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REVIEW ARTICLE

"Parkinson's disease" on the way to progressive supranuclear palsy: a review on PSP-parkinsonism

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Abstract

Progressive supranuclear palsy (PSP) is a progressive atypical parkinsonian syndrome characterised by postural instability, supranuclear ophthalmoplegia, dysarthria, dysphagia, executive dysfunction and other features. This clinical presentation represents the classic PSP-Richardson syndrome (PSP-RS). However, several other clinical subtypes have been recognised, including PSP-parkinsonism (PSP-P), probably the second most common PSP variant. Unlike PSP-RS, PSP-P often presents with an asymmetric onset, tremor and a moderate initial response to levodopa, especially during the first years of the disease, thus resembling Parkinson's disease (PD). It runs a more favourable course, but over time, PSP-P may evolve clinically into PSP-RS. Therefore, it may seem that PSP-P stands clinically between PD and PSP. There are several peculiarities that can distinguish PSP-P from these entities. As there is lack of systematic reviews on PSP-P in the literature, we decided to summarise all the necessary data about the epidemiology, clinical picture, neuroimaging, genetics and other aspects of this PSP variant in order to provide complete information for the reader.

Keywords PSP · Progressive supranuclear palsy-parkinsonism · Clinical picture · Diagnosis · Review article

Introduction

In the original article by Steele, Richardson and Olszewski in 1964 [1], the authors described nine cases with a distinct progressive brain disease featuring in particular vertical supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria, nuchal and upper trunk dystonic rigidity, mild dementia and other less constant symptoms. Very precise microscopic and macroscopic findings in all of these cases showed the presence of extensive subcortical neurofibrillary degeneration, predominantly in the globus pallidus, subthalamic nucleus, substantia nigra and dentate nucleus [1]. Steele-Richardson-Olszewski syndrome, or progressive supranuclear palsy (PSP), belongs to a group of clinically, morphologically and biochemically heterogeneous diseases called tauopathies. Pathological hallmarks of PSP are neurofibrillary tangles, globose tangles, tufted astrocytes and coiled bodies, containing the hyperphosphorylated 4R isoform of the tau protein [2]. The most common and the classic clinical presentation of this progressive disease described above is now termed Richardson syndrome (PSP-RS). It is characterised by insidious onset of non-specific symptoms, such as photophobia, blurred vision, unsteadiness and sporadic unprovoked falls. The disease runs a gradual progressive course, with developing apathy, depression, irritability, executive dysfunction, pseudobulbar palsy, dysarthria, slowing of predominantly vertical saccades, axial rigidity and an increasing frequency and severity of falls. Late stages are accompanied by swallowing difficulties and complete ophthalmoplegia and akinetic mutism [3, 4]. However, as Steele et al. in the summary of their seminal paper correctly assumed [1], it has been shown that the phenotypic spectrum of PSP is much broader. Several distinct clinical variants of PSP with typical PSP pathology have been described: PSP-parkinsonism (PSP-P), PSP-pure akinesia with gait freezing (PSP-PAGF), PSP-corticobasal syndrome (PSP-CBS), PSP-behavioural variant of frontotemporal dementia (PSP-bvFTD), PSP-progressive non-fluent aphasia (PSP-PNFA), PSP with speech and language dysfunction (PSP-SL), PSP-postural instability (PSP-PI), PSP-ocular motor dysfunction (PSP-OM), PSP-cerebellar ataxia (PSP-C), PSP-primary lateral sclerosis (PSP-PLS) and PSP-pallido-nigro-luysian degeneration and axonal atrophy (PSP-PNLA) [5–19].

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Clinical symptoms of PSP-P, probably the second most common PSP subtype, are very difficult to differentiate from Parkinson's disease (PD), especially in its early stage [9]. One could get the impression that PSP-P stands clinically somewhere between PD and PSP. Although there is general lack of data focusing on PSP-P in various aspects of the disease (imaging, genetics and others), we aimed to provide a review of this interesting subtype by putting all the available important information together.

Epidemiology

The prevalence of PSP is generally 5–6 cases per 100,000 and increases with age (in people above 80, it is 14.7 cases per 100,000). Median age of onset is 63 years, and mean survival time is 6–7 years [6]. The prevalence of PSP-P in the population has not been estimated; however, a number of studies indicate that it is the second most common clinical PSP subtype [5, 9, 19]. A recent study with a large sample of PSP patients showed that 36% of them represent PSP-P [20]. Data from 100 pathologically proven PSP cases showed that the mean age of onset was 62.0 years in PSP-RS, whereas 67.7 years in PSP-P, while the mean duration of the disease in PSP-P was much longer (12.8 years) than in PSP-RS (7.3 years), and the mean latency to final diagnosis in PSP-P was significantly more prolonged (10.0 years compared to 2.3 years in PSP-RS) [5]. Whereas the male-to-female ratio in PSP-RS is about 1.8:1, the sex distribution in the PSP-P phenotype was found to be equal [9]. Other studies focusing on the demographics of PSP-P are lacking.

Motor features and natural course

PSP-P as a subgroup of pathologically proven cases was first clinically described by Williams et al. [9]. Unlike PSP-RS, which is characterised by the early onset of postural instability and falls, supranuclear vertical gaze palsy and cognitive dysfunction, PSP-P patients often present with an asymmetric onset, tremor and moderate initial response to levodopa [9, 21]. This group is frequently confused with Parkinson's disease (PD), and during the first years, PSP-P and PD may even be indistinguishable [8, 10, 22]. On the other hand, clinical differences between PSP-RS and PSP-P (with more or less overlap) are more evident in the first 2 years, but after a few years, the clinical picture phenomenology may become similar [8, 21]. A prospective study of these PSP groups by Shoeibi et al. [23] showed that even when disease severity and clinical features at baseline were similar, patients with PSP-RS progressed significantly faster than those with PSP-P. Thus, PSP-P patients run a more favourable course with longer survival [24]. Over the course of the disease, PSP-P may evolve into PSP-RS [8, 25]. Therefore, clinical diagnosis of PSP-P is made retrospectively. For instance, it is made in a patient with levodopa-responsive parkinsonism who develop other features typical for PSP-RS [23]. Although PSP-P can be reminiscent of PD, features such as visual hallucinations, drug-induced dyskinesias and autonomic dysfunction are possibly exclusive features of PSP-P [10].

