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Differentiation of Progressive Supranuclear Palsy: clinical, imaging and laboratory tools

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Progressive supranuclear palsy (PSP) is the most common atypical parkinsonian syndrome comprising two main clinical subtypes: Richardson's syndrome (RS), characterized by prominent postural instability, supranuclear vertical gaze palsy and frontal dysfunction; and PSP-parkinsonism (PSP-P) which is characterized by an asymmetric onset, tremor and moderate initial therapeutic response to levodopa. The early clinical features of PSP-P are often difficult to discern from idiopathic Parkinson's disease (PD), and other atypical parkinsonian disorders, including multiple system atrophy (MSA) and corticobasal syndrome (CBS). In addition, rare PSP subtypes may be overlooked or misdiagnosed if there are atypical features present. The differentiation between atypical parkinsonian disorders and PD is important because the prognoses are different, and there are different responses to therapy. Structural and functional imaging, although currently of limited diagnostic value for individual use in early disease, may contribute valuable information in the differential diagnosis of PSP. A growing body of evidence shows the importance of CSF biomarkers in distinguishing between atypical parkinsonian disorders particularly early in their course when disease-modifying therapies are becoming available. However, specific diagnostic CSF biomarkers have yet to be identified. In the absence of reliable disease-specific markers, we provide an update of the recent literature on the assessment of clinical symptoms, pathology, neuroimaging and biofluid markers that might help to distinguish between these overlapping conditions early in the course of the disease.

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Introduction

Progressive supranuclear palsy (PSP) is the second most common parkinsonian condition that causes neurodegenerative parkinsonism after idiopathic Parkinson's disease (PD) (1). In the early clinical phase, the first 2 years, PSP remains difficult to diagnose as it overlaps clinically with PD, dementia with Lewy bodies (DLB), and other parkinsonian syndromes including multiple system atrophy (MSA) and corticobasal syndrome (CBS) (2). It is especially in the early clinical phase when an accurate diagnosis is important, as disease-modifying therapies will becoming available. In the vast majority of cases PSP presents clinically as Richardson's syndrome (RS), or *Steele-Richardson-Olszewski* syndrome which is characterized by prominent postural instability, supranuclear vertical gaze palsy and frontal dysfunction (1, 3). The classical description of RS, however, did not include all cases with neuropathologically confirmed PSP (4, 5). To account for the heterogeneity in this and subsequent studies, PSP was recently divided clinically and pathologically into two main phenotypes: classical RS and PSP-parkinsonism (PSP-P), the latter characterized by an asymmetric onset, tremor and moderate initial therapeutic response to levodopa. These features overlap with PD, at least early in the course of the disease (5, 6).

Heterogeneity is compounded by PSP presenting as CBS, with asymmetric dystonia, apraxia,

alien limb phenomena and cortical sensory loss (PSP-CBS), and as a syndrome with freezing at initial stages, called, pure akinesia with gait freezing (PAGF) variant, or rarely as a prominent speech disturbance without initial rigidity or tremor, called PSP – progressive non-fluent aphasia (7). These subtypes are not covered by the currently used diagnostic criteria (1).

In the absence of reliable, disease-specific markers of PSP and its subtypes, this review will highlight a number of important advances in our understanding of early clinical diagnosis, neuropathology, neuroimaging and biochemistry of PSP that have occurred within the recent past, to distinguish between clinical PSP and its subtypes and other parkinsonian syndromes.

