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Review article

Progressive Supranuclear Palsy Syndrome: An Overview

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ABSTRACT

Progressive supranuclear palsy (PSP) is a neurodegenerative disease, commonly observed as a movement disorder in the group of parkinsonian diseases. The term PSP usually refers to PSP-Richardson's syndrome (PSP-RS), the most typical clinical presentation. However, the broad concept of progressive supranuclear palsy syndrome (PSP-S) applies to a set of clinical entities that share a pathophysiological origin and some symptoms. According to its clinical predominance, PSP-S is divided into subtypes. PSP-S has clinical similarities with Parkinson's disease, and both pathologies are classified in the group of parkinsonisms, but they do not share pathophysiological traits. By contrast, the pathophysiology of corticobasal syndrome (CBS) depends on tau expression and shares similarities with PSP-S in both pathophysiology and clinical picture. An involvement of the immune system has been proposed as a cause of neurodegeneration. The role of neuroinflammation in PSP-S has been studied by neuroimaging, among other methods. As it is the case in other neurodegenerative pathologies, microglial cells have been attributed a major role in PSP-S. While various studies have explored the detection and use of possible inflammatory biomarkers in PSP-S, no significant advances have been made in this regard. This review is aimed at highlighting the most relevant information on neuroinflammation and peripheral inflammation in the development and progression of PSP-S, to lay the groundwork for further research on the pathophysiology, potential biomarkers, and therapeutic strategies for PSP-S.

1. Introduction

Progressive supranuclear palsy syndrome (PSP-S) is a sporadic neurodegenerative disease. In its classic presentation, it shows motor traits such as postural instability, oculomotor signs, parkinsonism, pseudobulbar palsy, and non-motor signs like behavioral changes and executive dysfunction (Giagkou et al., 2019). Prevalence estimates vary from 1.4 individuals per 100 000–8.3 per 100 000 (Fleury et al., 2018; Golbe et al., 1988). A mean age of onset of 63 years and a median survival after symptom onset of 6.9 years have been reported (Erkkinen et al., 2018).

In general, PSP-S is graded by diagnostic criteria established by The Movement Disorder Society (Höglinger et al., 2017), which include clinical features, neuropathological studies, therapeutic response, and

Abbreviations: 18F-FDG-PET, fluorine-18 fluorodeoxyglucose PET; 3-NT, 3-nitrotyrosine; 3-R, three microtubule-binding repeats; 4-R, four microtubule-binding repeats; AD, Alzheimer's disease; AGD, argyrophilic grain disease; AMP, cyclic adenosine monophosphate; ASO, antisense oligonucleotides; CBS, corticobasal syndrome; CRP, C-reactive protein; CSF, cerebrospinal fluid; EIF2AK3, PERK gene; FDG-PET, fluorodeoxyglucose positron emission tomography; GGT, globular glial tauopathies; GSK3B, glycogen synthase kinase 3 beta; GWAS, genome-wide association study; H1, haplotype H1; H1c, sub-haplotype H1c; H1d, sub-haplotype H1d; H1g, haplotype H1g; H1o, haplotype H1o; H2, haplotype H2; IFN, interferon; IL, interleukin; LMTX, methylthioninium; LRRK2, leucine-rich kinase 2 gene; MAPT, microtubule-associated protein tau gene; MARK, microtubule-affinity regulating kinase; MDS, Movement Disorder Society; MOPB, myelin basic protein gene; MiRNAs, microRNAs; MRI, Magnetic resonance imaging; MT, microtubule; MTB, microtubule-binding; NfL, neurofilament light chain; NLR, neutrophil-to-lymphocyte ratio; NK, natural killer; NO, nitric oxide; OS, oxidative stress; PBMCs, peripheral blood mononuclear cells; PET, positron emission tomography; PKA, protein kinase A; PKB, protein kinase B; PD, Parkinson's disease; PSP-P, Parkinsonism; PSP-C, Predominant cerebellar ataxia; PSP-CBS, Corticobasal syndrome; PSP-FTD, Frontotemporal degeneration; PSP-OM, Ocular motor dysfunction; PSP-PGF, Progressive gait freezing; PSP-PI, Postural instability; PSP-RS, PSP Richardson's syndrome; PSP-S, Progressive supranuclear palsy syndrome; P-tau, phosphorylated tau; PTBP2, polypyrimidine tract-binding protein 2; ROS, reactive oxygen species; SP-SL, Speech and/or language; SCP, superior cerebellar peduncle; Simoa, ultrasensitive single-molecule array; SN, substantia nigra; SPECT, single photon emission computed tomography; SPECT-HMPAO, hexamethylpropylpropylamine SPECT; SPECT-IMP, I-123-labeled iofetamine SPECT; STX6, syntaxin 6 gene; TGFβ, Transforming growth factor beta; TNF-α, tumor necrosis factor alpha; t-tau, total tau; USA, United States of America.

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imaging findings. The syndrome is classified into definite PSP-S, probable PSP-S, possible PSP-S, and conditions suggestive of PSP-S. These categories indicate the difficulty of clinical diagnostic in PSP-S, as a definitive diagnosis requires a neuropathological study, which is impossible to perform as the disease progresses. Therefore, the clinical classification of a patient showing clinical data of PSP-S strongly depends on the sensitivity and specificity of signs and symptoms. Whilst PSP-S phenotypes are defined by the presence and predominance of one or another symptom (e.g., asymmetric tremor at onset, bradykinesia, and rigidity in PSP-Parkinsonism), establishing a definitive diagnosis remains a challenge.

The clinical relevance of PSP-S stems from its inclusion in the group of diseases known as parkinsonism, being the second most common parkinsonian condition and the main differential diagnosis of Parkinson's disease (PD) (Parthimos and Schulpis, 2020). Although PSP-S is a rare disease, given its low prevalence, a deeper understanding of its pathophysiology and associated neurodegeneration is much needed. While there is a growing interest in the study of neuroinflammation and its link to immune status in various neurodegenerative pathologies, there is little information on PSP-S, raising interest in investigating the disease. Finally, a better understanding of the factors underlying PSP-S progression could allow us to devise novel therapeutic approaches to improve the patients' prognosis and quality of life.

1.1. Risk factors

A key issue in all neurodegenerative diseases are risk factors such as demographic, environmental, genetic, and other factors. Age and sex are the most prominent risk factors for PSP-S. Medical records of patients with tauopathies in Minnesota, USA, were reviewed in a longitudinal study conducted in the period 1991–2005. The incidence of tauopathies, including PSP-S, increased with age. The diseases were also more frequent in male patients than in females (Savica et al., 2013). Another factor that has been associated with an increased risk of PSP-S is drinking well water, especially after years of consumption. On the other hand, there is no evidence that exposure to a specific chemical, socioeconomic status, cigarette pack-years, or years living on a farm have any effect on the risk of PSP-S (Litvan et al., 2016).