In the early stage of PSP-P, unlike PSP-RS, patients are much less prone to display postural instability or to fall [9, 10, 21, 25]. Tremor [9, 10, 21] and asymmetry of the clinical picture [9, 10, 21, 25] are characteristic for PSP-P. Interestingly, although vertical supranuclear palsy rarely presents early in PSP-P [9, 25], saccades and pursuit are disturbed in both variants in this stage [21, 23, 25]. Other features, such as bradykinesia, limb or axial rigidity/dystonia, or even speech disturbance and dysphagia [9, 10, 21, 23, 25], do not significantly differentiate these two subtypes. However, it is important that only two series included also pathologically confirmed data [9, 10]. In the later stages, only tremor is still more frequently seen in PSP-P [9, 10, 21]. All of the other above-mentioned clinical features tend to be quite similar and common in the course of the disease [9, 10, 21, 23, 24]. Also, in the later stages, clinical features of pathologically proven and pure clinically observed cases in both conditions are more consistent than in early stages. To see a comparison of the clinical features of both phenotypes in the early and the late course of the disease expressed as a percentage, see Table 1 and Table 2, respectively.

One particular sign in the PSP-P group has been demonstrated by video fluoroscopy. The abnormal non-functional trembling movements of the tongue and palate during chewing and volitional swallowing, with the 6- to 8-Hz frequency that is typical for freezing episodes, was called "freezing of swallowing" [26].

Non-motor features

Cognitive dysfunctions, as well as other various non-motor symptoms, are present in PSP, even in the prediagnostic phase [27–29]. There are only limited but increasing data regarding the PSP-P subtype in this view. It seems that the overall degree of cognitive dysfunction measured by standard cognitive scales is lower than in PSP-RS [21, 23, 24, 30]. One study examined neuropsychiatric and cognitive profiles in PSP-P and PSP-RS within 24 months from motor symptom onset and showed that early phonological verbal fluency deficit is linked with PSP-RS patients, whereas apathy supported the diagnosis of PSP-P [25]. A recent work by Vaccaro et al. [31] using machine learning, an artificial intelligence approach, showed that digit span forwards, a measure of short-term memory, had an important role in differentiating PSP-P from PSP-RS. The bradyphrenia, disorientation,

Table 1 Comparison of early clinical features in PSP-P and PSP-RS

PSP-P					Early clinical features (%)	PSP-RS			
Williams et al. [9]	Williams et al. [10]	Srujiles et al. [21]	Shoeibi et al. [23]	Pellicano et al. [25]		Williams et al. [9]	Srujiles et al. [21]	Shoeibi et al. [23]	Pellicano et al. [25]
7.7	**19**	33.3	91.5	30	Postural instability	**84.4**	100	92.2	100
0		0	100	0	Falls	**85.7**	92.9	92.2	85.7
73.9		88.9			Bradykinesia	**75.6**	42.9		
52.5			80.9		Limb rigidity	**39.5**		87.5	
	27		85.1		Neck rigidity/dystonia			87.5	
8.7	**66**	33.3			Extra-axial dystonia	**0**	14.3		
26.1	**30**	100	93.6	30	Speech disturbance	**32.5**	92.9	96.9	57
4.3	**11**	66.7	63.8		Dysphagia	**2.7**	57.1	75.0	
4.3	**8**				Pyramidal signs	**7.7**			
0		33.3		18	Supranuclear gaze palsy	**70**	100		100
0		55.6	95.7* 95.7**	63	Abnormal saccades/pursuit	**63.6**	100	98.4* 98.4**	100
39.1	**51**	11.1			Tremor	**9.8**	7.1		
45	**46**	77.8		85	Asymmetric symptoms	**17.9**	21.4		14

Clinical data from pathologically proven cases are in bold

*Voluntary downward saccades

**Voluntary upward saccades

emotional incontinence and anxiety/depression items of the PSP-rating scale scores in PSP-P patients are lower compared to PSP-RS [23]. Moreover, the total Non-Motor Symptoms Scale (NMSS) scores of PSP-P patients are slightly lower, with the sleep/fatigue (87%), mood/cognition (68%) and gastrointestinal tract (56%) items being the most prevalent [28].

Clinical diagnostic criteria

The National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) clinical criteria published in 1996 [32] was replaced in 2017 by the Movement Disorder Society criteria for clinical diagnosis of PSP (MDS-PSP criteria) [33]. Although the former had excellent specificity, they showed limited sensitivity, mainly for PSP clinical variants other than PSP-RS. The overall sensitivity of the MDS-PSP criteria was 87.9%, compared with 45.5% for the NINDS-SPSP criteria [34]. These newly proposed criteria have been rapidly spread within the movement disorders community. The following four clinical domains were proposed: oculomotor dysfunction (O), postural instability (P), akinesia (A) and cognitive impairment and language disorders (C). Combinations of them graded by their level of certainty (3, highest; 2, mid; 3, lowest) lead to establishing the predominant PSP variant, with the following diagnostic categories, for instance, "probable" PSP-P, "possible" PSP-P or "suggestive" of PSP-P. Diagnosis of "definite" PSP can only be made post-mortem. The newly introduced category "suggestive of PSP" represents subtle early signs of the disease that do not meet the threshold for possible or probable PSP. Moreover, there are two categories of supportive features which can be helpful—clinical clues (CC1-CC4) and imaging findings (IF1, IF2) [33].

Of note, most of the reported studies comparing PSP-P and PSP-RS phenotype [9, 10, 21, 24] were published before the drafting the MDS-PSP criteria in 2017 [33]. In these studies, the clinical diagnosis was probably based on the subjective judgement.