Clinical diagnosis

Progressive supranuclear palsy remains a clinically based diagnosis. The differentiation of PSP from other atypical parkinsonian disorders can be challenging. In some cases, PSP presents with features of CBS, including apraxia, alien limb phenomena and cortical sensory loss (8, 9). Most PSP, but also some MSA cases, present with early falls and supranuclear vertical gaze palsy (10). Early autonomic dysfunctions including urinary urgency, frequency or nocturia without hesitancy, chronic constipation, postural hypotension, sweating abnormalities and erectile dysfunction are reasonable discriminators of MSA (11–15). Recently, Gilman et al. (11) introduced new clinical diagnostic criteria for MSA according to the predominance of parkinsonism vs ataxia. In this scheme, MSA-P and MSA-C distinguish between the predominant motor features consisting of parkinsonism with bradykinesia, rigidity, gait instability and cerebellar ataxia. The work-up of autonomic failure in MSA is mostly based on cardiac autonomic and neurourological tests (15). Multiple sensor pressure transducer measurements of bladder and urethral pressure characterized detrusor–urethral dyssynergia in patients with MSA more accurately than a single global measurement on 58% of these patients within 4 years of disease onset and in 76% of MSA patients thereafter (16).

Also, vascular pathology can mimic PSP (18); however, vascular pathology typically presents with predominant lower body involvement (19). Additionally, dementia can co-occur with parkinsonism in DLB, a disease in which cognitive impairment begins before or within 1 year of the presentation of parkinsonism (20).

Table 1 shows clinical features of autopsy-confirmed cases of PSP subtypes (RS, PSP-P and PAGF) in comparison with PD and MSA. Patients with PD have the longest disease duration compared with atypical parkinsonian syndromes, indicating a better prognosis of those with PD. Cases of RS are characterized by an early onset of postural instability and falls, vertical supranuclear gaze palsy and frontal behavioural dysfunction (6, 21), which distinguish them from other related disorders. More difficult is the differentiation of PSP-P from PD, especially in the early course of the disease (10, 21), as cases of PSP-P are characterized by asymmetric onset, predominant bradykinesia or tremor and a moderate initial therapeutic response to levodopa. PAGF is characterized by early occurring difficulties in initiating gait and freezing during walking, writing and speaking (7). Absence of limb rigidity and rest tremor, and almost total lack of response to L-dopa distinguish PAGF from PD (7, 22). Moreover, PSP-P may resemble DLB, but the occurrence of visual hallucinations, cognitive decline and fluctuating cognition with pronounced variation in attention and alertness may be helpful exclusion criteria of PSP-P (6, 11, 23).

Pathology

Progressive supranuclear palsy is characterized neuropathologically by neuronal loss, gliosis and the presence of tau-immunoreactive neuronal and glial cell inclusions affecting subcortical and some cortical regions (1, 10, 24, 25). By employing Gallyas–Braak silver staining methods and tau immunohistochemistry, it has been shown (26, 27) that the tau pathology is spread differently in PSP subtypes. In PSP-P tauopathy is more restricted and milder compared with RS, suggesting that in vivo detection of tau protein may have the potential to differentiate between these tauopathies (7, 28). Although both PSP and CBD share a common molecular pathology (4R tauopathy), there are morphological differences. For example, a signature lesion of PSP is the 'tufted' astrocyte while the astrocytic plaque is a hallmark lesion of CBD (29). PSP presenting as CBS is probably attributed to either pronounced cortical tauopathy (9) or asymmetrical tau pathology presenting with unilateral limb dystonia (30). Also cognitive decline may be present in a proportion of PSP patients; this may be related to hippocampal pathology (31). Also, TAR-DNA-binding protein 43 (TDP-43) immunoreactive inclusions, the major lesion seen in frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) may occur in a

Table 1 Demographic and early clinical features of PSP disorders (Richardson syndrome (RS), PSP-parkinsonism (PSP-P), pure akinesia with gait freezing (PAGF) compared with Parkinson's disease (PD) and multiple system atrophy (MSA) in cohorts of pathologically confirmed cases.

