Progressive Supranuclear Palsy: What Do We Know About it?

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Abstract: Progressive supranuclear palsy (PSP) is a progressive tauopathy characterized by supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria, axial rigidity, frontal lobe dysfunction, and dementia. The typical pathology includes neuronal loss, gliosis and microtubule-associated protein tau (MAPT)-positive inclusions in neurons and glial cells, primarily in basal ganglia, brainstem and cerebellum. The pathogenesis of PSP is not yet completely understood; however, there are several hypotheses. This article reviews the present knowledge about PSP, and the concepts underlying mitochondrial dysfunction, liperoxidation, and gene mutations. The clinical features of PSP are also discussed; these include vertical gaze palsy, pseudobulbar palsy, aphasia, dysarthria, axial rigidity, and neuropsychiatric symptoms, such as amnesia, irritability, loss of interest, and dementia. In terms of diagnosis, there is considerable interest in neuroimaging for detecting PSP; therefore, neuroimaging techniques such as magnetic resonance imaging (MRI) and [18F]-fluorodeoxyglucose positron-emission tomography (FDG-PET) are reviewed. A definitive diagnosis of PSP depends on pathology, and the introduction of new clinical subtypes challenges presents the widely adopted diagnosis criteria. PSP treatments such as serotonin antagonists, n2 receptor antagonists, and coenzyme Q10 are also discussed. There is no curative therapy for PSP; all of the available treatments are palliative.

Keywords: Diagnosis criteria, microtubule-associated protein tau, neuroimaging, progressive supranuclear palsy, pathogenesis.

1. INTRODUCTION

Progressive supranuclear palsy (PSP) is a debilitating progressive neurodegenerative disease, the pathogenesis of which is still not well understood. PSP was first reported in 1904 and was described as a unique disease by Steele, Richardson and Olszewski in 1964; thus, it is also named Steele-Richardson-Olszewski syndrome. This review provides an overview of the pathogenesis, clinical manifestations, pathology and treatment of PSP.

2. EPIDEMIOLOGY

Although PSP is a relatively uncommon neurodegenerative disorder compared to Parkinson’s disease (PD), its prevalence has been underestimated due to frequent misdiagnosis. It was reported that the age-adjusted prevalence of PSP in London was 6.4 per 100,000, which is higher than the rate of 4.4 per 100,000 of multiple system atrophy (MSA) [1]. The average prevalence is 5.3 per 100,000 [2,3]. To our knowledge, no investigation of the prevalence of PSP in China has been published. No difference in the incidence between the sexes has been found [4]. The mean age of onset is 66.4 years, the mean age of death is 73.5 years, and the mean disease duration is 7.0 years [5].

Because no disease-modulating therapy is clinically available, the median survival of PSP patients is 6 to 10 years [6].

3. PATHOGENESIS

Although great strides have been made in understanding various aspects of PSP and many hypotheses have been proposed, the exact etiology of PSP remains unclear. It was shown that the incidence of PSP in the French West Indies was elevated and PSP patients in Guadeloupe (an island in the French West Indies) consumed significantly more fruits and herbal tea did patients with PD and controls. Therefore, neurotoxic alkaloids contained in the tropical fruits and herbal teas could be a potential etiological factor [7]. Because autopsies were only performed for three patients, it is possible that they were actually sporadic PSP patients unrelated to the others [8]. A large number of studies indicate that PSP is a tauopathy associated with abnormal tau proteins. Tau protein, also named microtubule-associated protein tau (MAPT), is a microtubule-binding protein that plays pivotal roles in mobilizing and stabilizing microtubules. The tau gene is located in the chromosomal region 17q21, and contains 16 exons. There are six isoforms of the tau protein caused by alternative splicing of the tau gene [9]. For example, the inclusion of exon 10 results in the tau isoforms with four C-terminal repeats (4R), while its exclusion generates tau isoforms with three such repeats (3R). The 3R and 4R C-terminal repeats are microtubule-binding domains. Based on the inclusion or exclusion of exons 2 and 3, the tau protein is divided into 3 isoforms: 0N (excluding exons 2 and 3), 1N
(including exon 2) and 2N (including exons 2 and 3). Thus, the different splicing of exons 2, 3, and 10 produces 6 isoforms of the tau protein: 0N3R, 0N4R, 1N3R, 1N4R, 2N3R, and 2N4R [10,11]. The classification used most often in scientific research is the 3R or 4R isoform. In the normal brain, the 4R:3R ratio is close to 1:1, whereas in PSP, the excessive formation of exon 10 mRNAs leads to the overexpression and aggregation of the 4R isoforms [12]. As a result, MAPT-positive inclusions in PSP neurons and glial cells consist predominantly of the 4R isoform [13]. Chambers et al. found that the levels of the 4R tau isoform were increased in the brainstem but not in the frontal cortex or cerebellum [14]. Similarly, another study indicated that the 4R:3R ratios in the globus pallidus of PSP patients were significantly higher than those of healthy controls and patients with Alzheimer’s disease (AD) [15], which was confirmed by Ezquerra et al.