Neuropathology

As mentioned above, a definite diagnosis of PSP can be estimated only post-mortem [34]. The neuropathological signature of PSP is an accumulation of neurofibrillary tangles composed of tau protein and neuropil threads in the subthalamic nucleus, striatum, pallidum and brainstem regions (red nucleus, substantia nigra, pontine tegmentum, oculomotor nucleus), as well as the medulla oblongata, dentate nucleus and, to a lesser extent, in the cerebral cortex, together with so-called tufted astrocytes and oligodendroglial coiled bodies. The predominance of the 4R isoform of the tau protein leads to the designation of PSP as a primary 4R tauopathy [35]. According to the old classification proposed by Lantos

Table 2 Comparison of late clinical features in PSP-P and PSP-RS

PSP-P						Late clinical features (%)	PSP-RS				
Williams et al. [9]	Williams et al. [10]	Srujiles et al. [21]	Shoeibi et al. [23]	Jecmenica-Lukic et al. [24]	Pellicano et al. [25]		Williams et al. [9]	Srujiles et al. [21]	Shoeibi et al. [23]	Jecmenica-Lukic et al. [24]	Pellicano et al. [25]
96	**97**	100	92.9		100	Postural instability	**100**	100	93.8		100
86.6	**97**	67.7	100	95.2	63	Falls	**100**	100	92.6	96.1	100
96.9		100				Bradykinesia	**98.2**	100			
96.8			80.4			Limb rigidity	**98.1**		88.9		
	71		80.4			Neck rigidity/dystonia			90.1		
42.4	**92**	33.3				Extra-axial dystonia	**21.2**	7.1			
81.3		100	91.1	33.3	54	Speech disturbance	**90.2**	92.9	97.5	58.8	78
56.3	**75**	67.7	66.1	71.4		Dysphagia	**75.5**	64.3	72.8	58.8	
15.6						Pyramidal signs	**17**				
71.4	**68**	100			100	Supranuclear gaze palsy	**100**	100			100
	83	100	94.6* 94.6**		100	Abnormal saccades/pursuit		100	97.5* 98.8**		100
43.8	**58**	11.1				Tremor	**13**	7.1			
		67.7			54	Asymmetric symptoms		50			

Clinical data from pathologically proven cases are in bold

*Voluntary downward saccades

**Voluntary upward saccades

[36], these pathological changes represent type 1 (or typical) cases of PSP, hence PSP-RS. Type 2 (atypical) changes (variants of histological changes characteristic of either the severity or the distribution of abnormalities, or both) pointed to the clinical and pathological heterogeneity of the disease. In the original description of PSP, the authors hinted at the possibility of clinicopathologic variants or "forme frustes" [37], recognised today as clinical variants of PSP, e.g. PSP-P. Based on the prevailing site of the pathological-anatomic changes, we can divide atypical presentations of PSP into two categories: brainstem (or caudal-predominant) (including PSP-P and PSP-PAGF) and cortical (or rostral-predominant) (e.g. PSP-CBS or PSP-PLS) [38, 39]. Moreover, PSP-P differs from PSP-RS not only by anatomical distribution of histological changes but also by the lesser extent of glial pathology [40] and greater degree of the 3R tau isoform [9].

MRI

Typical findings on conventional MRI of the head in PSP patients (namely PSP-RS) include midbrain atrophy (with so-called hummingbird and morning glory signs on sagittal and axial images, respectively), atrophy of the superior cerebellar peduncles (SCP), signal changes of the periaqueductal region on T2-weighted images or hyperintensity of the SCP and brainstem tegmentum on FLAIR images [40]. Quantitative MRI measurements of brainstem structures have been proposed as potentially useful markers to distinguish patients with PSP-RS from those with PD and other parkinsonian syndromes [41, 42]. However, differentiating between the other PSP subtypes seems more problematic [43]. The study of Longoni et al. [44] evaluated MRI of 10 patients with PSP-RS, 10 with PSP-P, 25 with PD and 24 healthy controls (HC). The authors concluded that although midbrain atrophy relevantly distinguished typical (PSP-RS) and atypical PSP cases from HC and PD patients, PSP-P patients did not have midbrain atrophy as significant as in PSP-RS. Additionally, the SCP volume was found to be normal in PSP-P patients in comparison to PSP-RS [44]. In another study, a large cohort of 110 patients with an initial diagnosis of PD and 74 HC were prospectively observed for a period of 4 years. This study evaluated MRI data of the pons-to-midbrain ratio (P/M and P/M 2.0) and the MR parkinsonism index (MRPI and MRPI 2.0) as well as clinical data. Ten patients out of 110 developed vertical gaze abnormalities, suggesting the advancement into a PSP-P phenotype. The MRPI 2.0 turned out to be most suspicious when forecasting the evolution of vertical gaze abnormalities and clinical progression from PD to PSP-P [45]. The 3 T MRI study using automated surface-based analysis of five anatomical parts of the callosal body showed that patients with PSP-RS have a lower volume of the central part (labelled as CC3) compared to PSP-P patients. No significant differences in the pattern of callosal atrophy in PSP-P and early PD were found [46].

Other more complicated MRI methods have been studied. Nicoletti et al. [47] focused on the pathology of SCP in PSP-P, PSP-RS, PD and HC. MRI images of SCP were identified by tractography-based atlas of white matter tracts. Subsequently, the volume, mean diffusivity and fractional anisotropy were extracted from them. Both PSP-RS and PSP-P patients showed decreased volume and fractional anisotropy compared to PD patients and HC. PSP-RS patients had significantly altered fractional anisotropy and mean diffusivity in the left SCP compared with PSP-P patients. The authors stated that this fully automated method can distinguish PSP-P patients from both PSP-RS and PD with nearly 70% accuracy. Another promising result in differentiating PSP subtypes is MRI diffusion tensor imaging (DTI). Potrusil et al. [48] characterised the microstructural integrity of white matter (large fascicular bundles, such as anterior thalamic radiation, corticospinal tract, superior longitudinal fasciculus, corpus callosum and dentatorubrothalamic tract) using standardised probabilistic tractography combined with DTI and volumetric measures of subcortical structures (dorsal midbrain, globus pallidus and thalamus) in PSP-RS, PSP-P and PD patients. Diagnostic accuracy in determining these disorders was above 90%.