Patients characteristics	Williams et al. (5) RS	Williams et al. (5) PSP-P	Williams et al. (7) PAGF	Williams and Lees (6) MSA	Williams & Lees (6) PD
N (M/F)	56 (8/6)	33 (6/3)	7 (NS)	90 (41/49)	444 (273/171)
Age at disease onset (y)	66.1*	66.4	61	56	60.5
Disease duration (y)	6	9	13	8.1	15.8
Age at death (y)	72.1	75.5	ns	64.4	76.2
Falls	+++	–	–	++	–
Postural instability	+++	++	+	+	–
Bradykinesia	+	+++	–	–	+++
Rest tremor	+	++	–	–	+++
Asymmetric onset	+	++	–	–	+++
Pyramidal tract signs	+	+	–	+/++–	–
Gait freezing	–	–	++	–	–
Cognitive dysfunction	+++	++	–	+	–
Speech disturbance†	++	++	Speech freezing	–	–
Extra-axial dystonia	+	++	ns	–	ns
VSP	+++	+	–	–	–
Visual hallucinations	++	+	–	–	+
Non-specific eye symptoms	++		ns	+	ns
Autonomic dysfunction	–	–	–	++	–
Response to L-dopa	+/–	++	–	+–	+++
Tau load[n]	5	3	3	ns	ns
α-synuclein				α-synuclein	α-synuclein

*mean age and disease duration.

†Including early dysarthria or dysphagia.

–, absent; +, mild; ++, moderate; +++, marked; F, female; M, male; ns, not specified; VSP, vertical supranuclear palsy.

[n] score of tau pathology, quantitative assessment on a scale 1–12 (most severe) (7).

minority of CBS and PSP cases (32), further adding to disease heterogeneity.

PD, DLB and MSA are characterized by cellular aggregation of α-synuclein, a causal protein in the genesis of PD, with preferential degeneration of the presynaptic dopaminergic neurons. In particular, in the substantia nigra pars compacta (SNpc) of PD and DLB α-synuclein-immunoreactive inclusions called Lewy bodies and Lewy neuritis are seen (33). However, Lewy bodies are not confined to the brainstem and may be seen in limbic and neocortical areas in a proportion of cases (34). Lewy bodies may also be present in the periphery including the autonomic nervous system. In contrast, in MSA, α-synuclein deposits are found predominantly in oligodendrocytes. These glial cytoplasmic inclusions are called Papp-Lantos bodies, and are thought to contribute to the cause of multisystem degeneration (35).

In summary, parkinsonian disorders may be broadly divided into two molecular pathologies: tauopathies and synucleinopathies. These two molecular pathologies may cause clinically distinct diseases, or they may overlap clinically depending on where the burden of neuronal loss is most severe (36). Recently, clinicopathological studies indicate that PSP, MSA and PD have overlapping areas of neuronal loss and that the spatial pattern of neurodegeneration correlates better with clinical features than the presence of one molecular pathology (tauopathy) versus another (synucleinopathy) (12, 37, 38).

Neuroimaging

Structural magnetic resonance imaging (MRI) has a valuable role in discriminating atypical parkinsonian syndromes (39, 40). Using standard T1- and T2-weighted images, many studies reported abnormalities involving mainly midbrain atrophy, third ventricle dilatation, T2-periaqueductal hyperintensities, and frontal and temporal atrophy, Table 2. Using conventional 1.5 T MR imaging, visual or manual quantitative measurement of diameters and trans-sectional areas from structures known to be implicated in PSP from pathological studies, for example, the pons, the midbrain, the superior cerebellar peduncle (SCP) are presented. MRI can distinguish between PD and MSA, PSP and CBD, however, with low specificity and sensitivity (60% and 80%, respectively) on an individual basis and in general rather late in the disease process (42, 43). Of particular interest is the quantification of midbrain atrophy which is present in at least 75–80% of

clinically diagnosed PSP patients (42, 43) and exceeds that found in other parkinsonian disorders (40, 44).

