the 8 original cases had features of "probable PSP" since they demonstrated impairment in at least 3 of the 4 functional domains that have been shown to be predictive of PSP (ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction). Several recent clinical and pathological studies have led to the recognition that there are at least six other phenotypes of PSP, where the clinical distinctions are apparent within the first 2 years of presentation (Table 1). Recognizing these early differences is important for the sake of initiating proper medical therapy and for advising families about the prognosis of this disease.

Richardson syndrome (PSP-RS)

There is still some disagreement about the relative prevalence of PSP-RS, but it represented 54% of 103 autopsy-proven PSP cases in one series [2]. PSP-RS usually presents with frequent unexplained falls (usually backwards) and prominent postural instability. Supranuclear palsy affecting vertical gaze is found in about 80% of PSP-RS cases at onset. One longitudinal study demonstrated that PSP-RS patients had a median age of onset of 65.9 years and a median survival time of 6.8 years [4]. Several cognitive and behavioral features have been shown to be more prevalent among early PSP

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Received Date: 31 May 2018

Accepted Date: 28 Jun 2018

Published Date: 05 Jul 2018

Citation:

Lichter D, Koriesh A, Kapoor N, Hershey L. Progressive Supranuclear Palsy: New Diagnostic and Therapeutic Strategies. *Am J Gerontol Geriatr*. 2018; 1(2): 1007.

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Table 1: Clinical phenotypes of PSP and their presenting symptoms.

Phenotype	Presenting symptom	Symmetry	Gait instability and falls	Cognitive abnormalities	Response to levodopa	Reference
PSP-RS	frequent unexplained falls	Symmetrical	Early	Early	Poor	[1,2,4,5]
PSP-P	Bradykinesia and tremors	Asymmetrical	Later	Later	Initial moderate response for 2-3 years	[2,4,6]
PSP-PAGF	Gait unsteadiness and freezing	Symmetrical	Early	Later	Poor	[7]
PSP-PNFA	Non-fluent aphasia	Symmetrical	Later	Later	Poor	[8]
PSP-bvFTD	Behavioral and personality changes	Symmetrical	Later	Early	Poor	[9]
PSP-CBS	Apraxia – non-fluent aphasia – alien limb	Asymmetrical	Later	Early	Poor	[10]
PSP-C	Ataxia	Symmetrical	Variable	Variable	Poor	[11]

Abbreviations: PSP = Progressive Supranuclear Palsy; RS = Richardson Syndrome; P = Parkinsonism; PAGF = Pure Akinesia with Gait Freezing; PNFA = Progressive Non-Fluent Aphasia; bvFTD = Behavioral Variant Frontotemporal Dementia; CBS = Corticobasal Syndrome; C = Cerebellar Phenotype.

patients than among early PD patients [5]. For example, logopenia, apathy and executive dysfunction were found in most early PSP-RS patients (95%, 92% and 81%, respectively), while fewer early PD patients had these impairments (38%, 44% and 31%).

PSP-Parkinsonism (PSP-P)

PSP-P is the second most common clinical phenotype of PSP, accounting for about 33% of cases [2]. Its onset is characterized by asymmetrical rest tremors and bradykinesia. In comparison to PSP-RS, gaze palsy and cognitive impairment may be absent in the early stages. Patients with PSP-P usually show a moderately good response to levodopa that lasts for the first 2-3 years. The initial response to levodopa and the asymmetrical parkinsonism at onset make it a challenge to differentiate PSP-P from PD in the early stages. After 3-4 years, PD patients are more likely to develop drug-induced dyskinesias and autonomic dysfunction, while these are less commonly seen in PSP-P [6]. Compared to PSP-RS, symptoms progress more slowly in PSP-P, where the median survival is 11.2 years [4].