The effect of heavy metal exposure on tauopathies has also been studied. Specifically, chromium and nickel induce an increase in tau levels and its phosphorylation, mediating cell death by apoptosis; however, this is not specific to sporadic PSP-S (Alquezar et al., 2020). Furthermore, as it will be discussed in the Neuropathology section, consumption of the plant annonacin has been associated with the development of PSP-S, mediated by mitochondrial (Escobar-Khondiker et al., 2007; Stamelou et al., 2021).

Arterial hypertension has also been associated with the development of PSP-S (Rabadia et al., 2019). Hypertension could induce tau aggregation, as observed in murine models (Díaz-Ruiz et al., 2009); in turn, this has been linked to neuroinflammation (Dinh et al., 2014).

Finally, stress has been linked with PSP-S. In one study, a life stressor questionnaire was administered to patients with PSP-S and healthy controls. Exposure to high-severity stressful events prior to the clinical development of PSP-S was 3 times higher in cases than in controls (Kelley et al., 2017).

Along with the risk factors mentioned above, a systematic review analyzed several studies and concluded that a high educational level and the consumption of statins could be protective factors against the development of PSP-S (Park et al., 2021).

Nevertheless, none of the above-mentioned factors is strongly associated with PSP-S. Therefore, PSP-S is still considered to have an unknown etiology, and most cases are sporadic (Giagkou et al., 2019).

1.2. Genes associated to PSP-S

The microtubule-associated protein tau gene (*MAPT*), located on chromosome 17q21, encodes for the tau (Spillantini and Goedert, 2013). Different *MAPT* haplotypes have been studied as potential genetic risk factors for PSP-S. The *H1* haplotype increases the risk of developing the disease (Baker et al., 1999; Kouri et al., 2015), to the point that it has been considered the strongest risk factor (Höglinger et al., 2011). However, one study shows conflicting results, suggesting that cells expressing the haplotype *H1* increase the expression of α-synuclein levels, while those expressing the haplotype *H2* are associated with a higher expression of tau (Strauß et al. 2021). On the other hand, a case-control study and a case series have reported different *MAPT H1* sub-haplotypes as possible risk factors for the development of PSP-S: *H1c, H1d, H1g,* and *H1o* (Heckman et al., 2019). Despite continued efforts to study *MAPT* haplotypes and sub-haplotypes, the mechanism by which they contribute to the risk of PSP-S remains unclear. Nevertheless, there is consensus that this gene is clearly linked with the development of the disease (Spillantini and Goedert, 2013).

Other genes possibly associated to PSP-S are *MOPB*, *STX6,* and *EIF2AK3*, all of which have been studied by a genome-wide association study (GWAS). *STX6* encodes syntaxin 6, a SNARE-class protein. It is believed that genetic variations of STX6 could influence the movement of misfolded proteins from the endoplasmic reticulum to lysosomes through the endosomal system. On the other hand, *MOPB* encodes for the myelin basic protein in oligodendrocytes. Myelin or oligodendrocyte dysfunction is thought to contribute to the pathogenesis of PSP-S. Finally, *EIF2AK3* encodes PERK, which inhibits the synthesis of unfolded proteins that accumulate in the endoplasmic reticulum. It is believed that these non-folded proteins may increase the risk of developing PSP-S (Höglinger et al., 2011).

There is also interest in studying the leucine-rich kinase 2 gene (*LRRK2*) in PSP-S. This gene has traditionally been associated with sporadic and familial forms of PD (Nalls et al., 2019). However, its involvement in the development of PSP-S (via tau protein aggregation) and its role as a genetic modifier of PSP-S progression have recently been reported (Jabbari et al., 2021). A systematic review including 1039 PSP-S cases identified several pathologically relevant mutations in *LRRK2* (G2019S, R1441C, A1413T, and R1707K); however, the prevalence of autosomal dominant mutations remains low (0.17–0.34%) (Sanchez-Contreras et al., 2017). In contrast, a systematic review concluded that *LRRK2* is a very rare pathological gene, and thus it has little significance in the disease (Wen et al., 2021). Despite the ongoing controversy over whether *LRRK2* is relevant in the development of PSP-S, *LRRK2* kinase inhibitors and an antisense oligonucleotide targeting *LRRK2* expression could be useful as therapeutic approaches to modify the clinical course of tauopathies (Herbst et al., 2022).

Finally, although the involvement of *LRRK2* in the pathogenesis of PSP-S is still under study, this gene could be involved in neuroinflammation in other tauopathies and PD, but little is still known on its role in PSP-S (Herbst et al., 2022). The latter will be discussed in detail in the Neuroinflammation section.

Only a few genes have been associated to PSP-S. Considering the broad spectrum of the syndrome, characterizing genes that could be linked directly with the phenotypes of the disease may help us to explain its physiology and provide a more accurate diagnosis.

2. Neuropathology

The pathophysiological findings in PSP-S cases can be subdivided into microscopic and macroscopic. The relationship of PSP-S to tauopathies and the consequences of tau alterations can be described in microscopic terms, whereas the anatomical areas affected and their correlation with the clinical presentation of PSP-S require a macroscopic approach.

2.1. Microscopic context

Tau, the most abundant microtubule-associated molecule in the

human brain, is encoded by the *MAPT* gene, located on chromosome 17q21 (Spillantini and Goedert, 2013). It is mainly found in neurons, but under pathological conditions it can be expressed in glial cells. *MAPT* final transcripts can be detected in peripheral tissues, including striated and cardiac muscle, lung, pancreas, kidney, and fibroblasts (Buee et al. 2000). This Tau is involved in the stabilization of microtubules; it also provides support for the cytoskeleton and for cellular trafficking, especially transport, and plays a role in the stability of axonal microtubules. The biological activity of tau is regulated by its phosphorylation (Tudorică et al. 2017). Six tau isoforms are expressed in the human brain, with a length of 352–441 amino acids. These isoforms may have none, one, or two amino-terminal insertions (0 N, 1 N, 2 N) and three or four microtubule-binding repeats (MTB) (3-R or 4-R). 3-R and 4-R repeats are normally found in 1:1 ratio; changes in this ratio result in various conditions, grouped according to the predominant repeat (Tudorică et al. 2017) (Fig. 1). The 3-R group includes pathologies like Pick disease and *MAPT* mutation. The 4-R group includes PSP-S, corticobasal syndrome (CBS), argyrophilic grain disease (AGD), and globular glial tauopathies (GGT). All 4-R tauopathies are severe and lack validated biomarkers. Finally, a group of mixed 3-R and 4-R tauopathies has been described, including neurofibrillary tangle dementia, primary age-related tauopathy, Alzheimer's disease (AD), and *MAPT* mutation (Stamelou et al. 2021).