Transcranial sonography

In patients with PD, a hyperechogenic substantia nigra (SN) and normal echogenicity of lenticular nucleus (LN) on transcranial sonography (TCS) are characteristic findings. Normoechogenic SN is more typical in patients with PSP [49, 50]. Kostic et al. [50] compared the results of TCS in patients with PSP-RS and PSP-P and found that hyperechogenicity of SN was present in 73% of PSP-P patients, but in the PSP-RS group, this occurred in only 3 of 21 patients (14%). Conversely, hyperechogenicity of LN was more common in PSP-RS (67% vs 36%). Hyperechogenicity of SN in PSP-P and normoechogenicity in PSP-RS were also confirmed in the study of Ebentheuer et al. [50]. The third ventricle was significantly wider in the PSP-RS group compared to PSP-P in both studies (the mean width was 10.3 vs 7.1 mL and 11.2 vs 7.5 mL, respectively) [50, 51]. This was also confirmed by a Spanish group which focused mainly on measuring the mesencephalic area. Whereas PSP patients as a whole group have a smaller mesencephalic area compared to PD patients (with 4.27 cm^2 being the discrimination threshold with 100% positive predictive value), no differences were found in the mesencephalic area between the two PSP phenotypes [52].

SPECT

Presynaptic striatal dopamine imaging using the dopamine active transporter (DAT scan) is decreased in PSP in comparison to HC, but it cannot reliably distinguish between PD and other atypical parkinsonian syndromes. D2 receptor ligands imaging (most commonly [123I]-IZBM SPECT) assessing postsynaptic dopaminergic function is also mostly reduced in PSP [53]. There is lack of studies focusing on SPECT imaging in other PSP variants. Moreover, as far as we know, the only study regarding PSP-P is that of Lin et al. [54]. In the DAT scan, the mean striatal uptake was insignificantly reduced in the PSP-RS group compared to the PSP-P group. No difference in the putamen-to-caudate ratios was found between the two groups. In the [123I]-IZBM SPECT, striatal uptake was significantly reduced in the PSP-RS patients. However, it was mildly increased in the PSP-P group [54].

PET

^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, as a marker of neuronal damage, is a useful tool to achieve a differential diagnosis of neurodegenerative parkinsonism, even in early stages and in the absence of obvious MRI features [55]. The most common FDG-PET findings in PSP-RS are hypometabolism of the thalamus, caudate, midbrain and frontal lobes [56]. Compared to HC, PSP-P patients showed relative hypometabolism in the mesencephalon, caudate and thalamus (similarly as PSP-RS); however, the findings were more asymmetric, and there was higher hypometabolism in the putamen. Like in PSP-RS, they also showed relative hypermetabolism in the cerebellum, posterior insular cortex, primary motor cortex and somatosensory cortex; however, the occipital regions were spared in PSP-P patients [57]. Greater putaminal hypometabolism reflecting more severe parkinsonism with less pronounced involvement of the thalamus in PSP-P (putamen/thalamus ratio) can be a useful parameter differentiating these two PSP phenotypes with 100% sensitivity and 75% specificity. Moreover, PSP-P patients do not show as much frontal hypometabolism [58].

The number of new PET ligands with selective binding to aggregated tau inclusions has been developed as a biomarker of tau pathology, including ^{11}C- PBB3, ^{18}F- THK and ^{18}F-AV-1451 [52, 58, 59]. Using these ligands, most PSP patients show increased tracer binding in the pallidum, midbrain, dentate nucleus, thalamus, caudate nucleus and frontal cortex [59]. In the study of Whitwell [60], 105 various PSP patients, including 53 patients with PSP-RS and 12 with PSP-P, underwent volumetric MRI, followed by ^{18}F-AV-1451(or flortaucipir)-PET performed in more than half of them. All variants were associated with atrophy or increased uptake in the striatum, globus pallidus and thalamus. The PSP-P and also PSP-PAGF variants showed more restricted patterns of neurodegeneration, predominantly involving the striatum, globus pallidus, subthalamic nucleus and thalamus (with the highest uptake in the putamen and globus pallidus among all the PSP variants). Compared to the other PSP variants, PSP-P showed relatively spared midbrain volumes [60].

Genetics

In general, PSP is considered a sporadic neurodegenerative disease [61]. However, in a subset of patients, a familiar occurrence was observed, mainly on an autosomal dominant inheritance basis [62, 63]. To date, more than 10 genes have been reported to show a potential association with PSP [61]. The *MAPT* (microtubule-associated protein tau) mutation has been reported in both sporadic and familiar cases of PSP. In total, 15 different mutations have been described, leading to total prevalence in PSP of up to 14%. Haplotype H1, with 238 bp in intron 9, and especially H1c, as well as some other *MAPT* subhaplotypes, are overrepresented in PSP patients [61]. Leucine-rich repeat kinase 2 (*LRRK2*) mutations can cause, rarely, monogenic PSP [64]. One very nice description from Crete of a patient with typical PSP-P with the R1441H *LRRK2* mutation has been reported [65]. Moreover, several risk loci of PSP have been identified through genome-wide association studies, including *EIF2AK3*, *STX6*, *MOBP*, *DUSP10* and others [66, 67]. There are very limited data regarding the PSP-P phenotype associated with genetic abnormality. Another paper reports on a patient with PSP-P carrying *FBOX7* and *VPS35* variants. In addition to predominant alpha-synuclein pathology, tau-positive inclusions were also found in him [68].

Cerebrospinal fluid studies

Many studies have been performed in an effort to find a cerebrospinal fluid (CSF) biomarker reliable in distinguishing between patients with PSP and PD or other neurodegenerative diseases [6, 8, 69–72]. Owing to pathogenesis, one could assume that CSF tau protein levels should be increased in PSP. However, levels of total tau and phospho-tau in PSP patients are often in a normal range, or in the case of the 4-R isoform, even decreased compared to HC [6, 8, 69]. Neurofilament light chains (NF-L) in CSF, which are significantly higher in PSP compared to PD and HC [6, 69–71], contribute to more rapid neurodegeneration and more severe course of the disease [6]. But no significant differences in the levels of CSF tau protein or NF-L have been found regarding the PSP phenotypes, including PSP-P [21, 69, 70].