Pure akinesia with gait freezing (PSP-PAGF)

These patients present with a gait disturbance that remains isolated for at least the first two years [7]. The slowness and unsteadiness gradually progress to a start hesitation with gait freezing, as well as a stuttering, or stammering of speech. Other features may include facial hypomimia, hypophonia, and micrographia. The absence of eye movement and cognitive problems in the first 5 years are keys that differentiate PSP-PAGF from PSP-RS. Lack of an asymmetrical tremor and response to levodopa are features that distinguish PSP-PAGF from PSP-P. Absence of significant subcortical white matter change distinguishes PSP-PAGF from vascular parkinsonism. Lack of urinary incontinence distinguishes PSP-PAGF from Normal Pressure Hydrocephalus (NPH). The median disease duration for PSP-PAGF is 11 years, similar to that seen in PSP-P [7].

Progressive non-fluent aphasia (PSP-PNFA)

This subtype of PSP is characterized by non-fluent aphasia at the onset, rather than falls, eye movement abnormalities, or cognitive dysfunction [8]. Difficulty with speech production may include hesitancy, agrammatism, or phonetic errors. Some PSP-PNFA patients may initially have isolated speech apraxia, where words are produced very slowly, with errors of timing and prosody. These patients later develop classic signs of PSP.

Behavioral variant of frontotemporal dementia (PSP-bvFTD)

Fewer than 4% of bvFTD cases have PSP pathology, but there are some PSP patients whose first symptoms consist of personality

changes, lack of empathy, aggressive outbursts, hyperphagia, neglected hygiene, or socially inappropriate behavior [9]. As the disease progresses, the patients develop at least one PSP-RS symptom or sign (falls, vertical gaze palsy, or axial rigidity). Midbrain volumes are small, as in PSP-RS.

Corticobasal syndrome (PSP-CBS)

Patients with PSP-CBS present with asymmetrical cortical features that imitate CBS: limb apraxia, alien limb phenomenon, or cortical sensory loss [10]. In later stages, they develop one or more of the typical signs of PSP-RS.

Cerebellar ataxia (PSP-C)

This rare phenotype of PSP presents with ataxia, and they are often mistaken for the cerebellar variant of MSA [11]. Patients with PSP-C have both truncal and limb ataxia, unlike other PSP syndromes, where truncal ataxia is more prominent. Some patients with PSP-C eventually develop all three typical PSP problems (supranuclear palsy, cognitive abnormalities and frequent falls), while others do not.

Neuropathology of PSP

Richardson syndrome

On macroscopic examination of the brain in PSP-RS, there is usually mild atrophy of the frontal lobes and marked atrophy of the midbrain [6]. Under the microscope, there is neuronal loss in substantia nigra, subthalamic nucleus, globus pallidus and superior cerebellar peduncle in addition to mild atrophic changes in both the nucleus Basalis of Meynert and the cerebellar dentate nuclei (Table 2). Microscopic changes with either silver stain or tau immunohistochemistry reveal neurofibrillary tangles in the same areas where there is neuronal loss. Tufted astrocytes are unique to PSP and differ from the astrocytic plaques associated with CBS. Tau-staining lesions in the oligodendroglia appear as “coiled bodies” and are accompanied by tau-positive thread-like processes in the subcortical white matter.

PSP-parkinsonism

The locations of neuronal loss in PSP-P brains are not qualitatively different from the sites of cell loss seen in PSP-RS (subthalamic nucleus, substantia nigra and globus pallidus), but PSP-P patients have significantly lower PSP-tau scores (grading the severity of tau deposits in neurofibrillary tangles, tufted astrocytes, coiled bodies and threads) in PSP-P (median = 3), compared to PSP-RS (median = 5) [12]. This milder tau pathology is thought to explain the longer disease duration and the transient beneficial response to levodopa that is seen in patients with PSP-P.

Table 2: Clinical phenotypes of PSP and neuropathologic changes.