Along with altered repeat ratios, abnormally hyperphosphorylated tau leads to the formation of neurofibrillary tangles in neurons. Depositions accumulate in glial cells, including tufted astrocytes and oligodendroglial coiled bodies, resulting in neuronal loss and astrogliosis (Kovacs et al., 2018). Tau phosphorylation, among other post-translational modifications, is mediated by specific kinases, including cyclic adenosine monophosphate (AMP)-dependent protein kinase A (PKA), protein kinase B (PKB), and microtubule-affinity regulating kinase (MARK) (Tudorică et al. 2017). The pathophysiological traits of PSP-S are due to neuron loss, gliosis, and accumulation of 4-R tau (Giagkou et al. 2019) (Fig. 2).

Early PSP-S has also been associated with mitochondrial dysfunction. This has been demonstrated in humans by imaging and postmortem immunochemical studies. Using fluorodeoxyglucose positron emission tomography (FDG-PET), a decreased glucose metabolism in the frontal lobes, cingulate gyrus, basal ganglia, thalamus, midbrain, and pons in PSP-S patients has been reported (Höglinger et al. 2010). Furthermore, postmortem evidence of oxidative stress has been found in the brain of PSP-S patients by immunohistochemical analysis (Höglinger et al. 2010).

Another study correlated chronic consumption of plants of the Annonaceae family with the occurrence of atypical parkinsonism (Caparros-Lefebvre and Lees, 2005). These plants are known to produce inhibitors of mitochondrial complex 1, so this finding supports the theory of mitochondrial dysfunction as a major contributor in the pathophysiology of PSP-S (Stamelou et al., 2010). Extracts of these plants produce neurodegeneration when administrated intravenously to rats (Champy et al., 2004).

Finally, mitochondrial dysfunction could be linked to tau aggregation in PSP-S, as it has been reported that dysfunction of mitochondrial complex 1 increases oxidative stress and activates tau-kinases, leading to hyperphosphorylation and subsequent aggregation of tau. Notably, this complex also causes aggregates of α-synuclein in PD (Höglinger et al. 2010). Further studies on the role of mitochondrial dysfunction in PSP-S are required to elucidate the pathways involved in the onset of this disease.

The presence of α-synuclein accumulations, including Lewy bodies (found in approximately 20% of patients), has also been suggested to play a role in the pathophysiology of PSP-S (Stamelou et al. 2021). The presence of Lewy bodies is thought to be due to a synergy between α-synuclein and tau in catecholaminergic neurons (Aguirre et al. 2015). However, one study reported inconsistent results on the involvement of α-synuclein in PSP-S, as it was only found in a few patients and could be due to normal aging (Tong et al. 2010). Although α-synuclein is often found in patients with PSP-S, its role in the clinical picture of this disease has not been established (Aguirre et al. 2015).

2.2. *Macroscopic context*

Stamelou et al. (2021) proposed a neuropathological staging system for the group of 4-R tauopathies (Stamelou et al. 2021):

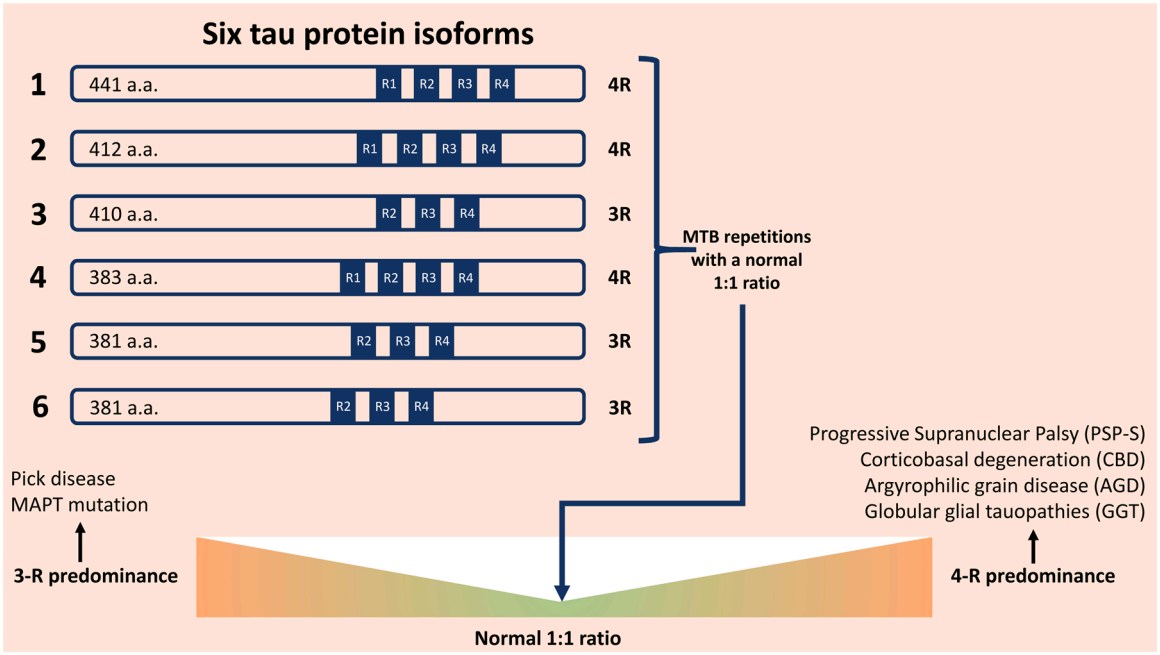

Fig. 1. Tau isoforms. The six isoforms of the tau range in length from 381 to 441 amino acids (a.a.) and have amino-terminal insertions (N) and microtubule-binding repeats (MTB). MTBs can consist of three (3-R) or four repeats (4-R), and a healthy subject shows a 1:1 ratio of both. Alterations in this ratio, with predominance of either 3-R or 4-R, result in various disorders. These are classified into two groups, according to the predominant repeat.