PSP is considered to be sporadic, and mutations in the tau gene are not identified in most PSP patients [16,17]. However, some case studies have revealed that PSP can be inherited, suggesting that genetic factors might act in its pathogenesis [18]. Tau gene mutations are linked with familial PSP, and they may produce atypical PSP features. In an investigation of a kindred with two siblings with atypical PSP, which resulted from a consanguineous marriage, a homozygous deletion of codon 296 (delN296) was found in one of the siblings. The delN296 mutation, located in exon 10 of the tau gene, may increase exon 10 inclusion [19]. Ros et al. analyzed the clinical, pathological, and molecular data of one family with early-onset autosomal dominant PSP and found that the tau gene G303V mutation was identified in the 4 pathologically proven proband and in other family members.

Moreover, this mutation was associated with the overexpression of the 4R tau isoform and tau protein aggregation. Thus, the G303V mutation has association with autosomal dominant PSP [20]. A point mutation (R5L) in MAPT was detected in a PSP patient; this mutation altered the ability of tau to promote microtubule assembly [21]. Moreover, other MAPT mutations, such as R406W and S305S, also generate a PSP phenotype [22,23]. An ancestral inversion of 900 kb of chromosome 17q21 includes MAPT and neighboring genes such as CRHR1, IMP5 and Saitohin (STH) and has two major haplotypes, H1 and H2. The H1 haplotype is associated with several parkinsonisms, including PSP. Pastor et al. demonstrated that a specific subhaplotype (H1E’A) was present in 16% of PSP patients but was absent in controls [24]. Another study found a strong association between the H1E’C and H1Q subhaplotypes and PSP/cortical basal ganglionic degeneration (CBD) [25]. In addition, the authors found that the H1-rs242557A allele subhaplotype was increased in PSP/CBD [26]. STH is a nested gene located in intron 9 of tau. Although its function remains unknown, it appears to encode a protein which has a brain expression pattern resembling that of the tau, and its expression has a significant correlation with the 4R:3R tau ratio, especially in the globus pallidus [13]. Therefore, the incidence of hereditary PSP is underestimated; this form accounts for some proportion of PSP.

There are piles of evidence suggesting that mitochondrial dysfunction plays a key role in the pathogenesis of PSP. Reduced complex I activity, ATP production and oxygen consumption, accompanied with elevated antioxidant enzyme activity and oxidative damage to lipids, have been observed in PSP cybrid lines [27]. Moreover, combined 31P- and 1H-magnetic resonance spectroscopy (MRS) of probable PSP patients at early stages revealed decreased concentrations of 5 high-energy phosphates in the basal ganglia and frontal lobes, which were the most frequently involved regions. Because the neuronal marker N-acetylaspartate was not altered, the authors concluded that the mitochondrial dysfunction was not due to neuronal loss but could be an upstream phenomenon in neurodegeneration [28].

Like presenting similar clinical features in PD, PSP are also closely associated with inflammatory responses seen in PD [29,30]. Lipoperoxidation has an effect on the pathogenesis of PSP and is involved in the formation of neurofilbrillary tangles (NFTs) in PSP, but not in AD. Increased concentrations of 4-hydroxynonenal (HNE) and thiobarbituric acid reactive substances (TBARS), 2 major products of lipid peroxidation, were identified in PSP compared to controls, whereas 8-hydroxyguanosine (8-OHG, indicating protein and nucleic acid oxidation) did not show any variations between control and PSP brains [31]. Research by Borghi research supports the hypothesis that lipoperoxidation is selectively impaired in PSP, whereas all oxidative markers are elevated in AD. This research indicated that cdk5 mediated the effects of lipoperoxidation on tau protein aggregation through the overproduction of the kinase that participates in tau protein phosphorylation [32]. Nonetheless, protein oxidation also appears to play a role in PSP: studies have shown that oxidative damage to phosphoglycerate kinase 1 (PGK-1) and fructose bisphosphate aldolase A was markedly increased in the frontal cortex in PSP [33]. In addition, glial fibrillary acidic protein (GFAP) is thought to be an important target of oxidative damage in the striatum in PSP; however it remains unknown whether GFAP oxidation is the result of phospho-tau deposition or just an unrelated event [34]. Because elevated brain glutamate levels have been found in several sites in PSP, scientists have proposed that excitatory amino acids may act in the pathogenesis of PSP [35]. The pathogenesis of PSP is illustrated in Fig. (1).