Phenotype	Atrophy/cell loss	Microscopic changes	Reference
PSP-RS	Cell loss in the STN, SN, GP, superior cerebellar peduncles, nucleus basalis of Meynert, cerebellar dentate nuclei	Tau positive changes in BG/BS neurons, neurofibrillary tangles and tufted astrocytes; Tau positive changes in oligodendroglia.	6
PSP-P	Less severe cell loss in STN, SN, GP than in PSP-RS.	Less severe tau changes (3:5) in frontal lobes, BS, BG, cerebellum, than in PSP-RS.	6
PSP-PAGF	Severe cell loss in STN, SN, and GP, but relative sparing of superior cerebellar peduncles.	Axon spheroids & iron-like pigment in SN and GP. Tau changes are mild in the cortex.	6,7
PSP-PNFA	More severe atrophy in frontal lobes, compared to PSP-RS.	More tau changes (NF tangles, etc) in frontal lobes than in PSP-RS.	8
PSP-bvFTD	Midbrain volume was as small in PSP-bvFTD as in PSP-RS.	Greater tau pathology than in PSP-RS.	6, 9
PSP-CBS	More severe atrophy in frontal & parietal lobes, compared to PSP-RS.	More tau changes (NF tangles etc) in frontal & parietal lobes than in PSP-RS.	6, 10
PSP-C	Cerebellar nuclei		11

Abbreviations: PSP = Progressive Supranuclear Palsy; RS = Richardson Syndrome; BG = Basal Ganglia; BS = Brainstem; P = Parkinsonism; GP = Globus Pallidus; PAGF = Pure Akinesia with Freezing Gait; STN = Subthalamic Nucleus; SN = Substantia Nigra; NF = Neurofibrillary; bvFTD = Behavioral Variant of Fronto-Temporal Dementia; MB = Midbrain; CBS = Corticobasal Syndrome; C = Cerebellar phenotype.

PSP-Pure akinesia with gait freezing

These brains show severe atrophy of the subthalamic nuclei, globus pallidus and substantia nigra. There is relative sparing of the superior cerebellar peduncles in PSP-PAGF brains, a pattern unlike that of PSP-RS, where the cerebellar peduncles are affected early and to a moderate degree [6]. Microscopically, there are axonal spheroids and iron-like pigment deposits in the substantia nigra and globus pallidus in PSP-PAGF. As with PSP-P, the PSP-tau scores are also significantly lower in PSP-PAGF, compared to those seen in PSP-RS [12].

The cortical PSP syndromes

Brains of patients with **PSP-PNFA** show more severe atrophy and more severe tau pathology in the frontal lobes, especially in the inferior frontal gyrus [8]. Pathological features of the 4 cases in this series included the typical features of PSP in the brainstem and basal ganglia, combined with tau-positive neuronal and glial pathology in the neocortex. In 3 autopsy-confirmed cases of PSP-bvFTD, there were small midbrain volumes, just as could be seen in PSP-RS [9]. In 5 clinical and autopsy-proven cases of PSP-CBS, the investigators found an increased tau burden in the mid-frontal and inferior parietal cortices in 3 of the cases [10]. In the other 2, there were pathological signs of co-existing Alzheimer Disease (AD) in one case and DLB in another. In a large clinical series of MSA patients, only 62% had the correct diagnosis at autopsy. DLB and **PSP-C** were the most likely conditions to be confused in life with MSA [11].

Neurogenetics of PSP

Family histories in PSP patients

PSP is generally considered to be a sporadic disorder, but one Rotterdam study found that 33% of 172 patients with PSP had at least one first degree relative with either dementia or parkinsonism, a higher percentage than had been reported among controls [13]. A retrospective autopsy study done in Japan demonstrated that 15% of PSP patients had a family history of either PSP, parkinsonism, or dementia [14].

Association of the MAPT gene with PSP

The tau protein is known to play an important role in axonal transport. Several studies have shown an association between the Microtubule-Associated Protein Tau (MAPT) gene and both PSP and CBS [15-17]. There are two inversion variants of the MAPT gene, H1 and H2. The H1 haplotype confers risk for both PSP and CBD, while the H2 haplotype appears to be neuroprotective [18]. In one

pathological study of tau burden in various PSP subtypes, the two cases of PSP carrying the H2 protective allele had the two lowest PSP-tau scores [12]. A large Genome Wide Association (GWA) study of 1114 autopsied PSP cases and 3287 controls showed that a mutation in the MAPT gene at a single nucleotide polymorphism, or SNP (rs8070723), conferred the greatest risk for PSP with an OR of 5.50 [19].