Treatment

Patients with PSP (typically PSP-RS) do not respond or only very poorly respond to levodopa and other dopaminergic drugs. Marked and long-standing responsiveness to levodopa rather excludes a diagnosis of PSP [73]. Neifort et al. [74] reported that 31% of PSP patients showed minimal and 6% showed moderate improvement. These patients likely represented a mixed sample of various PSP forms. However, Williams et al. [9] were the first to describe levodopa responsiveness that is also in PSP-P patients, 50% of whom were levodopa responsive (with more than 30% improvement in symptoms) compared to 14% in PSP-RS. Levodopa-induced dyskinesias were rare in both groups but slightly more frequent in PSP-P patients (6% vs 2%) [9]. To our best knowledge, there is no effective and long-acting drug for symptomatic treatment of PSP-P and no anti-tau or other pathogenetic-based treatment in clinical studies regarding PSP-P.

Conclusion

PSP-P is the second most common PSP clinical variant and is, in general, underreported. In this review, we have provided complex information regarding its epidemiology, clinical point of view, neuropathology, diagnostic methods and treatment. The diagnosis can be made retrospectively based on clinical features (especially in the later stages) using the MDS-PSP diagnostic criteria. Moreover, several clues pointing to PSP-P can also be obtained from neuroimaging or other diagnostic methods, useful both for routine clinical praxis and research. However, further studies mainly focused on biomarkers or treatment of PSP-P patients are specifically needed.

Author contribution Idea of the article (JN), literature search (JN, MB, BJ), draft (JN), critical revision of the work (JN, MB, BJ).

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval None.

Informed consent None.

References

1. Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol 10:333–359. https://doi.org/10.1001/archneur.1964.00460160003001
2. Götz J, Halliday G, Nisbet RM (2019) Molecular pathogenesis of the tauopathies. Annu Rev Pathol 14:239–261. https://doi.org/10.1146/annurev-pathmechdis-012418-012936
3. Ling H (2016) Clinical Approach to Progressive Supranuclear Palsy. J Mov Disord 9:3–13. https://doi.org/10.14802/jmd.15060
4. Colosimo C, Bak TH, Bologna M, Berardelli A (2014) Fifty years of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 85:938–944. https://doi.org/10.1136/jnnp-2013-305740
5. Respondek G, Stamelou M, Kurz C, Ferguson LW, Rajput A, Chiu WZ, van Swieten JC, Troakes C, Al Sarraj S, Gelpi E, Gaig C, Tolosa E, Oertel WH, Giese A, Roeber S, Arzberger T, Wagenpfeil S, Höglinger GU, Movement Disorder Society-endorsed PSP Study Group (2014) The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. Mov Disord 29:1758–1766. https://doi.org/10.1002/mds.26054
6. Parthimos TP, Schulpis KH (2020) The progressive supranuclear palsy: past and present aspects. Clin Gerontol 43:155–180. https://doi.org/10.1080/07317115.2019.1694115
7. Lopez G, Bayulkem K, Hallett M (2016) Progressive supranuclear palsy (PSP): Richardson syndrome and other PSP variants. Acta Neurol Scand 134:242–249. https://doi.org/10.1111/ane.12546
8. Alster P, Madetko N, Koziorowski D, Friedman A (2020) Progressive supranuclear palsy-parkinsonism predominant (PSP-P)-a clinical challenge at the boundaries of PSP and Parkinson's disease (PD). Front Neurol 11:180. https://doi.org/10.3389/fneur.2020.00180
9. Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, Holton JL, Revesz T, Lees AJ (2005) Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 128:1247–1258. https://doi.org/10.1093/brain/awh488
10. Williams DR, Lees AJ (2010) What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-parkinsonism (PSP-P)? Mov Disord 25:357–362. https://doi.org/10.1002/mds.22977
11. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ (2007) Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord 22:2235–2241. https://doi.org/10.1002/mds.21698
12. Ling H, de Silva R, Massey LA, Courtney R, Hondhamuni G, Bajaj N, Lowe J, Holton JL, Lees A, Revesz T (2014) Characteristics of progressive supranuclear palsy presenting with corticobasal syndrome: a cortical variant. Neuropathol Appl Neurobiol 40:149–163. https://doi.org/10.1111/nan.12037
13. Hassan A, Parisi JE, Josephs KA (2012) Autopsy-proven progressive supranuclear palsy presenting as behavioral variant frontotemporal dementia. Neurocase 18:478–488. https://doi.org/10.1080/13554794.2011.627345
14. Rohrer JD, Paviour D, Bronstein AM, O'Sullivan SS, Lees A, Warren JD (2010) Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis. Mov Disord 25:179–188. https://doi.org/10.1002/mds.22946
15. Whitwell JL, Stevens CA, Duffy JR, Clark HM, Machulda MM, Strand EA, Martin PR, Utianski RL, Botha H, Spychalla AJ, Senjem ML, Schwarz CG, Jack CR Jr, Ali F, Hassan A, Josephs KA (2019) An evaluation of the progressive supranuclear palsy speech/language variant. Mov Disord 6:452–461. https://doi.org/10.1002/mdc3.12796
16. Kurz C, Ebersbach G, Respondek G, Giese A, Arzberger T, Höglinger GU (2016) An autopsy-confirmed case of

progressive supranuclear palsy with predominant postural instability. Acta Neuropathol Commun 4:120. https://doi.org/10.1186/s40478-016-0391-7

17 Xu Z, Lim T, Au WL, Tan L (2017) Progressive supranuclear gaze palsy with predominant cerebellar ataxia: a case series with videos. J Mov Disord 10:87–91. https://doi.org/10.14802/jmd.16059

18. Nagao S, Yokota O, Nanba R, Takata H, Haraguchi T, Ishizu H, Ikeda C, Takeda N, Oshima E, Sakane K, Terada S, Ihara Y, Uchitomi Y (2012) Progressive supranuclear palsy presenting as primary lateral sclerosis but lacking parkinsonism, gaze palsy, aphasia, or dementia. J Neurol Sci 323:147–153. https://doi.org/10.1016/j.jns.2012.09.005

19. Ahmed Z, Josephs KA, Gonzalez J, DelleDonne A, Dickson DW (2008) Clinical and neuropathologic features of progressive supranuclear palsy with severe pallido-nigro-luysial degeneration and axonal dystrophy. Brain 131:460–472. https://doi.org/10.1093/brain/awm301