4. CLINICAL FEATURES

The main clinical manifestations of PSP include supranuclear gaze palsy (especially when staring down), pseudobulbar palsy, dysarthria, axial rigidity and dementia [36]. These features are described in detail below.

The symptoms and signs of PSP frequently present as movement problems which include bradykinesia, frequent falls, dysarthria and dysphagia. The gait of a PSP patient is clumsy and unstable, resembling that of a “drunken sailor” or a “dancing bear” [37]. Patients frequently fall backward. Most patients display parkinsonisms of symmetrical bradykinesia and rigidity, which mainly involve the axial muscles. Obvious extensor rigidity and dystonia of the neck muscles produce an erect posture with retrocollis. The joint of bradykinesia, postural instability, neck hyperextension and supranuclear gaze palsy cause mobility difficulties and recurrent falls. Dysarthria and dysphagia appear in the early stage of the disease, and severe bucking often necessitates the use of a stomach tube.
The pathogenesis of PSP is not yet completely understood, but it is likely caused by a combination of factors. Neurotoxic alkaloids may play a role in PSP development because residents of Guadeloupe, who consume more tropical fruits and herbal tea, appear to be more susceptible to PSP. Microtubule-associated protein tau (MAPT) plays a crucial role in the disease, and an elevated 4R:3R tau ratio, MAPT gene mutations and the H1 haplotype are all considered to be the possible etiological agents. Liperoxidation has been found to be selectively involved in PSP due to the production of HNE and TBARS. Although other experiments have suggested that protein peroxidation (e.g., damage to PGK-1, fructose bisphosphate aldolase A and GFAP) plays a role in PSP. Moreover, evidence of mitochondrial dysfunction has been found in PSP; this phenomenon appears to function upstream of disease development. Toxic levels of excitatory amino acids, such as glutamate, constitute another hypothesis; their increased content has been demonstrated in PSP.

Vision problems in PSP patients include diplopia, blurred vision, photophobia, sore eyes, blepharospasm and blephar disuse. Patients suffer from slowed vertical saccades, which eventually develop into the complete loss of vertical eye movements. PSP patients easily dirty their neckties because they have difficulty staring downward, which is termed “the dirty tie phenomenon”. Vertical gaze palsy is a critical feature of PSP; it may occur early at disease onset, or it may arise several years after onset, although some patients never develop this feature. Due to difficulty with eye movements and eyelid opening, the faces of PSP patients appear to be worried or astonished [38]. The retrocollis, stiff gait with legs extended, and surprised facial appearance of PSP make it quite different from PD, which is associated with bending forward, flexed knees, and an absence of expression. Generally, the treatment response of PSP to levodopa is poor, whereas PD patients tend to exhibit excellent response to levodopa.

Like other neurodegenerative diseases such as PD and AD [39], cognitive dysfunctions are also very common in PSP. Approximately 62.5% of PSP patients suffer cognitive dysfunction at some point [40]. The cognitive and behavioral impairments in PSP, which are associated with the frontal lobe dysfunction, are characterized by executive functions that require shifting between mental tasks and spontaneous motor behavior, e.g., palilalia, motor perseveration, and compulsive spitting [41]. Neuropsychiatric symptoms are not rare; these include personality changes, amnesia, irritability, loss of interest, down spirits and difficulty focusing [4,42]. Approximately 18% of patients experience anxiety and depression, and 90% display apathy [43]. Patients’ quality of life is severely affected by motor and non-motor symptoms, and they eventually become handicapped both physically and psychiatrically at last, requiring care from others within 3 to 4 years of diagnosis [4,6]. The major causes of death include aspiration pneumonia, neurogenic respiratory failure, and pulmonary emboli [44,45], of which pneumonia accounts for 45% of deaths [44].

Because the clinical manifestations of PSP are heterogeneous and some “atypical” PSP patients are confirmed pathologically, neurologists have introduced a classification system including 5 subtypes of PSP to more clearly define the patients’ clinical features [46]. In this system, PSP with the above mentioned symptoms is called Richardson’s syndrome (RS).