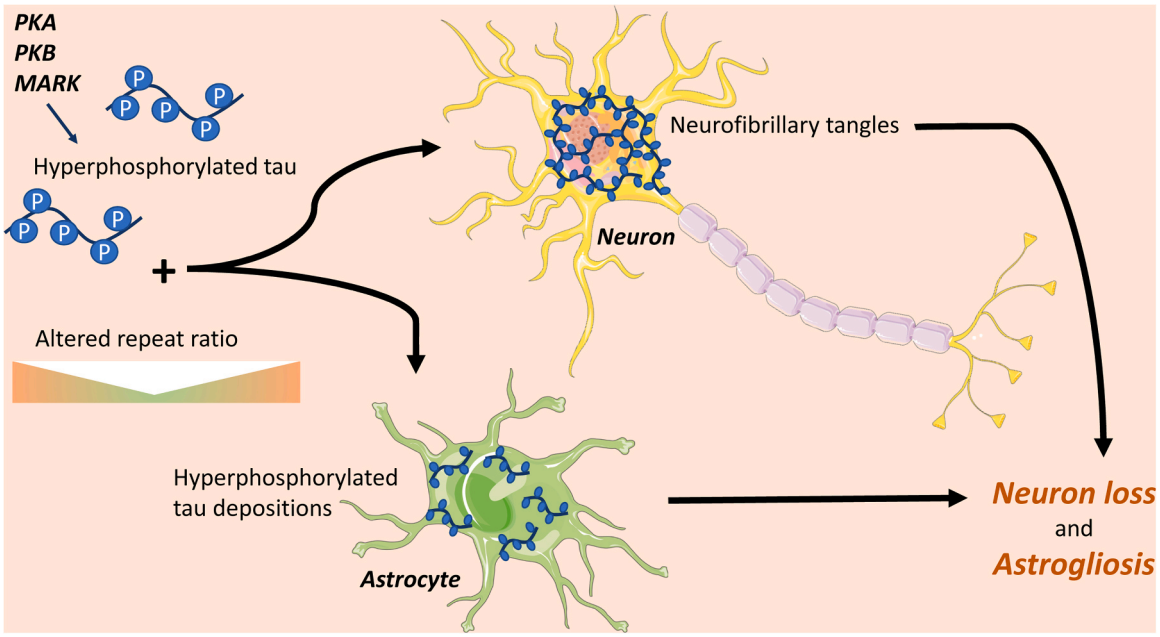

Fig. 2. Tau hyperphosphorylation. Post-translational modifications of tau, especially phosphorylation, is specifically mediated by kinases like cyclic adenosine monophosphate (AMP)-dependent protein kinase A (PKA), protein kinase B (PKB) and microtubule-affinity regulating kinase (MARK). Hyperphosphorylated tau with an altered repeat ratio leads to tau depositions in astrocytes and neurons, which in turn results in neuron loss and astrogliosis.

a) Stage 1 and 2: progressive involvement of neurons and oligodendroglia in the globus pallidus, neurons in the subthalamic nucleus, and astroglia in the striatum.
b) Stage 3 and 4: involvement of astroglia in the frontal cortex, and neurons and oligodendroglia in the dentate nucleus of the cerebellum.
c) Stage 5 and 6: involvement of astroglia in the occipital cortex.

The pathophysiology of various PSP-S phenotypes is thought to be related to the anatomical site where tau are deposited, and it may also be influenced by the cell type involved (Kovacs et al. 2020). This has been addressed in postmortem studies on PSP-S patients (Respondek et al. 2014), and also by comparing tau loads in patients with different phenotypes (Kovacs et al. 2020). In a retrospective study assessing the anatomopathological differences in PSP-S phenotypes and their correlation with MDS criteria, total and subcortical tau levels were higher in the PSP Richardson's syndrome (PSP-RS) phenotype than in PSP-S, but no differences were found in other subtypes (Sánchez-Ruiz de Gordoa et al. 2022). Despite this microscopic evidence, it is not clear which pathophysiological event determines each PSP-S subtype. However, it has been macroscopically observed that PSP-S usually involves atrophy in the subthalamic nucleus and brainstem tegmentum, along with depigmentation of the substantia nigra (Stamelou et al. 2021). Other brain regions could be involved, depending on the phenotype of PSP-S. This has an impact on the clinical presentation of PSP-S, which shows predisposition for specific anatomical sites, and such regions could be evidenced by imaging studies. The subtypes of PSP-S and the pathophysiological correlation with anatomical regions and clinical manifestations are described below (Adam et al. 2017; Coughlin and Litvan, 2020; Giagkou et al. 2019).

3. Clinical features

PSP-S is classified into different phenotypes, which correlate with the macroscopic areas predominantly affected in the disease.

3.1. Richardson's syndrome (PSP-RS)

This is the classical subtype and the most frequent. Its presents with spontaneous unexplained falls, unsteady walk, bradykinesia, behavior changes (apathy, disinhibition), cognitive slowing, executive dysfunction (difficulty in planning or multitasking), speech alterations (slowing, ataxic, spastic, and hypophonic), and dysphagia. Other early signs of PSP-RS are less gain and slowness of vertical (greater than horizontal) saccadic eye movements, decreased or absent optokinetic nystagmus, reading difficulty, and apraxia of eyelid opening. The distinctive clinical feature for diagnosis is the vertical supranuclear gaze palsy, but its onset is variable, being absent up to 3–4 years after disease onset in some cases (Adam et al. 2017; Respondek and Hoglinger, 2016). The areas commonly affected in PSP-S are relatively specific to PSP-RS, and atrophy in the subthalamic nucleus and brainstem tegmentum are typical (Stamelou et al. 2021).

3.2. Parkinsonism (PSP-P)

The second most frequent syndrome within PSP-S, it presents with asymmetric tremor at onset, bradykinesia, rigidity, and a slower progression than PSP-RS. This subtype resembles PD most closely, meeting the clinical criteria of parkinsonism. However, late-stage PSP-P shows clear differences with PD. For instance, levodopa-induced dyskinesias, autonomic dysfunction, and visual hallucinations are less frequent in PSP-P than in PD (Adam et al. 2017). PSP-P has a more benign clinical course and a longer survival than PSP-RS (Coughlin and Litvan, 2020). The most affected anatomic areas in this subtype are cortical, cerebellar, and pontine structures, along with those involved in motor functions (Giagkou et al. 2019).

3.3. Progressive gait freezing (PSP-PGF)

Initially a pure gait disorder, it is characterized at later stages by progressive gait disturbance, with start hesitation and subsequent gait freezing. Sometimes it includes difficulties with initiating or completing speech or writing, but without tremor, rigidity, dementia, nor movement abnormalities within the first five years of progression (Adam et al.

2017; Respondek and Hoglinger, 2016). This subtype seems to share with PSP-P the involvement of anatomical structures (Giagkou et al. 2019).

3.4. Corticobasal syndrome (PSP-CBS)

PSP-CBS exhibits reduced limb motor function, with apraxia, foreign limb syndrome, and impaired cortical sensory function (Adam et al. 2017; Respondek and Hoglinger, 2016). As the disease progresses, clinical signs include dystonia and myoclonus (Coughlin and Litvan, 2020). As other subtypes, this syndrome mainly affects cortical areas, causing cognitive signs (Coughlin and Litvan, 2020; Giagkou et al. 2019).

On the other hand, CBS shows asymmetric involuntary movements (especially rigidity, tremor, dystonia, and myoclonus), apraxia, cortical sensory deficit, and foreign limb phenomena (Jabbari et al. 2020). Thus, it is very difficult to make a differential diagnosis between PSP-CBS and CBS based on clinical data alone. This is why imaging findings or new diagnostical approaches will be helpful.