20. Morgan JC, Ye X, Mellor JA, Golden KJ, Zamudio J, Chiodo LA, Bao Y, Xie T (2021) Disease course and treatment patterns in progressive supranuclear palsy: a real-world study. J Neurol Sci 421:117293. https://doi.org/10.1016/j.jns.2020.117293

21. Srulijes K, Mallien G, Bauer S, Dietzel E, Gröger A, Ebersbach G, Berg D, Maetzler W (2011) In vivo comparison of Richardson's syndrome and progressive supranuclear palsy-parkinsonism. J Neural Transm (Vienna) 118:1191–1197. https://doi.org/10.1007/s00702-010-0563-8

22. Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Höglinger GU (2017) Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. Lancet Neurol 16:552–563. https://doi.org/10.1016/S1474-4422(17)30157-6

23. Shoeibi A, Litvan I, Tolosa E, Ser TD, Lee E, Investigators TAUROS (2019) Progression of two progressive supranuclear palsy phenotypes with comparable initial disability. Parkinsonism Relat Disord 66:87–93. https://doi.org/10.1016/j.parkreldis.2019.07.010

24. Jecmenica-Lukic M, Petrovic IN, Pekmezovic T, Kostic VS (2014) Clinical outcomes of two main variants of progressive supranuclear palsy and multiple system atrophy: a prospective natural history study. J Neurol 261:1575–1583. https://doi.org/10.1007/s00415-014-7384-x

25. Pellicano C, Assogna F, Cellupica N, Piras F, Pierantozzi M, Stefani A, Cerroni R, Mercuri B, Caltagirone C, Pontieri FE, Spalletta G (2017) Neuropsychiatric and cognitive profile of early Richardson's syndrome, progressive supranuclear palsy-parkinsonism and Parkinson's disease. Parkinsonism Relat Disorders 45:50–56. https://doi.org/10.1016/j.parkreldis.2017.10.002

26. Maetzler W, Rattay TW, Hobert MA, Synofzik M, Bader A, Berg D, Schaeffer E, Rommel N, Devos D, Bloem BR, Bender B (2016) Freezing of swallowing. Mov Disord Clin Pract 3:490–493. https://doi.org/10.1002/mdc3.12314

27. Robbins TW, James M, Owen AM, Lange KW, Lees AJ, Leigh PN, Marsden CD, Quinn NP, Summers BA (1994) Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. J Neurol Neurosurg Psychiatry 57:79–88. https://doi.org/10.1136/jnnp.57.1.79

28. Chaithra SP, Prasad S, Holla VV, Stezin A, Kamble N, Yadav R, Pal PK (2020) The non-motor symptom profile of progressive supranuclear palsy. J Mov Disord 13:118–126. https://doi.org/10.14802/jmd.19066

29. Painous C, Martí MJ, Simonet C, Garrido A, Valldeoriola F, Muñoz E, Cámara A, Compta Y (2020) Prediagnostic motor and non-motor symptoms in progressive supranuclear palsy: the step-back PSP study. Parkinsonism Relat Disord 74:67–73. https://doi.org/10.1016/j.parkreldis.2020.03.003

30. Lee YC, Williams DR, Anderson J (2018) Prospective characterization of cognitive function in typical and 'brainstem predominant' progressive supranuclear palsy phenotypes. J Mov Disord 11:72–77. https://doi.org/10.14802/jmd.17067

31. Vaccaro MG, Sarica A, Quattrone A, Chiriaco C, Salsone M, Morelli M, Quattrone A (2020) Neuropsychological assessment could distinguish among different clinical phenotypes of progressive supranuclear palsy: A Machine Learning approach. J Neuropsych. https://doi.org/10.1111/jnp.12232.10.1111/jnp.12232

32. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 47:1–9. https://doi.org/10.1212/wnl.47.1.1

33. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, Mollenhauer B, Müller U, Nilsson C, Whitwell JL, Arzberger T, Englund E, Gelpi E, Giese A, Irwin DJ, Meissner WG, Pantelyat A, Rajput A, van Swieten JC, Troakes C et al (2017) Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord 32:853–864. https://doi.org/10.1002/mds.26987

34. Ali F, Martin PR, Botha H, Ahlskog JE, Bower JH, Masumoto JY, Maraganore D, Hassan A, Eggers S, Boeve BF, Knopman DS, Drubach D, Petersen RC, Dunkley ED, van Gerpen J, Uitti R, Whitwell JL, Dickson DW, Josephs KA (2019) Sensitivity and specificity of diagnostic criteria for progressive supranuclear palsy. Mov Disorders 34:1144–1153. https://doi.org/10.1002/mds.27619

35. Kovacs GG (2015) Invited review: Neuropathology of tauopathies: principles and practice. Neuropathol Appl Neurobiol 41:3–23. https://doi.org/10.1111/nan.12208

36. Lantos PL (1994) The neuropathology of progressive supranuclear palsy. J Neural Transm Suppl 42:137–152. https://doi.org/10.1007/978-3-7091-6641-3_11

37. Williams DR, Lees AJ, Wherrett JR, Steele JC (2008) J. Clifford Richardson and 50 years of progressive supranuclear palsy. Neurology 70:566–573. https://doi.org/10.1212/01.wnl.0000286938.39473.0e

38. Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA (2010) Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol 23:394–400. https://doi.org/10.1097/WCO.0b013e32833be924

39. Kovacs GG, Lukic MJ, Irwin DJ, Arzberger T, Respondek G, Lee EB, Coughlin D, Giese A, Grossman M, Kurz C, McMillan CT, Gelpi E, Compta Y, van Swieten JC, Laat LD, Troakes C, Al-Sarraj S, Robinson JL, Roeber S, Xie SX, Höglinger GU (2020) Distribution patterns of tau pathology in progressive supranuclear palsy. Acta Neuropathol 140:99–119. https://doi.org/10.1007/s00401-020-02158-2

40. Sakurai K, Tokumaru AM, Shimoji K, Murayama S, Kanemaru K, Morimoto S, Aiba I, Nakagawa M, Ozawa Y, Shimohira M, Matsukawa N, Hashizume Y, Shibamoto Y (2017) Beyond the midbrain atrophy: wide spectrum of structural MRI finding in cases of pathologically proven progressive supranuclear palsy. Neuroradiology 59:431–443. https://doi.org/10.1007/s00234-017-1812-4