Association of the MOBP gene with PSP

In a secondary analysis, these authors found that there were other SNPs (or modifiers) that also carried increased risk for PSP, including a second SNP on MAPT (rs242557) and others on three different non-MAPT genes [19]. One was on the Myelin Associated Oligodendrocyte Basic Protein (MOBP) gene on chromosome 3 (rs1768208), the Syntaxin 6 (STX6) gene on chromosome 1 (rs1411478) and the eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3) gene on chromosome 2 (rs7571971). The role of the STX6 gene in PSP is of interest, since syntaxin 6 is a SNARE-class protein that regulates vesicle membrane fusion. A more recent GWA study with 152 CBD patients and 3311 controls demonstrated that there were several shared SNP/transcript level associations between CBD and PSP, including rs8070723/MAPT, rs242557/MAPT and rs1768208/MOBP [20]. As noted by these authors, the MOBP locus was first non-MAPT genetic risk factor that has been shown to be common to both CBD and PSP. MOPB is one of the most abundant oligodendrocyte-expressing proteins in the brain besides myelin basic protein. The link between PSP and the MOBP gene is of particular interest, given the results of recent diffusion tensor imaging studies verifying white matter changes in PSP brains (see Neuroimaging of PSP).

Neuroimaging of PSP

Midbrain atrophy on MRI is the imaging hallmark of PSP with the appearance on the sagittal view now being referred to as the "hummingbird sign" [21] (Figure 1). In one study of patients with PSP, PD and MSA, a Midbrain/Pons (M/P) area ratio of less than or equal to 0.52 was shown to be 100% specific for PSP [22]. This sign predated the clinical diagnosis of PSP by a mean of 15 months in 14 of 17 (82%) of the patients in whom it was identified. Similarly, in an autopsy-confirmed cohort of 6 PSP patients and 23 non-PSP patients, all non-PSP patients had M/P ratios higher than 0.50, whereas all but one of the PSP patients had a ratio lower than 0.50 [23].

Diffusion Tensor Imaging (DTI) studies have shown that PSP patients have widespread changes in White Matter (WM) bundles

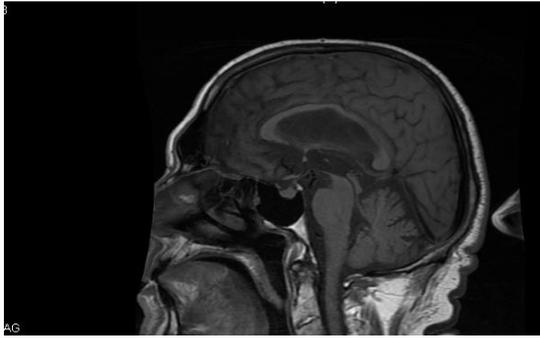


Figure 1: The "hummingbird sign". This patient had symptoms and signs of PSP-parkinsonism. The midbrain/pons ratio was less than 0.5, supporting the diagnosis of PSP.

in cerebellar peduncles, thalamic radiations, corticospinal tracts, corpus callosum, and longitudinal fasciculi [24,25]. In one study, the indices of WM damage correlated well with global scores of cognitive impairment (mean brain fractional anisotropy score *vs.* MMSE: $r=0.66$; $p<0.001$) [24]. In another, damage to WM tracts predicted global disease severity, executive dysfunction and apathy [25]. In the latter study, superior cerebellar peduncle and corpus callosum damage distinguished PSP from PD with an accuracy of 89% for the cerebellar peduncle and 80% for the corpus callosum. One recent longitudinal DTI study showed that over a 6-month period, the most prominent changes in PSP brains *vs.* controls were higher rates of fractional anisotropy reduction in the superior cerebellar peduncles and higher rates of diffusivity in the caudate nuclei [26].

Tau PET imaging studies are not yet available for routine clinical use, but there is currently much active research in this area. The recent development of selective *in-vivo* tau PET imaging ligands has provided information about tau pathology in PSP and other degenerative disorders. The [18F] AV-1451 ligand, which has high binding affinity for tau in paired helical filaments in Alzheimer brains, has limitations in PSP. Binding of the [18FAV-1451 ligand in PSP brains shows lack of correlation with severity of motor dysfunction, absence of binding to tau in cortical regions, and variable subcortical binding [27,28]. This ligand has low affinity for the tau lesions in PSP brains, where tau exists in straight filaments. The PET ligand PBB3 shows more robust ability to capture wide-range tau pathologies, including the 4-repeat isoforms of PSP [29].