By using 3D T1-weighted images of the brainstem (45, 46) a successful differentiation between RS and PSP-P patients has been achieved with a high sensitivity and specificity of 90% and 96%, respectively. Although all measurements appropriately differentiated PSP-RS from PD, the magnetic resonance parkinsonism index (MRPI) (pons area/midbrain area × middle cerebellar peduncle width/superior cerebellar peduncle width) was the only measure to successfully differentiate between the two (45). Similarly, MRPI has been found to successfully differentiate MSA-parkinsonism and controls (47, 48), or unclassifiable parkinsonism patients on an individual basis (49). The MRPI proved more accurate, than the midbrain/pons ratio for differentiation of patients with PSP from PD (Table 3). In summary, structural MRI is useful as a measure of downstream pathological events and as a measure of pathologic processes closely linked to neurodegeneration.

Further visual, indirect signs of midbrain atrophy include the atrophy of the lenticular nucleus (LN), comprising the putamen and the globus pallidus (50). The atrophy of the rostral tegmentum, the pontine base and the cerebellum on mid-sagittal view of MR imaging called the *penguin sign* (39) was observed in a large portion of PSP patients, in particular RS patients (Fig. 1). Another feature which is commonly present in PSP is the *morning glory sign,* a peculiar MR finding of midbrain atrophy with concavity of the lateral margin of the midbrain tegmentum, resembling the lateral margin of the morning glory flower (39) (Fig. 2). This sign is found often in RS patients and is believed to be related to the presence of supranuclear gaze palsy, possibly due to degeneration in the cranial and dorsal part of the midbrain (51). This sign occurs particularly often in RS patients, as shown by MR imaging data from our PSP cohort (Fig. 2). Only limited data are available with regard to the midbrain atrophy among PSP subtypes as yet (12).

Functional imaging, in particular positron emission tomography (PET), has provided important insight into the pathogenesis of movement disorders, too. Dopamine acts in the central nervous system through activation of dopamine receptors, which are present in the pre- and post-synaptic cleft. Imaging presynaptic dopaminergic terminal function with either striatal 18F-dopa uptake or

Table 2 Diagnostic accuracy of conventional 1.5-T MRI in differentiating between PSP from PD and MSA adjusted from Stamelou et al. (80)

References	Cohort size*	Diagnostic sign	Sensitivity (%)	Specificity (%)	PPV (%)
Schrag et al. (42)	PSP 35; MSA 31; CON 44	Dilatation 3rd ventricle	77	80 PSP vs MSA	NA
		AP midbrain diameter <17 mm on axial T2-weighted images†	23	96 PSP vs MSA	
		Frontal lobe atrophy	17	96 PSP vs MSA	
Yekhlef et al. (81)	PSP 30; MSA 28; PD 32	Putaminal score	32	93 MSA vs PSP	82
		Cortical score (T1)	33 PSP vs PD	97 PSP vs PD	91
		Midbrain score (T1)			
		Total score	70 vs PD	91 vs PD	89
Oba et al. (39)	PSP 21; MSA 25; PD 23	Ratio midbrain area/pons area (midsagittal T1-weighted)	100 vs MSA, PD	100 vs MSA, PD	NA
		Midbrain area (midsagittal T1-weighted; penguin sign)	100 vs MSA, PD	91.3 vs MSA, PD	NA
Paviour et al. (82)	PSP 19; MSA 10; PD 12, CON 12	SPC area (on axial and sagittal T1-weighted images)	74 vs PD, MSA	94 vs PD, MSA	90
Quattrone et al. (43)	PSP 33; MSA-P 19; PD 108; CON 50	Pons area/midbrain area (P/M) (midsagittal T1-weighted images)	90.9 vs PD	93.5 vs PD	81.1. vs PD
			97 vs MSA-P	94.7 vs MSA-P	97 vs MSA-P
		P/M × MCP/SCP	100 vs PD,MSA-P	100 vs PD, MSA-P	100 vs PD, MSA-P
Cosottini et al. (83)	PSP 15; MSA-P 7	Midbrain area (midsagittal T1-weighted images)	100 vs MSA-P	90.5 vs MSA-P	NA
		Midbrain area/pons area	86.7 vs MSA-P	100 vs MSA-P	NA
Hussl et al. (48)	PSP 22; MSA-P 26; PD 75	Midbrain area (midsagittal T1 gradient-echo images)	63.3 vs PD, MSA-P 77.8 vs PD, MSA-P	94.7 vs PD, 84.6 vs MSA-P 76 vs PD	77.8 vs PD, MSA-P 50 vs PD
		P/M × MCP/SCP		92.3 vs MSA-P	90 vs MSA-P

*All patients with clinically probable disease, none neuropathologically confirmed.