3.5. Speech and/or language (PSP-SL)

This progressive syndrome is characterized by agrammatism in language production, apraxia of speech (effortful, halting speech with inconsistent speech sound, errors, and distortions) (Adam et al. 2017) and progressive non-fluent aphasia (Coughlin and Litvan, 2020). Diagnostic criteria recognize this phenotype as a predominantly speech or language disorder, to which the motor signs of PSP-RS are added (years later in some cases) (Adam et al. 2017; Respondek and Hoglinger, 2016). This phenotype is included in the cognitive group, so it mainly affects the cortical area (Coughlin and Litvan, 2020; Giagkou et al. 2019).

3.6. Frontotemporal degeneration (PSP-FTD)

Subjects with PSP-FTD usually start with behavioral symptoms and at a later stage they develop motor symptoms of PSP-RS. Among behavioral symptoms, an early and progressive deterioration of personality (apathy, disinhibition, and hyperorality) and cognition has been described (Adam et al. 2017; Coughlin and Litvan, 2020; Respondek and Hoglinger, 2016).

3.7. Predominant cerebellar ataxia (PSP-C)

The patients show cerebellar ataxia as the first and main symptom. Motor signs include saccade movement impairment and unexplained falls. A Mayo Clinic autopsy series found that some PSP-C patients were misdiagnosed with multiple system atrophy. Clinical signs can be very similar in both diseases, but PSP-C patients did not suffer dysautonomia, as required to meet criteria for multiple system atrophy (Adam et al. 2017; Respondek and Hoglinger, 2016).

3.8. Ocular motor dysfunction (PSP-OM)

The patients have decreased vertical velocity and amplitude, with relatively preserved horizontal saccadic eye movements; this subtype usually present with PSP-RS-like symptoms (Parthimos and Schulpis, 2020; Respondek and Hoglinger, 2016).

3.9. Postural instability (PSP-PI)

The hallmark is a tendency to fall. Unprovoked falls are the predominant clinical manifestations in this subtype (Parthimos and Schulpis, 2020; Respondek and Hoglinger, 2016).

3.10. Primary lateral sclerosis (PSP-PLS)

This phenotype shows corticospinal tract degeneration, with upper motor neuron signs, and cortical atrophy in the precentral gyrus (Parthimos and Schulpis, 2020; Respondek and Hoglinger, 2016).

The main brain areas affected in each PSP-S subtype are shown in Fig. 3. Given that PSP-S affects different brain areas, a broad clinical spectrum is to be expected; thus, new tools for an accurate diagnosis and for monitoring the progression of each patient are much needed.

4. Neuroimaging and biomarkers

4.1. Neuroimaging

Imaging studies have provided valuable information on PSP-S. Magnetic resonance imaging (MRI) has allowed us to identify atrophy of the mesencephalon with relative preservation of the pons, a pathognomonic finding called the hummingbird or penguin sign; in general, midbrain atrophy is a consistent finding across all PSP-S groups (Stamelou et al., 2021). Similarly to the clinical features, MRI imaging data vary according to PSP-S subtype and are classified into two main groups: those with cortical involvement and those with subcortical involvement. The former group shows temporal lobe atrophy in addition to midbrain atrophy, whilst the second shows less in the midbrain, medulla, and central structures, with relatively preserved cortical volumes. Because of the similarities of CBS with PSP-S, the MRI features of the former should be noted, showing relative preservation of the pons and midbrain, but severe atrophy of central structures and cerebral cortex (Jabbari et al. 2020).

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to assess PSP-S patients. Using fluorine-18 fluorodeoxyglucose PET (18F-FDG-PET), glucose hypometabolism has been observed in midline frontal structures, midbrain, and cortical and subcortical motor areas. Similarly, frontal and prefrontal cortex and hypoperfusion have been observed with hexamethylpropylpropylamine SPECT (SPECT-HMPAO) and I-123-labeled iofetamine SPECT (SPECT-IMP), respectively (Alster et al., 2019). In the context of PET studies, ligands, including tau PET tracers, are imaging tools with great diagnostic potential in tauopathies. The [^{11}C]PBB3 tau tracer was first studied, observing its accumulation in expected anatomical regions, especially in PSP-S and CBS. [^{18}F]AV1451, the best studied PET tracer to date, has been useful to identify with greater specificity areas of frequent tau pathology in PSP-S and CBS patients. Finally, the new tau tracer [^{18}F]PI-2620 has been assessed to identify tau aggregation in AD, but it has been found to be of limited utility in 4R-tau pathology (Tezuka et al., 2021). In PSP-S patients, elevated [^{18}F]PI-2620 binding has been reported in the globus pallidus and subthalamic nucleus, but not in other regions. In addition, there is no correlation with disease severity or duration; these findings reassert the limited usefulness of this tau PET tracer to detect 4 R tau pathology (Brendel et al., 2020).

Thus, we need to develop imaging studies especially suited for PSP-S diagnosis, that correlate with clinical data and the areas affected by the disease.

4.2. Biomarkers: cerebrospinal fluid and peripheral blood

Although clinical signs are key in PSP-S diagnosis, a few biomarkers have been proposed as diagnostic aids. Most biomarkers aim at detecting of tau, so they could be valuable for an early diagnosis and staging of tauopathies. Biomarkers could also be useful to identify future therapeutic targets to improve the evolution of patients with PSP-S or other tauopathies (Magdalinou et al., 2015; Zhang et al., 2022). Our current knowledge on biomarkers for PSP-S will be discussed below.

When biomarkers for PSP-S were evaluated in cerebrospinal fluid (CSF), total tau (t-tau) and phosphorylated tau (p-tau) were found to be

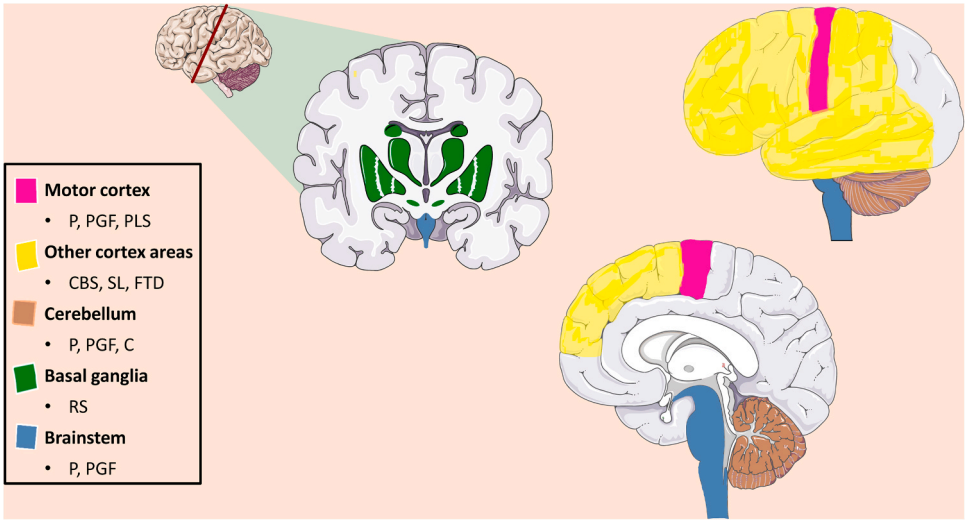

Fig. 3. Brain involvement according to PSP-S clinical phenotype. PSP-S subtypes affecting the motor cortex include parkinsonism type (PSP-P), progressive gait freezing (PSP-PGF), and primary lateral sclerosis (PSP-PLS). Separate areas of the cerebral cortex are affected by corticobasal syndrome subtype (PSP-CBS), speech and/or language (PSP-SL), and frontotemporal degeneration (PSP-FTD). The cerebellum is affected in the subtypes PSP-RS, PSP-PGF, and predominant cerebellar ataxia (PSP-C). Basal nuclei are affected in the Richardson's syndrome subtype (PSP-RS). Finally, the brainstem is affected in PSP-RS and PSP-PGF.