41. Cosottini M, Ceravolo R, Faggioni L, Lazzarotti G, Michelassi MC, Bonuccelli U, Murri L, Bartolozzi C (2007) Assessment of midbrain atrophy in patients with progressive supranuclear palsy with routine magnetic resonance imaging. Acta Neurol Scand 116:37–42. https://doi.org/10.1111/j.1600-0404.2006.00767.x

42. Gröschel K, Kastrup A, Litvan I, Schulz JB (2006) Penguins and hummingbirds: midbrain atrophy in progressive supranuclear palsy. Neurology 66:949–950. https://doi.org/10.1212/01.wnl.0000203342.77115.bf

43. Picillo M, Tepedino MF, Abate F, Erro R, Ponticorvo S, Tartaglione S, Volpe G, Frosini D, Cecchi P, Cosottini M, Ceravolo R,

Esposito F, Pellecchia MT, Barone P, Manara R (2020) Midbrain MRI assessments in progressive supranuclear palsy subtypes. J Neurol Neurosurg Psychiatry 91:98–103. https://doi.org/10.1136/jnnp-2019-321354
44. Longoni G, Agosta F, Kostić VS, Stojković T, Pagani E, Stošić-Opinćal T, Filippi M (2011) MRI measurements of brainstem structures in patients with Richardson's syndrome, progressive supranuclear palsy-parkinsonism, and Parkinson's disease. Mov Disord 26:247–255. https://doi.org/10.1002/mds.23293
45. Quattrone A, Morelli M, Vescio B, Nigro S, Le Piane E, Sabatini U, Caracciolo M, Vescio V, Quattrone A, Barbagallo G, Stanà C, Nicoletti G, Arabia G, Nisticò R, Novellino F, Salsone M (2019) Refining initial diagnosis of Parkinson's disease after follow-up: a 4-year prospective clinical and magnetic resonance imaging study. Mov Disord 34:487–495. https://doi.org/10.1002/mds.27621
46. Lenka A, Pasha SA, Mangalore S, George L, Jhunjhunwala KR, Bagepally BS, Naduthota RM, Saini J, Yadav R, Pal PK (2017) Role of corpus callosum volumetry in differentiating the subtypes of progressive supranuclear palsy and early Parkinson's disease. Mov Disord Clin Pract 4:552–558. https://doi.org/10.1002/mdc3.12473
47. Nicoletti G, Caligiuri ME, Cherubini A, Morelli M, Novellino F, Arabia G, Salsone M, Quattrone A (2017) A fully automated, atlas-based approach for superior cerebellar peduncle evaluation in progressive supranuclear palsy phenotypes. Am J Neuroradiol 38:523–530. https://doi.org/10.3174/ajnr.A5048
48. Potrusil T, Krismer F, Beliveau V, Seppi K, Müller C, Troger F, Göbel G, Steiger R, Gizewski ER, Poewe W, Scherfler C (2020) Diagnostic potential of automated tractography in progressive supranuclear palsy variants. Parkinsonism Relat Disord 72:65–71. https://doi.org/10.1016/j.parkreldis.2020.02.007
49. Berg D, Godau J, Walter U (2008) Transcranial sonography in movement disorders. Lancet Neurol 7:1044–1055. https://doi.org/10.1016/S1474-4422(08)70239-4
50. Ebentheuer J, Canelo M, Trautmann E, Trenkwalder C (2010) Substantia nigra echogenicity in progressive supranuclear palsy. Mov Disord 25:773–777. https://doi.org/10.1002/mds.22981
51. Kostić VS, Mijajlović M, Smajlović D, Lukić MJ, Tomić A, Svetel M (2013) Transcranial brain sonography findings in two main variants of progressive supranuclear palsy. Eur J Neurol 20:552–557. https://doi.org/10.1111/ene.12034
52. Sastre-Bataller I, Vázquez JF, Martínez-Torres I, Sahuquillo P, Rubio-Agustí I, Burguera JA, Ferrer JM, Valero C, Tembl JI (2013) Mesencephalic area measured by transcranial sonography in the differential diagnosis of parkinsonism. Park Relat Disord 19:732–736. https://doi.org/10.1016/j.parkreldis.2013.04.010
53. Whitwell JL, Höglinger GU, Antonini A, Bordelon Y, Boxer AL, Colosimo C, van Eimeren T, Golbe, Kassubek J, Kurz C, Litvan I, Pantelyat A, Rabinovici G, Respondek G, Rominger A, Rowe JB, Stamelou M, Josephs KA, Movement Disorder Society-endorsed PSP Study Group (2017) Radiological biomarkers for diagnosis in PSP: where are we and where do we need to be? Mov Disord 32:955–971. https://doi.org/10.1002/mds.27038
54. Lin WY, Lin KJ, Weng YH, Yen TC, Shen LH, Liao MH, Lu CS (2010) Preliminary studies of differential impairments of the dopaminergic system in subtypes of progressive supranuclear palsy. Nucl Med Commun 31:974–980. https://doi.org/10.1097/MNM.0b013e32833e5f90
55. Zhao P, Zhang B, Gao S, Li X (2020) Clinical, MRI and 18F-FDG-PET/CT analysis of progressive supranuclear palsy. J Clin Neurosci 80:318–323. https://doi.org/10.1016/j.jocn.2020.06.008
56. Zalewski N, Botha H, Whitwell JL, Lowe V, Dickson DW, Josephs KA (2014) FDG-PET in pathologically confirmed spontaneous 4R-tauopathy variants. J Neurol 261:710–716. https://doi.org/10.1007/s00415-014-7256-4
57. Martí-Andrés G, van Bommel L, Meles SK, Riverol M, Valentí R, Kogan RV, Renken RJ, Gurvits V, van Laar T, Pagani M, Prieto E, Luquin MR, Leenders KL, Arbizu J (2020) Multicenter validation of metabolic abnormalities related to PSP according to the MDS-PSP criteria. Mov Disord 35:2009–2018. https://doi.org/10.1002/mds.28217
58. Srulijes K, Reimold M, Liscic RM, Bauer S, Dietzel E, Liepelt-Scarfone I, Berg D, Maetzler W (2012) Fluorodeoxyglucose positron emission tomography in Richardson's syndrome and progressive supranuclear palsy-parkinsonism. Mov Disord 27:151–155. https://doi.org/10.1002/mds.23975
59. Alster P, Madetko NK, Koziorowski DM, Królicki L, Budrewicz S, Friedman A (2019) Accumulation of tau protein, metabolism and perfusion-application and efficacy of positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in the examination of progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). Front Neurol 10:101. https://doi.org/10.3389/fneur.2019.00101
60. Whitwell JL, Tosakulwong N, Botha H, Ali F, Clark HM, Duffy JR, Utianski RL, Stevens CA, Weigand SD, Schwarz CG, Senjem ML, Jack CR, Lowe VJ, Ahlskog JE, Dickson DW, Josephs KA (2020) Brain volume and flortaucipir analysis of progressive supranuclear palsy clinical variants. NeuroImage Clin 25:102152. https://doi.org/10.1016/j.nicl.2019.102152
61. Wen Y, Zhou Y, Jiao B, Shen L (2021) Genetics of progressive supranuclear palsy: a review. J Parkinsons Dis 11:93–105. https://doi.org/10.3233/JPD-202302
62. Ros R, Gómez Garre P, Hirano M, Tai YF, Ampuero I, Vidal L, Rojo A, Fontan A, Vazquez A, Fanjul S, Hernandez J, Cantarero S, Hoenicka J, Jones A, Ahsan RL, Pavese N, Piccini P, Brooks DJ, Perez-Tur J, Nyggard T et al (2005) Genetic linkage of autosomal dominant progressive supranuclear palsy to 1q31.1. Ann Neurol 57:634–641. https://doi.org/10.1002/ana.20449
63. Rojo A, Pernaute RS, Fontán A, Ruíz PG, Honnorat J, Lynch T, Chin S, Gonzalo I, Rábano A, Martínez A, Daniel S, Pramstaller P, Morris H, Wood N, Lees A, Tabernero C, Nyggard T, Jackson AC, Hanson A, de Yébenes JG (1999) Clinical genetics of familial progressive supranuclear palsy. Brain 122:1233–1245. https://doi.org/10.1093/brain/122.7.1233
64. Sanchez-Contreras M, Heckman MG, Tacik P, Diehl N, Brown PH, Soto-Ortolaza AI, Christopher EA, Walton RL, Ross OA, Golbe LI, Graff-Radford N, Wszolek ZK, Dickson DW, Rademakers R (2017) Study of LRRK2 variation in tauopathy: progressive supranuclear palsy and corticobasal degeneration. Mov Disord 32:115–123. https://doi.org/10.1002/mds.26815
65. Spanaki C, Latsoudis H, Plaitakis A (2006) LRRK2 mutations on Crete: R1441H associated with PD evolving to PSP. Neurology 67:1518–1519. https://doi.org/10.1212/01.wnl.0000239829.33936.73
66. Höglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, van Swieten JC, Heutink P, Wszolek ZK, Uitti RJ, Vandrovcova J, Hurtig HI, Gross RG, Maetzler W, Goldwurm S, Tolosa E et al (2011) Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet 43:699–705. https://doi.org/10.1038/ng.859
67. Sanchez-Contreras MY, Kour N, Cook CN, Serie DJ, Heckman MG, Finch NA, Caselli RJ, Uitti RJ, Wszolek ZK, Graff-Radford N, Petrucelli L, Wang LS, Schellenberg GD, Dickson DW, Rademakers R, Ross OA (2018) Replication of progressive supranuclear palsy genome-wide association study identifies SLCO1A2 and DUSP10 as new susceptibility loci. Mol Neurodegener 13:37. https://doi.org/10.1186/s13024-018-0267-3
68. Menšíková K, Tučková L, Kolařiková K, Bartoníková T, Vodička R, Ehrmann J, Vrtěl R, Procházka M, Kaňovský P, Kovacs GG (2019) Atypical parkinsonism of progressive supranuclear