It was originally believed that PSP patients did not have the characteristic parkinsonian features, such as tremor. However, a small group of pathologically confirmed PSP patients have distinct clinical features, such as normal eye movements, focal dementia, and parkinsonisms that present as resting tremors, resembling idiopathic PD [5]. This subtype is called PSP-parkinsonism (PSP-P). Gait difficulties and limb rigidity is more common and severe in these patients than in those with RS, although axial rigidity is often the earliest sign. Limb symptoms can be asymmetric [47]. Jerky postural tremors and even 4 to 6-Hz resting tremors are common [4,48]. A proportion of patients have moderate or even good improvements related to bradykinesia and rigidity after levodopa therapy [5,45], although excellent efficacy is rarely observed. Some patients begin responding poorly after...
several years of good response [42]. During the initial 2 years of the disease course, PSP-P and RS are not difficult to differentiate; however, during the following 6 years, they can become quite similar. Some PSP-P patients never develop the eye movement problems that are traits of RS. For those who have all the clinical features of RS and PSP-P, such as parkinsonism, postural instability, recurrent falls, cognitive decline and eye movement abnormalities, but with parkinsonism being the dominant symptom, a diagnosis of PSP-P is recommended [5]. The cognitive dysfunction and recurrent falls associated with PSP-P occur later than in RS, and the median survival time of PSP-P is 3 years longer that of than RS [49]. PSP-P is frequently misdiagnosed as PD; the major distinctions between them are that PSP-P progresses more rapidly, is associated with axial rigidity, may respond poorly to levodopa, and has no olfactory sensation loss, whereas PD progresses more slowly, has more limb rigidity than axial rigidity, and can include olfactory sensation loss. The prevalence of PSP-P is difficult to calculate. In Williams’s research, PSP-P made up 32% of all the 103 patients with PSP pathology in the Queen Square Brain Bank (QSBB) series, and RS made up 54% [5].

PSP-pure akinesia with gait freezing (PSP -PAGF) was first described in 1974. Patients with PSP-PAGF have pure akinesia alone on the early stage, including paradoxical kinesia and freezing of gait, speech and writing; however, they exhibit normal eye movements and intact cognition, and parkinsonism such as rigidity and tremors are absent for a long time after onset. The benefits of levodopa in these cases are extremely limited. Axial rigidity and stiff neck without limb rigidity, as well as supranuclear gaze palsy and blepharospasm, can appear in the advanced stage of PSP-PAGF. The frontal lobal limbic cognitive dysfunction and thought retardation are not obvious in these patients as in RS [50]. The mean disease course of PSP-PAGF is 11 years.

PSP-corticobasal syndrome (PSP-CBS), another subtype of PSP is featured by asymmetric dyspraxia and cortical sensory loss, including alien limb phenomena, jerky dystonia of the limbs with rigidity, and bradykinesia that is unresponsive to levodopa [51]. PSP-CBS resembles CBD in some respects and is a rare subtype of PSP, as demonstrated by a study by Tsuboi in which only 5 patients in 160 patients with PSP presented with the asymmetric limb dystonia, apraxia, and alien limb phenomena typical of PSP-CBS [52]. Most patients with PSP-CBS will at last present postural instability, although this occurs much later than in RS [53]. Vertical ophthalmoplegia is also observed in these patients, especially ipsilateral to the apraxia side, and is characterized by an increased latency to initiate saccadic eye movements, which causes compensatory head tilts [54]. This symptom should be distinguished from the slowness of saccadic eye movements in RS. Patients may 10 develop a mild slowing of saccades in the late stage; however, this is milder than that in RS.

PSP-progressive non-fluent aphasia (PSP-PNFA) is characterized by non-fluent aphasia consisting of non-fluent spontaneous speech, irreverant, agrammatism, and phonemic errors that produce substantial efforts in speech production [55]. Apraxia of speech is evident during serial repetition and is an isolated, early sign of PNFA. Although PNFA can also be observed in the spectrum of frontotemporal dementia syndromes, such as corticobasal syndrome, Josephs et al. found that five of seven patients with PNFA and evident early apraxia of speech actually had PSP-tau pathology [56].

5. PATHOLOGY AND NEUROCHEMISTRY

Pathology is the gold standard for the diagnosis of PSP. In general, the pathological changes associated with PSP contain neuron loss, granular-vascular degeneration, NFTs and gliosis in the basal ganglion, brain stem and cerebellum [57]. The most unique pathological characteristics are NFTs, neuritophils threads and tufted astrocytes, which are mainly distributed within the substantia nigra, globus pallidus, subthalamic nucleus, midbrain, pontine reticular formations and thalamus [58]. NFTs, which are produced by abnormally phosphorylated tau protein, also present in other tauopathies, such as AD, CBD, and Pick’s disease. Tau-positive NFTs can be observed in the above areas under light microscopy. Clustered astrocytes and NFTs can also be found in the frontal lobe, especially the motor cortex [59]. However, the NFTs found in PSP have distinct features compared to other tauopathies. The NFTs in PSP consist of unpaired, straight filaments 15 to 18 nm in length, in contrast to the mostly paired, helical, 22-nm-long filaments found in AD. The immunostaining and ultrastructural features of PSP NFTs resemble those of CBD; nonetheless, the NFTs in CBD are located in axons, unlike the neuronal location in PSP. Furthermore, the NFTs in the white matter of CBD are distributed in oligodendrocytes, opposed to astrocytes in PSP.