decreased with respect to healthy controls. Decreased p-tau levels were linked to accelerated disease progression (Rojas et al., 2018); this is interesting, as the opposite is true in AD (Wagshal et al., 2015). Another biomarker in CSF is neurofilament light chain (NfL), a marker of degeneration of large myelinated axons (Petzold and Petzold, 2005). Several studies have reported higher NfL levels in PSP-S patients with respect to healthy controls and to patients with Parkinson's disease, dementia, and dementia with Lewy bodies (Parthimos and Schulpis, 2020).

Several plasma biomarkers have also been proposed. Circulating NfL levels have been quantified to discriminate PD from other parkinsonian diseases, such as PSP-S. A study in which plasma NfL was quantified by an ultrasensitive single-molecule array (Simoa) method reported that NfL levels were increased in PSP-S patients with respect to PD patients and healthy controls. It has been hypothesized that plasma and CSF NfL levels are not increased in PD patients due in part to the less severe and widespread axonal degeneration observed in this disease (Hansson et al., 2017). In another study, increased serum NfL levels correlated with a worse functional, motor, and cognitive function in PSP-S patients. Furthermore, 119 PSP-S patients died during follow-up, and the short survival of these individuals was associated with high NfL levels. The authors concluded that serum NfL is a promising biomarker to assess PSP-S severity and could be used as a prognostic tool for patient survival (Donker Kaat et al., 2018).

Other potentially useful biomarkers are microRNAs (miRNAs). A systematic review on this subject discusses the role of miRNA dysregulation in different parkinsonian syndromes, including PSP-S (Bougea, 2022). One study reported that miRNAs could regulate the abundance of tau isoforms. Using the TargetScan algorithm, the authors explored the involvement of different miRNAs and observed an underexpression of miR-132 and an overexpression of the polypyrimidine tract-binding protein 2 (PTBP2) in PSP-S patients with respect to healthy controls. miR-132 was inversely correlated with PTBP2. It was suggested that changes in the miR-132/PTBP2 pathway could contribute to the abnormal binding of tau exon 10, which could imply that miRNAs are involved in the pathogenesis of PSP-S (Smith et al., 2011).

In another study, miRNAs from the forebrain of PSP-S patients and healthy controls were analyzed by TaqMan arrays and SYBR Green quantitative real-time PCR, finding an overexpression of miR-147 and miR-518e. Moreover, target genes of miR-147a (NF1, ACLY, ALG12) and miR-518e (CPEB1, JAZF1, RAP1B) were repressed. The authors concluded that miRNAs could also be involved in the development of PSP-S, specifically by repressing these target genes and probably by overexpressing neurotoxic proteins (Tatura et al., 2016).

Microarray chips were also used to analyze 2632 miRNAs in the CSF from PSP-S patients and healthy controls. From 32 miRNAs reported as upregulated, the most significant were miR-204–3p, miR-873–3p, and miR-6840–5p, which were involved in the ubiquitin proteosome system and autophagy (Nonaka et al., 2022).

Despite these results, the use of miRNAs in clinical practice remains limited, mainly due to the heterogeneity of studies and data scarcity (Bougea, 2022). miRNAs and other biomarkers could be useful for establishing an early diagnosis of PSP-S, following patients, and predicting survival.

5. Therapeutic advances

The few therapeutic options currently available for PSP-S aim to palliate the most common symptoms: bradykinesia and rigidity (levodopa), apathy and locomotion (amantadine), cognitive impairment (donepezil and rivastigmine), and eyelid-opening apraxia with blepharospasm (botulinum toxin injections). Unfortunately, some of these drugs have shown little clinical effect, such as levodopa treating bradykinesia and rigidity (Parthimos and Schulpis, 2020).

Based on our knowledge of PSP-S pathology, specific drugs that slow the progression of the disease have been sought after. Some of the most promising candidate drugs are described below.

In tauopathies, microtubule (MT) destabilization is caused by tau hyperphosphorylation and the ensuing lack of tubulin stabilizing MT structure. Paclitaxel showed efficacy as a MT stabilizer, but its clinical usefulness was hindered by its poor capacity to cross the BBB (Duggal and Mehan, 2019). Abeotaxane failed to alleviate PSP-S symptoms (Tsai et al., 2020). Epothilone D was effective in reducing amyloid accumulations, but clinical trials were discontinued after the occurrence of adverse effects (Fernandez-Valenzuela et al., 2020). CNDR-51657 was administrated orally to 9-month-old female PS19 mice. No adverse effects were reported, and it is a promising candidate for MT stabilization, currently under study (Zhang et al., 2018).

Inhibiting tau aggregation was proposed as a treatment approach, and it has shown promise in alleviating the disease. LMTX (methylthioninium) inhibits tau aggregation by blocking interprotein interactions (Melis et al., 2015). A phase III clinical trial demonstrated no

clinical benefit in AD patients (Gauthier et al., 2016). CLR01 reduced tau aggregation (Di et al., 2021), but no clinical trials have been conducted.

Another potential approach is regulating post-translational modifications of tau. Sodium selenate targets phosphatases, to control tau hyperphosphorylation. Larger placebo-controlled studies are required to confirm its usefulness (Vivash et al., 2022). Salsalate failed to show therapeutic effect as an anti-inflammatory drug, decreasing tau acetylation (Min et al., 2015). Further studies aimed at reducing tau expression are currently underway. Antisense oligonucleotides (ASO) reduced tau levels by 74% (Chakravarthy et al., 2020). mTOR inactivation (rapamycin) has reduced tau aggregation in mouse models (Salama et al., 2019) but may only work on early AD in humans. USP13 knockdown resulted in lower tau levels and increased clearance rates in mouse models (Liu et al., 2019).

Studies on immunization against tau-related pathogenic components are underway. Whilst some works have shown promising results, all of them require further research. Tau antibodies (especially IgG4) may either show clinical benefit (e.g., intracellular rTg4510 targeting in mouse models) or not (e.g., scFv targeting extracellular tau).