Management of PSP

Pharmacologic interventions

While there is currently no disease modifying therapy for PSP, some treatment strategies have been successful for symptomatic management. There is typically a poor response to levodopa in PSP-RS patients. However, some patients with the PSP-P phenotype may show moderate motor improvement with levodopa for the first 2-3 years [2]. Dopamine agonists and amantadine have also been observed to provide benefit in a few PSP-P patients during the early years [30]. Botulinum toxin can be used for dystonic manifestations, such as nuchal rigidity, and to relieve spasticity in the legs. Donepezil has been tried for memory impairment and has shown modest improvement, but it may worsen motor functions [31]. Rivastigmine also demonstrated slight improvement in logical memory and verbal-fluency after 3 months of treatment, although the findings were not consistent among all patients [32]. Coenzyme Q10 failed

to show clinical or cognitive benefit for PSP patients in a double blind randomized trial where a dose of 2400 mg/day (*vs.* placebo) was used for 12 months [33]. Riluzole, a glutamatergic modulator, did not produce any survival benefit in patients with PSP, according to a large, double-blind placebo controlled trial lasting 36 months [34]. Rasagiline, an MAO-B inhibitor, has been shown to have neuroprotective effects in preclinical models of neurodegeneration, but it failed to demonstrate benefit for PSP patients in a small 1-year randomized double-blind placebo-controlled study using symptom progression on the PSP-Rating Scale as the primary endpoint [35].

Non-pharmacological interventions

Occupational and physical therapy can help in preventing falls by teaching PSP patients transfer methods, use of bathroom safety equipment, and in use of weighted walkers. Treadmill-plus training in early PSP patients has been shown to be as effective as robot assisted gait training [36]. Balance and eye movement training have been demonstrated to be effective in improving gaze control after 5 weeks [37]. Speech therapy evaluation is helpful to teach patients how to swallow safely and to assess the need for diet consistency modification with disease progression. Speech training using Lee Silverman Voice Treatment[®] has been shown to be effective in increasing maximum phonation duration and voice volume in PSP patients [38]. Botulinum toxin injections can be administered by specialists into the cricopharyngeal muscle for the treatment of neurogenic dysphagia if the swallowing problem is due to hyperactivity of that muscle [39]. Education of caregivers is the key component to managing the cognitive and affective disturbances that arise during the course of PSP [40].

Conclusion

There are at least 6 clinical variants of PSP besides the classical "Richardson syndrome". The PSP-parkinsonism variant is important to recognize, since it responds to levodopa for the first 2-3 years. The anatomical locations of neuronal loss in PSP-parkinsonism are not different from those of PSP-Richardson syndrome, but there are fewer tau deposits in the neurofibrillary tangles and tufted astrocytes. Mutations on the Microtubule-Associated Protein Tau (MAPT) gene on chromosome 17 confer the greatest risk for PSP, but there is also increased risk with mutations on the Myelin Associated Oligodendrocyte Basic Protein (MOBP) gene and other genes. Midbrain atrophy, manifested as the "hummingbird sign" on MRI sagittal view, is the imaging hallmark of PSP. Several studies have shown that a midbrain/pons ratio of 0.50-0.52 has 100% specificity for PSP, when the comparison groups include other movement disorders. Non-pharmacologic interventions, such as treadmill training, eye-movement training, and speech therapy are discussed in this review.

Authorship and Contributions

David Prepared the first draft of the neuroimaging section; conceptualization; revising the manuscript.

Ahmed Koriesh Prepared the first draft of the clinical phenotypes and management sections, including Table 1.

Nidhi Kapoor Prepared the first draft of neuropathology section, including Table 2.

Linda Hershey Prepared the first draft of the abstract and neurogenetics section, Figure 1; conceptualization; preparing the

final revision of the manuscript.

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