†Midbrain diameter on axial scans <17 mm to differentiate PSP from MSA (42).

Studies with N> 10 patients; CON, healthy controls; PPV, positive predictive value; NA, not applicable; P/M – pons to midbrain area ratio; P/M × MCP/SCP middle cerebellar peduncle/superior cerebellar peduncle.

Table 3 Sensitivity and specificity of MRI measurement of brainstem structures in patients with Richardson's syndrome (RS), progressive supranuclear palsy – parkinsonism (PSP-P) and idiopathic Parkinson's disease (PD). The study by Morelli et al. (46, 49) shows 100% sensitivity, specificity and diagnostic accuracy between the groups when using the magnetic resonance parkinsonism index (pons area/mibrain area × middle cerebellar peduncle width/ superior cerebellar peduncle width)

	Longoni et al. 2011 (45)				Morelli et al. (46, 49)				
Diagnosis	RS*	PSP-P†	PD*	Controls	PSP*	PSP†	PD†	PD*	Controls
Number of subject	10	10	25	24	42	42	132	132	38
Age (years)	62.5	67.3	65.5	63.8	66.7	66.7	63.4	63.4	68.8
Hoehn & Yahr score	3.1 (2–5)	2.9 (1–4)	1.9 (1–3)	–	4 (3–5)	4 (3–5)	2 (1–3)	2 (1–3)	–
UPDRS-MS	28.5 (9–52)	37.0 (14–58)	18.9 (10–35)	–	34 (24–50)	34 (24–50)	21 (7–36)	21 (7–36)	–
MMSE	26.5	27.4	28.1	–	NA	NA	NA	NA	–
Sensitivity %	90	60	100	–	100	92.9	100	88.1	100* (97.6†)
Specificity %	96	96	92	–	99.4	85.3	92.2	88.3	100* (92.1†)
Diagnosis accuracy %	94	86	97	–	99.5	86.8	99.4	88.2	100* (95.0†)

*Imaging by means of magnetic resonance parkinsonism index (MRPI).
†Imaging by means of pons/midbrain MRI ratio (see text for further details).
Values are mean or number of subjects (for further details, see text).
UPDRS-III (Unified Parkinson's Disease Rating Scale - Motor Score) (84).
Hoehn & Yahr score (85).
MMSE – Mini-Mental State Examination (86).
NA, not applicable.

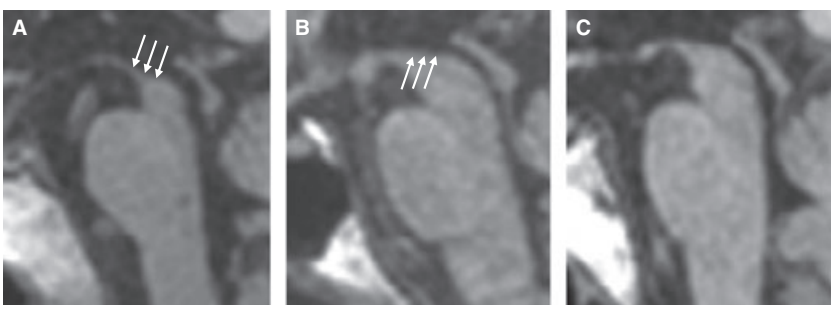

Figure 1. Mid-sagittal T1-weigted images of the rostral midbrain and pons of a patient with Richardson's syndrome (A) with marked atrophy of midbrain tegmentum and a distinct *penguin sign* (arrows). This was not observable in a PSP-parkinsonism patient (B). (C) For comparison, the midbrain tegmentum of a patient with idiopathic Parkinson's disease, with no abnormality (unpublished data).