Various strategies have been explored to prevent or reduce tau aggregation. Drugs under development could decrease protein aggregates and thus delay the progression of the disease. However, it should be noted that, whilst some of these therapeutic strategies have shown minor benefit or caused adverse effects, they are still under evaluation as potential treatments for tauopathies (Zhang et al., 2022).

6. Immunology

6.1. Neuroinflammation status

Neuroinflammation has been recognized as a central component of neurodegenerative disorders such as PD and AD, but little is known about its impact on PSP-S and other diseases such as CBD. This topic has drawn great interest, as it could contribute to our understanding of the pathogenesis of PSP-S.

Several studies have explored a possible link between the pathogenesis of PSP-S and neuroinflammation. [11 C]PK11195 PET was used to detect neuroinflammation in a group of PSP-S patients. Intracellular neurofibrillary tangles and activated microglia were reported in the basal ganglia, midbrain, frontal lobe, and cerebellum of the patients (Gerhard et al., 2006).

Other studies combined [11 C]PK11195 PET to evaluate neuroinflammation by detecting activated microglia and [18 F]AV-1451 PET to identify tau in PSP-S patients. Microglial activation and increased aggregation of tau was found in cortical and subcortical areas of the brain of PSP-S patients; thus, neuroinflammation coexists with a known pathogenic factor for PSP-S (Malpetti et al., 2021; Malpetti et al., 2020). Neuroinflammation was proposed to increase PSP-S severity and progression (Malpetti et al., 2021).

Yet another study used [11 C]PK11195 PET to identify microglial activation in PSP-S patients. [11 C]PK11195 binding was higher in the thalamus, putamen, and pallidum in PSP-S patients with respect to healthy controls. Additionally, [11 C]PK11195 binding in the pallidum, midbrain, and pons correlated with PSP-S severity. These findings support the relevance of neuroinflammation in the pathogenesis of PSP-S (Passamonti et al., 2018).

In addition to PET, other methods have been used to assess microglial activation in PSP-S patients. The expression of genes such as *CXCR4* and those coding for microglial proteins has been assessed in the context of the disease (Conway et al., 2018). Increased expression of *CXCR4* was found in the cerebellum of PSP-S patients. Among the microglial genes, *CXCL12* has been associated with PSP-S (Alster et al., 2020).

Microglia activation leads to the secretion of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in PSP-S patients (van Olst et al., 2020). For instance, IL-1β levels have been correlated with microglia activation (Fernández-Botrán et al., 2011). Higher levels of C-reactive protein (CRP) and the proinflammatory cytokines TNF-α, IL-1β, and IL-6 have also been reported in the CSF of PSP-S patients with respect to PD patients (Starhof et al., 2018). Similarly, increased levels of IL-2 have been found in PSP-S patients with respect with healthy controls. Interestingly, IL-2 is expressed by neurons and glial cells of the prefrontal cortex (Rydbirk et al., 2019); that study also reported an increased expression of glycogen synthase kinase 3 beta (*GSK3B*) mRNA (Rydbirk et al., 2019). *GSK3B,* along with IL-2, regulates T and natural killer (NK) cells, so higher levels of both proteins suggest an association of PSP-S with peripheral inflammation, as it will be discussed in the next section.

Another important piece of evidence for the relevance of neuroinflammation in PSP-S is oxidative stress (OS). OS has only been studied indirectly in the context of PSP-S, by detecting higher levels of antioxidants such as SOD and glutathione in the brain of patients, where they are expressed as a defense mechanism (Cantuti-Castelvetri et al., 2002; Sian et al., 1994). On the other hand, iron has been found in the substantia nigra (SN) and globus pallidus of PSP-S patients (Galazka--Friedman et al., 2012); it is noteworthy that these brain areas show the highest levels of microglial activation, which could correlate with neuroinflammation (Bradaric et al., 2012).

LRRK2 has been suggested to activate the inflammasome, but whether it directly activates the NLRP3 inflammasome or follows an indirect pathway has not been elucidated (Liu et al., 2017; Weindel et al. nd). On the other hand, the NLRP3 inflammasome is thought to trigger neuroinflammation and eventually cause protein aggregation of α-synuclein and tau in PD and AD, respectively (Gordon et al., 2018; Heneka et al., 2013). The relevance of the NLRP3 inflammasome was confirmed by a study reporting that its inhibition prevents tau aggregation and AD progression (Ising et al., 2019). Although it has been studied in parkinsonian disorders such as PD and tauopathies such as AD, the role of LRRK2 and NLRP3 in PSP-S has not yet been explored.

Little is known on the function of neurotrophic factors such as the glial cell line-derived neurotrophic factor (GDNF) in PSP-S. In PD, GDNF is thought to have a protective effect on dopaminergic neurons, and decreased GDNF levels have been reported in neurons in PD. GDNF is also believed to have a protective role on glial cells and neurons in AD; both increased CSF levels and decreased serum levels have been reported (the latter possibly related to the stage of AD). Finally, serum and CSF GDNF levels were increased in PSP-S patients (specifically PSP-RS and PSP-P subtypes) with respect to healthy controls. Serum increase was higher in PSP-P, and CSF increase was higher in PSP-RS. Increased GDNF levels in CSF could indicate more severe atrophy and thus greater neurological deterioration, whereas serum increase could indicate a protective mechanism against neurodegeneration (or an early marker of disease). Nevertheless, more robust studies are required to confirm these hypotheses (Alster et al., 2024).

6.2. Peripheral inflammation status

Inflammation in tauopathies is not limited to the central nervous system, and inflammation signs have been detected in peripheral blood. As most papers have studied the role of inflammation in AD, there is little information on its link to PSP-S (Didonna, 2020).

In a study, serum cytokines were quantified, the phenotype of peripheral blood mononuclear cells (PBMCs) was determined by flow cytometry, and both parameters were compared between a PSP-S patient and his healthy twin brother. Increased IFNα2, TNFβ, IL-6, and IFNγ levels were found in the PSP-S patient, supporting the proinflammatory background of the disease. In line with this, higher levels of MCP-3 and MCP-1 were found, which could lead to increased monocyte (Schiess et al., 2016). Another study used the neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker and showed that this parameter was increased in PSP-S patients compared to PD patients and healthy controls (Inci et al., 2020). This NLR-related finding has been replicated in the most frequent PSP-S subtype, PSP-RS (Alster et al., 2021).

In another paper, serum fractalkine and 3-nitrotyrosine (3-NT) were

quantified by ELISA. Whilst both parameters were increased in PSP-S patients, they have been correlated to PD severity (Gupta et al., 2022).

Only one paper has reported changes in blood lymphocyte populations in PSP-S patients with respect to healthy controls. A shift in peripheral CD4+ and CD8+ T-cell populations toward higher counts of memory T cells (CD45RA−CD45RO+) and a reduction of naïve T cells (CD45RA+CD45RO−) was observed, in addition to higher counts of CD56+ NK cells, but not CD56+CD57 (Rydbirk et al., 2019). This study also reported higher GSK3B and IL-2 levels in PSP-S, which could explain the changes in lymphocyte populations (Rydbirk et al., 2019).