palsy-parkinsonism (PSP-P) phenotype with rare variants in FBXO7 and VPS35 genes associated with Lewy body pathology. Acta Neuropathol 137:171–173. https://doi.org/10.1007/s00401-018-1923-y
69. Jabbari E, Zetterberg H, Morris HR (2017) Tracking and predicting disease progression in progressive supranuclear palsy: CSF and blood biomarkers. J Neurol Neurosurg Neuropsychiatry 88:883–888. https://doi.org/10.1136/jnnp-2017-315857
70. Constantinescu R, Rosengren L, Eriksson B, Blennow K, Axelsson M (2019) Cerebrospinal fluid neurofilament light and tau protein as mortality biomarkers in parkinsonism. Acta Neurol Scand 140:147–156. https://doi.org/10.1111/ane.13116
71. Coughlin DG, Litvan I (2020) Progressive supranuclear palsy: advances in diagnosis and management. Parkinsonism Relat Disord 73:105–116. https://doi.org/10.1016/j.parkreldis.2020.04.014
72. Luk C, Compta Y, Magdalinou N, Martí MJ, Hondhamuni G, Zetterberg H, Blennow K, Constantinescu R, Pijnenburg Y, Mollenhauer B, Trenkwalder C, Van Swieten J, Chiu WZ, Borroni B, Cámara A, Cheshire P, Williams DR, Lees AJ, de Silva R (2012) Development and assessment of sensitive immuno-PCR assays for the quantification of cerebrospinal fluid three- and four-repeat tau isoforms in tauopathies. J Neurochem 123:396–405. https://doi.org/10.1111/j.1471-4159.2012.07911.x
73. Constantinescu R, Richard I, Kurlan R (2007) Levodopa responsiveness in disorders with parkinsonism: a review of the literature. Mov Disord 22:2141–2295. https://doi.org/10.1002/mds.21578
74. Nieforth KA, Golbe LI (1993) Retrospective study of drug response in 87 patients with progressive supranuclear palsy. Clin Neuropharmacol 16:338–346. https://doi.org/10.1097/00002826-199308000-00006
75. Hammes J, Drzezga A, van Eimeren T (2018) The role of tau imaging in parkinsonian disorders. Curr Neurol Neurosci Rep 18:86. https://doi.org/10.1007/s11910-018-0898-3