Similar to its clinical heterogeneity, PSP also exhibits heterogeneous pathological findings. RS has the classic pathological features as described above. The tau pathology in PSP-P is less severe than in RS but has a similar distribution pattern, which affect the subthalamic nucleus and substantia nigra the most severely [49,60]. The regions with the greatest severity are the cerebral cortex, pons, caudate, cerebellar dentate nucleus, and cerebellar white matter. Although the substantia nigra is severely affected in PSP-P, dopamine is less severely depleted from the extranigral midbrain, which might explain the clinical features that distinguish PSP-P from RS, including tremors and moderate levodopa responsiveness [5]. The severity of the tau pathology is milder in patients with PSP-PAGF than in patients with RS; tau depositions are less obvious in the cerebellum, dentate nucleus, and pontine nuclei [50]. This restricted pathological distribution in PSP-PAGF can explain its clinical differences from RS and its better prognosis.

PSP-CBS has severe tau pathology in the midfrontal and inferior parietal cortices, but not in the motor cortex, which distinguishes it from RS. The distribution pattern of its tau pathology is highly similar to that of CBD [52]. Patients with PSP-PNFA have more obvious tau deposition in the temporal cortex and superior frontal gyrus than do RS patients, although the pathology in the brainstem and subcortical gray matter regions is less severe [61]. Similar to other neurodegenerative diseases such as PD and AD [39], multiple neurotransmitter systems are impaired in PSP patients due to the involvement of various sites in the brain. Presynaptic and 12 postsynaptic damages to the nigrostriatal pathway produce
alterations in the dopamine system [62]. Unlike PD, PSP does not affect the mesolimbic and mesocortical dopaminergic systems [63].

The nucleus basalis of Meynert and the pedunculopontine nucleus are both cholinergic nuclei; hence, their involvement in PSP causes extensive cholinergic deficits. Biopsies and in vivo experiments have revealed cholinergic deficits in the striatum [64], thalamus [65] and brainstem [66]. As the major synthetic enzyme of acetylcholine, choline acetyltransferase (CAT) exhibits decreased activity in the caudate, putamen, nucleus acumbens and frontal cortex of PSP patients. This cholinergic deficiency partially explains the mechanism of dementia [67]. The γ-aminobutyric acid (GABA) system is also involved in PSP. It has been reported that the GABAergic system is moderately but widely damaged in the basal ganglia of PSP patients. Serotonergic receptors are mildly impaired in the cerebral cortex but those in the basal ganglia remain normal. Adrenoceptors are also widely diminished due to damage to the locus ceruleus [40].

6. NEUROIMAGING

Neuroimaging, especially magnetic resonance imaging (MRI), plays a pivotal role in the diagnosis and differentiation of PSP. Typically, axial T1W MRI examinations of PSP patients show the atrophy of the midbrain tectum and tegmentum, periaqueductal gray matter and quadrigeminal plate; as a result, the aqueduct of sylvius is enlarged (Fig. 2) [68,69]. The global midbrain atrophy is particularly obvious, and this characteristic is valuable for differentiating PSP from PD [70]. The shape of the midbrain on T2W MRI resembles a mouse head with two large ears, call the “mouse ear sign”. The anterior-posterior diameter of the midbrain is reduced, and a threshold of less than 17 mm has a low sensitivity but a high specificity in differentiating PSP from MSA [71,72]. Patients can also present atrophy of the frontal and parietal lobes, with the third ventricle dilated to resemble a balloon [73]. On sagittal T1W MRI, due to the atrophy of the rostral and caudal midbrain tegmentum, the shape of the midbrain resembles a hummingbird or a penguin silhouette, which is referred to as the “hummingbird sign” or the “penguin silhouette sign” (Fig. 3) [74]. The superior profile of the midbrain on midsagittal T1W spin-echo sections is valuable for the differentiation of PSP: the upper midbrain appears flat or concave because of the atrophy of the midbrain in PSP, whereas the upper midbrain appears convex in PD (Fig. 4) [75]. Using the criteria that the area of the midbrain on midsagittal T1W is less than 70 mm², and the midbrain/pons is smaller than 0.15, we can effectively discriminate PSP from PD and multiple system atrophy of the parkinsonian type (MSA-P) [76,77]. Although the differentiation of PSP can be based on a calculation of the area of the midbrain on midsagittal T1W, there remain some overlaps between the size of the midbrain area in PSP and MSA-P. Therefore, Oba et al. studied the ratio of the area of the midbrain to the area of the pons and found that this ratio was significantly smaller in PSP patients than in PD patients, MSA-P patients, or healthy controls, with no overlap between values [76]. However, Quattrone et al. found an overlap between the ratio of the area of the midbrain to the area of the pons in PSP and MSA-P; therefore, they coined the term “MR parkinsonism index”. Quattrone et al. measured the widths of the superior cerebel-
patients do not exhibit such changes [82]. The SCP signals of PSP patients on proton density-weighted MRI become obscure, or even disappear [83]. On diffusion tensor imaging (DTI) in PSP, the mean diffusivity increases in the decussation of SCP, indicating that the cerebellar outflow tract has been damaged [84]. Voxel-based morphometry (VBM) provides helpful information for the diagnosis of PSP. The volumes of the pons, midbrain, thalamus and striatum in PSP brains are significantly decreased, and the volume of the frontal gray matter is slightly decreased when calculated using MRI-based volumetry [85]. The extreme atrophy of the midbrain tegmentum, pons and frontal eye field can be used to differentiate PSP 15 from CBD with an accuracy of 94% [86]. Similarly, VBM indicates obvious volume losses in the midbrain, hypothalamus and cerebellar peduncle. Using this feature as a differentiation criterion for diagnosis results in a sensitivity of 83% and a specificity of 79% [87]. Atrophy is most evident in the midbrain and SCP of PSP patients, whereas it is most predominant in the pons and MCP of MSA patients. Thus, the mean volume of the midbrain in PSP is 30% less than in PD patients or healthy controls and 15% less than in MSA-P [88,89]. Furthermore, the mean volume of the SCP in PSP is 30% less than in MSA-P, PD or healthy controls, and the volume of the pons in MSA-P is 25% less than in PSP [89].