As mentioned above, several studies have been conducted to elucidate the role of interleukins in PSP-S. IL-1 and IL-6 have been widely studied in the context of neuroinflammation and peripheral inflammation. In this regard, increased levels of IL-1β and IL-6 in serum and of IL-6 in CSF were reported in PSP-S patients with respect to healthy controls. However, the impact of this finding on the progression of the disease remains to be elucidated (Madetko-Alster et al., 2023).

Despite the interesting findings in studies on the role of peripheral inflammation, further experiments with more robust methodology are required to conclude on the impact of PSP-S on peripheral inflammation, and vice versa.

7. Discussion

There is growing consensus that neuroinflammation is a key feature of neurodegeneration, and a neuroimmunological approach has become widespread in the two most common neurodegenerative diseases, AD and PD. However, the role of neuroinflammation in PSP-S has been little studied even though its relevance can be inferred from the clear overlap with AD, PD.

As a tauopathy, PSP-S has common traits with AD, and neuroinflammation is related to the presence of tau. The origin of tau aggregation remains largely unknown, but there is mounting evidence that neuroinflammation is involved in tangle formation (Didonna, 2020). The notion that neuroinflammation might precede protein aggregation is supported by the higher levels of proinflammatory cytokines such as IL-1β, TNF-α, and GM CSF in the CSF of patients with mild cognitive impairment (Tarkowski and Andreasen, 2003). Among these cytokines, IL-1β and TNF-α, which are secreted by activated microglia, promote tau hyperphosphorylation and aggregation (Gorlovoy et al., 2009).

Considering this evidence, mostly collected from studies on AD, it could be hypothesized that cytokines such as IFNα2, TNFβ, IL-6 and IFNγ could also play a significant role in the pathophysiology of PSP-S (Schiess et al., 2016), specifically in the post-translational changes of tau leading to its pathological aggregation.

Tau aggregation could also aggravate neuroinflammation via feedback mechanisms, amplifying initial neurotoxicity (Didonna, 2020) and mediating further microglial activation (Morales et al., 2013). M2, the microglial phenotype typically associated with the early stages of tauopathies, is linked to the production of anti-inflammatory interleukins such as IL-4, IL-10, IL-13 and TGF-β; in later stages, the M2 phenotype shifts to M1, triggering a proinflammatory process mediated by reactive oxygen species (ROS), nitric oxide (NO), and cytokines such as IL-1β, IL-6, IL-12, IL-23, and TNF-α (Tang and Le, 2016). Although CBS and PSP-S exhibit the most pathophysiological and clinical similarities among tauopathies, little is known on the role of neuroinflammation and peripheral inflammation in the progression of both diseases. Thus, the current knowledge of tau in CBS could be useful to elucidate the pathophysiology of PSP-S.

On the other hand, as a parkinsonian disorder, PSP-S also shares some traits with PD. The importance of this in clinical practice is such that PSP-S constitutes an important differential diagnosis of PD. As in AD with tau, neuroinflammation is closely related to α-synuclein in PD. Specifically, the bridge between neuroinflammation and neurodegeneration in PD is thought to be microglial-derived oxidative stress (Gao et al., 2011). Microglial cells activated by diffusible and oligomeric α-synuclein may be the primary driver in the early stages of PD-like neurodegeneration (Garcia et al., 2022). Finally, aggregation of misfolded α-synuclein is thought to induce mitochondrial dysfunction in microglia (Sarkar et al., 2020); thus, like tau in AD, misfolded α-synuclein would enhance neuroinflammation in PD. Microglia are the most well-studied neuroinflammatory cells in the context of neurodegeneration in AD and PD, and this could be a common trait with PSP-S. However, additional information is required to conclude whether microglia participate in protein aggregation in PSP-S, and whether their involvement results in a neuroinflammatory cascade and further neurodegeneration.

Whilst the role of inflammation in the central nervous system seems to be clear, inflammation mediators in peripheral blood could allow us to identify possible biomarkers for neurodegenerative diseases and improve our understanding on the role of immune cells in these disorders.

Finally, to understand the role of neuroinflammation in neurodegeneration, it is essential to determine the origin of the inflammatory process. While there is no explanation for the specific etiology of neuroinflammation in PSP-S, the study of risk factors could help elucidate it. Risk factors include demographic (being the age and sex best described in PSP-S), environmental (smoking, exposure to chemicals or heavy metals), and medical (systemic arterial hypertension) causes (Savica R et al., 2013; Litvan et al., 2016; Alquezar et al., 2020; Rabadia et al., 2019). Genetic factors, specifically different MAPT haplotypes, have also been reported to increase the risk of developing PSP-S; MOPB, STX6, EIF2AK3, and LRRK2 have also been linked to the disease (Baker et al., 1999; Kouri et al., 2015; Höglinger et al., 2011; Strauß et al., 2021; Heckman et al., 2019; Spillantini and Goedert, 2013; Jabbari et al., 2021; Sanchez-Contreras et al., 2017). These genetic factors are of utmost importance, as they specifically lead to protein aggregation and neurodegeneration. Interestingly, little has been published on the relationship between genetic background and inflammation in PSP-S. It is crucial to establish the link between general risk factors and genetic factors with inflammation and the ensuing neurodegeneration in PSP-S and other neurodegenerative diseases, as this could pave the way for new disease markers, protective factors, preventive strategies in public health, and even therapeutic approaches.

8. Conclusion

In the context of the immune response in PSP-S, the coexistence of neuroinflammation with tau aggregation and neurodegeneration may explain, at least in part, the pathogenesis of the disease. However, little is still known on the mechanism by which these factors are interrelated. The current literature on the subject has not determined whether neuroinflammation is the cause or the effect of neurodegeneration. Thus, despite the findings herein discussed, more information is required to determine the true role of neuroinflammation in the pathogenesis of PSP-S.

Further research on the role of immune cells and soluble mediators could provide valuable information on PSP-S. For instance, understanding the role of immune cells in the pathophysiology of PSP-S could allow us to compare their counts in each disease subtype, correlate them with imaging findings, and determine their impact on the progression or severity of PSP-S. In addition, studying peripheral inflammation, especially serum levels of interleukins, could allow us to identify early markers of the disease. Finally, knowing the role of proinflammatory cells and molecules such as neurotrophic factors or interleukins in each PSP-S subtype could guide us in the search for immunomodulatory drugs and develop a disease-modifying therapy.

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Eduardo Ichikawa-Escamilla: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Rodrigo A. Velasco-Martinez:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Laura Adalid-Peralta:** Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

EI-E and LA-P conceived, designed, and organized the manuscript. All authors collaborated in manuscript writing. All authors reviewed and criticized the manuscript. All authors read and approved the final manuscript.

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