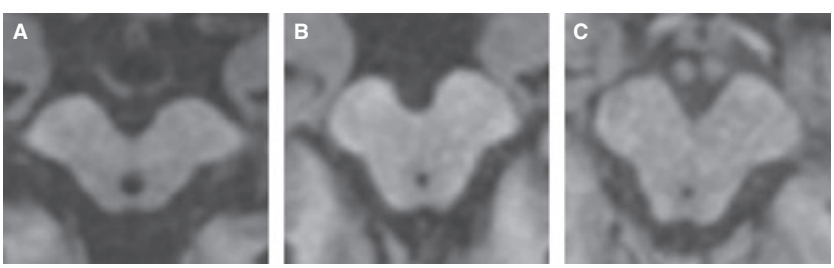

Figure 2. Axial T1-weigted images of the midbrain of a patient with Richardson's syndrome (A) with the concave shape of the lateral margin of the posterior tegmentum called *morning glory sign* with atrophy of the entire midbrain. (B) A patient with PSP-parkinsonism with the convex lateral margins of posterior tegmentum without prone midbrain atrophy. (C) For comparison, a typical slice of the midbrain including the tegmentum of a patient with idiopathic Parkinson's disease, with no abnormality of the midbrain tegmentum is presented (unpublished data).

with a dopamine transporters (DAT) SPECT marker shows high sensitivity for detecting atypical parkinsonian syndromes, but only poor specificity for discriminating them from PD (50) as all of these disorders have a presynaptic dopaminergic deficit at some stage. Postsynaptic ligands, however, proved successful in the differentiation of PSP from PD (52, 53) especially early

in the disease course. Studies investigating the dopaminergic system of PSP subtypes are as yet not available, except one preliminary study showing different alterations of DAT and D2 receptor function between the RS and PSP-P groups (54). Using [^{18}F] fluorodeoxyglucose (FDG)-PET, some investigators differentiated demented PD patients from non-demented PD patients (55), suggesting that FDG-PET may differentiate PSP from other atypical parkinsonian entities. Recently, we found pronounced thalamic and frontal hypometabolism in RS patients, and pronounced putaminal hypometabolism in PSP-P patients using FDG-PET (56). Thus, FDG-PET may be a promising imaging marker to differentiate PSP subtypes *in vivo*.

Transcranial sonography (TCS) has been proposed as a promising non-invasive tool for the differentiation of parkinsonian syndromes. The best described ultrasound features in the differential diagnosis of parkinsonian syndromes are substantia nigra (SN) and lentiform nucleus (LN) hyperechogenicity. Cross-sectional studies suggest that specific changes of the LN as well as the third ventricle occur in patients with PSP and MSA, but not in DLB or PD (2010) (57). A normoechogenic SN is a typical finding in patients with PSP, at least of the RS type, whereas in patients with PD a hyperechogenic SN is characteristic, as shown recently in a study on 34 PSP patients (27 RS, 7 PSP-P) (58). Also, a hyperechogenic area of the LN may indicate MSA or PSP rather than PD (57, 59, 60), and third ventricular dilatation (>10 mm) combined with LN hyperechogenicity may discriminate PSP from PD with positive predictive value of 89% (60).

Fluid biomarkers

The CSF analyses represent the most direct and convenient means to study biochemical changes occurring in the central nervous system as they are directly related to specific pathomechanisms of neurodegeneration (61). In Alzheimer's disease, promising CSF biomarkers are based on assays measuring disease-related proteins including amyloid beta 42 ($A\beta_{42}$) and phospho-tau (e.g. P-tau181) (62). In PD, DJ-1 and α-synuclein have been proposed as promising markers.