It has been reported that in disseminated weighted imaging (DWI), the relative apparent diffusion coefficient (rADC) of the globus pallidus and caudate nucleus is increased. An increased rADC of the putamen can discriminate PSP and MSA-P from PD, but it cannot discriminate PSP from MSA-P [90]. [18F]-fluorodeoxyglucose positron-emission tomography (FDG-PET) is capable of detecting early PSP even the MRI feature is not prominent. Metabolism is decreased dominantly in the brainstem and mesiofrontal area of PSP patients, whereas it is decreased predominantly in the putamen and cerebellum of MSA patients; this feature can successfully discriminate PSP from MSA [91].

7. OTHER TESTS

Numerous tests in addition to MRI are employed to study PSP. Although the dentate nucleus of the cerebellum exhibits degenerative changes in pathological findings, and SCP atrophy is shown by MRI, cerebellar ataxia is rare in PSP. However, a transcranial magnetic stimulation study showed that cerebellar inhibition was reduced in PSP, suggesting that Purkinje cells or the dentatothalamocortical pathway are involved in this disease [92].
Electroencephalograph (EEG) studies of PSP patients display unspecific disseminated abnormalities, including a mildly to moderately disseminated slow wave, which presents as a slowed background rhythm and increased θ waves specific to the bilateral temporal lobes or distributed globally. A bilateral, high-amplitude δ rhythm can be observed and is most prominent in the frontal lobe, whereas regional abnormalities are rare [93]. Ondo et al. used computerized posturography to measure the balancing ability of PSP and PD. These authors found that the limits of stability (LOS) of the PSP patients were significantly longer than those of the PD patients, whereas the sensory organization testing (SOT) scores of the PSP patients were significantly worse than those of the PD patients. Therefore, computerized posturography may be employed to differentiate PSP, although further research is hampered by the limitations of the equipment [94].

There is a lack of biomarkers for the diagnosis of PSP. Borroni et al. detected two forms of the tau protein in cerebrospinal fluid (CSF): an extended (55 kDa) form and a C-terminal truncated (33 kDa) form. This group found that the 33kD-tau:55kD-tau ratio in PSP (0.46±0.16) was significantly smaller than in healthy controls and patients with PD, frontotemporal dementia (FTD), CBD or dementia with Lewy body (DLB). Thus, they suggested that the 33kD-tau:55kD-tau ratio be considered as a tool for the differentiation of PSP [95,96]. However, Kuiperij believed this method to be unreliable because 33kD-tau and 55kD-tau were likely the light and heavy chains of IgG [97]. Borroni responded that the experimental schedule adopted in the study by Kuiperij was not identical to that of Borroni [98].

8. DIAGNOSIS

Because the clinical features of PSP are varied and some patients present with atypical symptoms, the diagnosis of PSP is not simple, which is reflected by an average period of latency until a correct diagnosis of 3 to 4 years [99]. The traditional diagnostic criteria drafted by the National Institute of Neurological Disorders and Stroke (NINDS) and the Society for PSP (SPSP), were published in 1996 [100]. These criteria define three diagnostic categories, possible, probable and definite (Table 1), as well as exclusion criteria. The diagnosis of possible or probable PSP depends primarily on the specific clinical features. The presence of the typical PSP neuropathology is obligatory for a definite diagnosis. Because various subtypes have now been identified but the criteria have not been corrected, the use of these traditional diagnostic categories might exclude some atypical PSP cases (the 4 subtypes other than RS). For this reason, we believe it is necessary to revise the criteria.

9. PHARMACOLOGICAL TREATMENT

It has been well documented that pharmacological medications are normally used to provide neuroprotection or slow down the progression of neurodegenerative diseases [101-103]. There have been numerous explorations of treatments for PSP, although no curative therapy has been established. Most “effective” treatments only briefly alleviate symptoms and do not change the prognosis. As a result, the current therapies for PSP are only symptomatic and supportive.

Table 1. NINDS/SPSP clinical diagnosis criteria for PSP [100].

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<th>Mandatory inclusion criteria for possible PSP:</th>
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<tr>
<td>• Gradually progressive disorder</td>
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<td>• Onset at age 40 or later</td>
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<td>• Either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls within the first year of disease onset</td>
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<td>• No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria</td>
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<th>Mandatory inclusion criteria for definite PSP:</th>
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<td>• Clinically probable or possible PSP and histopathological evidence of typical PSP</td>
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<th>Supportive criteria:</th>
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<td>• Symmetrical akinesia or rigidity, proximal more than distal</td>
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<td>• Abnormal neck posture, especially retrocollis</td>
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<td>• Poor or absent response of parkinsonism to levodopa</td>
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<td>• Early dysphagia and dysarthria</td>
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<td>• Early onset of 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</td>
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<th>Mandatory exclusion criteria:</th>
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<td>• Recent history of encephalitis</td>
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<td>• Alien limb syndrome, cortical sensory deficits, focal frontal or temporo-parietal atrophy</td>
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<td>• Hallucinations or delusions unrelated to dopaminergic therapy</td>
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<td>• Cortical dementia of Alzheimer’s type</td>
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<td>• Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia</td>
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<td>• Severe, asymmetric parkinsonian signs</td>
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<td>• Neuroradiologic evidence of relevant structural abnormality</td>
</tr>
<tr>
<td>• Whipple’s disease, confirmed by polymerase chain reaction, if indicated</td>
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As mentioned above, multiple transmitter systems are impaired in PSP; therefore, drugs acting on these transmitters have been applied. Compared to PD, the effects of these medicines on PSP are limited and unsustainable. Most PSP patients do not respond well to dopamine [104]; although PSP-P is partially sensitive to levodopa, the effect does not last long. Jackson et al. reported that the dopamine receptor agonists pergolide and bromocriptine improved symptoms of PSP, whereas Jankovic found that pergolide was ineffective [105]. The new-generation dopamine receptor agonist pramipexole was also shown to be ineffective [106].

Choline system drugs produce various effects in PSP patients. The cholinesterase physostigmine does not alleviate ophalmoplegia, parkinsonian symptoms, bulbar palsy [107]
or linguistic function \[108\] in PSP patients, although it slightly improved spatial attention \[109\]. In another study, Fabbrini et al. administered donepezil 10 mg per day for 3 months to patients with PSP. Measurements of the patients’ cognitive functions, motor symptoms and daily activities demonstrated no significant alterations \[110\]. Similarly, the M-receptor agonist RS-86 did not improve motor function, eye movement or cognitive function \[111\].

Methysergide, a serotonin antagonist, also demonstrated no improvements in PSP patients, according to research by Duncombe \[112\]. Among the tricyclic antidepressants, amitriptyline produced an overall improvement, whereas desipramine predominantly improved apraxia of eyelid opening \[113,114\]. Engel reported that low-dose amitriptyline therapy in one individual with PSP produced benefits including remission of bradykinesia, dysarthria and dysphagia, and another patient received significant relief from severe rigidity, bradykinesia, impaired balance, and blepharospasm \[115\].