At a group level, some studies have shown that α-synuclein in CSF may distinguish PD patients from controls (63); (64, 65), but not others (66). Using an enzyme-linked immunosorbent assays (ELISA) Aerts et al. (66) found in a cohort of 142 patients with PD or atypical parkinsonian disorders that CSF α-synuclein was not suitable as a biomarker to differentiate between PD and atypical parkinsonian disorders, including PSP. Furthermore, no difference was observed between the α-synucleinopathies (PD, MSA and DLB) and a group of 4R tauopathies (PSP and CBD). Recent studies of MSA patients showed increased levels of tau protein and neurofilament light protein (NFL) which are markers of neuronal damage (64, 67). The amount of NFL in CSF were normal in PD, but elevated in MSA and PSP. Multivariate analysis revealed that the level of neurofilament light chain alone may differentiate between PD and MSA/PSP (68), but cannot differentiate between the different atypical parkinsonian disorders (69). This observation was extended to CBD by showing similarly high levels of NFL (69). In patients with PSP, concentrations of almost all brain-specific proteins seem to be within the same range as observed for patients with PD, thus not sufficiently allowing to differentiate between these cohorts. Some investigations have demonstrated DJ-1 and α-synuclein levels in plasma or serum associated with PD (70) and DLB (71), but not others (72). Both oligomeric and phosphorylated oligomeric forms of α-synclein were detected in post-mortem CSF which may be useful in distinguishing between PD, DLB and MSA (73).

The most promising biofluid candidate to date is tau, an unfolded microtubule-associated protein that is important for the stabilization of microtubules (74). The ratio between the smaller and the larger tau forms (33/35 kDa) in CSF was reduced in a small group of PSP patients compared with controls (75, 76). However, this finding was not replicated by others (77), potentially due to a slightly different study protocol (see comment in (75). Recently, Süssmuth et al. (78) found higher total tau levels in a cohort of PSP-P and MSA patients compared with RS, PD and controls. Again, this finding was not confirmed by others (21). In general, CSF analyses to differentiate PSP from other atypical parkinsonian disorders, including PD, have relatively high specificity, but only moderate sensitivity (79).

Conclusion

Two main clinical phenotypes are associated with pathological PSP: Richardson syndrome and PSP-parkinsonism. Other less common atypical parkinsonian conditions, with pathologically confirmed PSP hallmarks include PSP-CBD and PAGF. The clinical differentiation of PD from atypical parkinsonian disorders (PSP, CBD and

MSA) is in flux, but important for the patient's management and recruitment into clinical trials. Today, the diagnostic accuracy of atypical parkinsonian disorders is poor in some centres, and there is scope for improvement. Structural and functional imaging using MRI, TCS and SPECT/PET techniques using radio-labelled molecules have great promise in improving the diagnostic accuracy in atypical cases. However, the downsides of the functional neuroimaging methods are relatively high costs and low availability. A growing body of evidence hints at the importance of CSF biomarkers in the diagnosis of atypical parkinsonian syndromes. However, specific diagnostic biomarkers still have to be identified. There is an urgent need, however, for biomarkers to diagnose neurodegenerative diseases early in their course, when therapy is likely to be most effective, and to monitor responses of patients to new therapeutics. One drawback of many studies is that they are cross-sectional and retrospective. Also, a significant proportion of studies have no post-mortem pathologic assessment so the accuracy of the clinical diagnosis is uncertain and the contribution of comorbidity to the clinical phenotype will go unrecognized. Thus, there is a need for prospective longitudinal studies with pathological assessment to determine the accuracy of the clinical diagnosis. The accurate detection of a specific molecular pathology in the preclinical or prodromal stage will facilitate the administration of therapeutics, when they become available. Preclinical treatment is more likely to be effective in stopping or slowing neurodegeneration that symptomatic treatment where neuronal loss may be so severe as to be irreversible.

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Conflict of interest

The authors report no conflict of interest.

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