The $\alpha_2$ receptor antagonist idazoxan has been shown to decrease patients’ motor subscale scores on the United Parkinson's Disease Rating Scale (UPDRS), with prominent improvements in balance, gait, and measures of digital dexterity. However, idazoxan treatment did not improve ophthalmoplegia, and it produced significant side effects \[116\]. In a trial of 14 PSP patients treated with amantadine, Rajrut observed that 6 (42.9%) had some improvement, although the results were not dramatic \[117\]. Zolpidem, a short-acting hypnotic drug, has been shown to ameliorate motor symptoms and improve eye movement slowness \[118\]. The mechanism of the improvement in motor function by zolpidem might be the selective inhibition of GABAergic inhibitory neurons in the internal globus pallidus and in the substantia nigra pars reticulata, which causes the activation of the thalamus and cerebral cortex \[119\]. Zolpidem has been shown to facilitate saccadic eye movements by inhibiting the substantia nigra pars reticulata to activate the superior colliculus \[120\], although these benefits were transient. A recent report documented that a PSP patient had sustained improvements in motor function, pseudobulbar symptoms and ocular motility 2 months after taking a controlled-release formulation of zolpidem \[121\].

Because mitochondrial complex I is impaired in PSP and coenzyme Q10 21 (CoQ10) is a physiological cofactor of mitochondrial complex I, researchers assessed the responses of PSP patients to CoQ10 in a randomized, placebo-controlled trial. The administration of CoQ10 (5mg/kg per day) for 6 weeks decreased the concentrations of low-energy phosphates (adenosine diphosphate and unphosphorylated creatine), thus increasing the ratios of high-energy phosphates to low-energy phosphates (adenosine triphosphate to adenosine diphosphate and phospho-creatine to unphosphorylated creatine). In addition, the patients’ scores on the PSP rating scale and the Frontal Assessment Battery improved moderately but significantly \[122\].

Since PSP is a tauopathy, the tau protein has become a novel target for treatments. It has been predicted that we can use splice modifiers which stabilize the tau stem loop to reverse the altered 4R:3R ratio, thus inhibiting the tau pathology in PSP. Varani showed that neomycin bound to the tau RNA stem-loop, suggesting that this drug might provide a new treatment for PSP \[123\]. Similarly, mitoxantrone is another stem-loop stabilizer with therapeutic potential \[124\]. Moreover, using small molecules that bind to tau mRNA, thus modifying splicing and translation, has become another possibility \[125\]. It has been reported that grape seed-derived polyphenolic extracts (GSPE) can prevent tau fibrillation into neurotoxic aggregates and can promote the dissociation of preformed tau aggregates \[126\]. Therefore, GSPE is a potential novel therapeutic agent for PSP \[127\].

In additions to pharmacological treatment, practicing also plays an important role in the treatment and rehabilitation of PSP. For example, balance training combined with eye movement training significantly improved stance time and walking speed in a study by Zampieri \[128\]. Symptomatic treatments are also essential; these include stomach tubes for patients with dysphagia and choking. Antibiotics are necessary to treat the most frequent complication of PSP, pneumonia. Careful nursing 22 is critical to prevent pneumonia, bedsores, and trauma or bonefractures caused by recurrent falls. Botulinum toxin-A is a candidate for relieving rigidity and blepharospasm \[129\].

In summary, various therapeutic strategies for PSP have been applied. Some of these treatments improve motor and non-motor functions, although they are often palliative and short-acting. Nonetheless, the patient samples in these clinical trials were generally too small to produce convincing conclusions.

CONCLUSION

As PSP receives increased attention, it becomes better understood. Nonetheless, the etiology of this disease is not yet completely understood. Environmental factors, genetic factors, mitochondrial dysfunction and lipoperoxidation are some of the hypothesized causes of PSP, and PSP is likely to be the result of a combination of these factors. In addition to the classic PSP (RS), atypical subtypes such as PSP-P, PSP-PAGF, PSP-CBS and PSP-PNFA have been identified. As a tauopathy, the pathology of PSP is of great importance for diagnosis; it presents as star-shaped astrocytic tufts and NFTs. Neuroimaging, especially MRI combined with VBM, assists the diagnosis of PSP. Research into PSP therapies is developing due to progress in our knowledge of the mechanism. However, no effective symptomatic, disease-modifying or neuroprotective treatments are presently available. In conclusion, many fields of PSP remain unclear and require intensive further investigation.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>8OHG</td>
<td>8-hydroxyguanosine</td>
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<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<td>CAT</td>
<td>Choline acetyltransferase</td>
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<td>CBD</td>
<td>Cortical basal ganglionic degeneration</td>
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<td>CoQ 10</td>
<td>Coenzyme Q 10</td>
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<td>CSF</td>
<td>Cerebral spinal fluid</td>
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<td>DLB</td>
<td>Lewy body dementia</td>
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<td>DTI</td>
<td>Diffusion tensor imaging</td>
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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the 973 Project (2011CB510000), National Natural Science Foundations of China (Grant NO: 81071031, 81271427), 985 project grant (82000-3281901), Scientific Research Foundation of Guangzhou (Grant NO: 2014J4100210), and National Natural Science Foundation of Guangdong of China (S201101000471) to Q. W.

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[Received: ???????????????]


[129]}