

## Refining Clinical Diagnosis of Progressive Supranuclear Palsy: Implications for Disease Modification Trials



The importance of ensuring an accurate diagnosis of progressive supranuclear palsy (PSP) is critical for the development of effective disease-modifying therapies that are specifically directed at the reduction of tau aggregation in the pathogenesis of this disorder. This rare, (incidence of 0.3-1.1/100,000/year; prevalence of 1.3-6.4/100,000) and devastating neurodegenerative disorder presents as an akinetic-rigid syndrome with a variety of signs and symptoms, including ocular motor dysfunction, postural instability, frontal lobe and bulbar dysfunction. The manifold symptoms and broad phenotypic variability of PSP may in part account for its diagnostic challenges, particularly in the early stages of the disease. This review will delineate various diagnostic schema in defining PSP with an overall aim of improving diagnostic accuracy in clinical trials, resulting in decreased patient heterogeneity with accompanying improvement of signal detection in the assessment of putative therapeutic agents.

PSP is considered a tauopathy, a class of neurodegenerative diseases characterised by the pathological aggregation of the microtubule-associated protein known as tau in the brain. Tau protein binds to microtubules, and plays an important role in neuronal cytoskeletal stability. The hyperphosphorylation of tau results in tau protein aggregates, sometimes referred to as paired helical filaments. Alternative splicing of exons 2, 3, and 10 of the tau gene generates six tau isoforms. The inclusion or exclusion of exon 10 produces isoforms with four (4R) or three (3R) microtubule binding sites. Normal brains have similar levels of 4R and 3R; however, in PSP, 4R dominates and PSP is often referred to as a 4R tauopathy. To date, disease-modifying trials in PSP have sought to demonstrate neuroprotective effects primarily by decreasing tau pathology through various mechanisms that reduce tau phosphorylation and/or increase microtubule stability. Typical neuropathological signs of PSP include excessive intra-axonal accumulation of phosphorylated tau protein in the basal ganglia and brain stem producing neurofibrillary tangles (NFT) which spread transynaptically throughout the brain, resulting in neuronal loss and gliosis in a manner that seems to correlate with the clinical progression of the disease. The neuropathological criterion for diagnosis of definite PSP requires a high presence of NFT in at least three of the following brain areas: striatum, oculomotor complex, medulla, or dentate nucleus, and unfortunately requires sampling cerebral tissue in order to ensure accurate diagnosis. Contrasting with this distinctive neuropathological profile, the clinical presentation of PSP is quite heterogeneous and is associated with pronounced variability in regional distribution, severity of abnormal tau accumulation and neuronal loss associated with different stages of disease progression.

The characteristic pattern of signs and symptoms of PSP can be quite dissimilar from patient to patient. The most frequent initial symptom of PSP is a loss of balance while walking (i.e. unexplained falls or a stiffness and awkwardness in gait), followed by personality changes, bulbar symptoms, and visual problems. PSP patients typically present with a peculiar akinetic-rigid motor disorder that in most cases differs markedly from that observed in Parkinson's disease (PD). PSP symptoms tend to be more prominent in axial segments, leaving limb function relatively preserved, and unlike the onset of symptoms in PD, postural stability is compromised early on in the course of illness. Although individuals with PD can benefit from levodopa, patients with the classic PSP phenotype called Richardson's Syndrome (PSP-RS, which accounts for approximately 55% of all PSP)<sup>1</sup> respond marginally and only briefly to levodopa therapy. Auspiciously, this lack of motoric response to dopaminergic drugs can be supportive in differentiating the PSP-RS phenotype and PD. This is important as PSP patients are often misdiagnosed for several years as having PD, and in the absence of diagnostic biomarkers, this misdiagnosis often goes uncorrected until relatively late in the disease course. This is particularly problematic as patients with PSP-RS have the most rapid clinical decline trajectory and may become dependent on caregivers within three to four years from the onset. Regrettably, patients with PSP-RS classically have a survival rate of only approximately seven years.

Other clinical subtypes of PSP include PSP-parkinsonism (PSP-P) and PSP-pure akinesia with gait freezing (PSP-PAGF) which typically have a more benign course, and a slower rate of disease progression than PSP-RS<sup>2</sup>, with a survival period of at least a decade or more. Both of these subtypes have an overall tau burden that is comparatively less than that seen in PSP-RS with the distribution of abnormal tau being relatively restricted to the brain stem. As such, the phenotypes of PSP-P and PSP-PAGF are sometimes referred to as the 'brain stem' variants of PSP, as opposed to the more 'cortical' variants which present with predominantly cortical features. These more cortical clinical subtypes include the behavioural variant of frontotemporal dementia (PSP-bvFTD) which accounts for 5% of all PSP; PSP-corticobasal syndrome (PSP-CBS), PSP- and PSP-progressive non-fluent aphasia (PSP-PNFA) which both account for 1% of all PSP. Finally, a PSP-cerebellar subtype accounts for less than <1% with the remaining percentage made up of a combination of these subtypes or still unrecognised forms of PSP.<sup>1</sup>

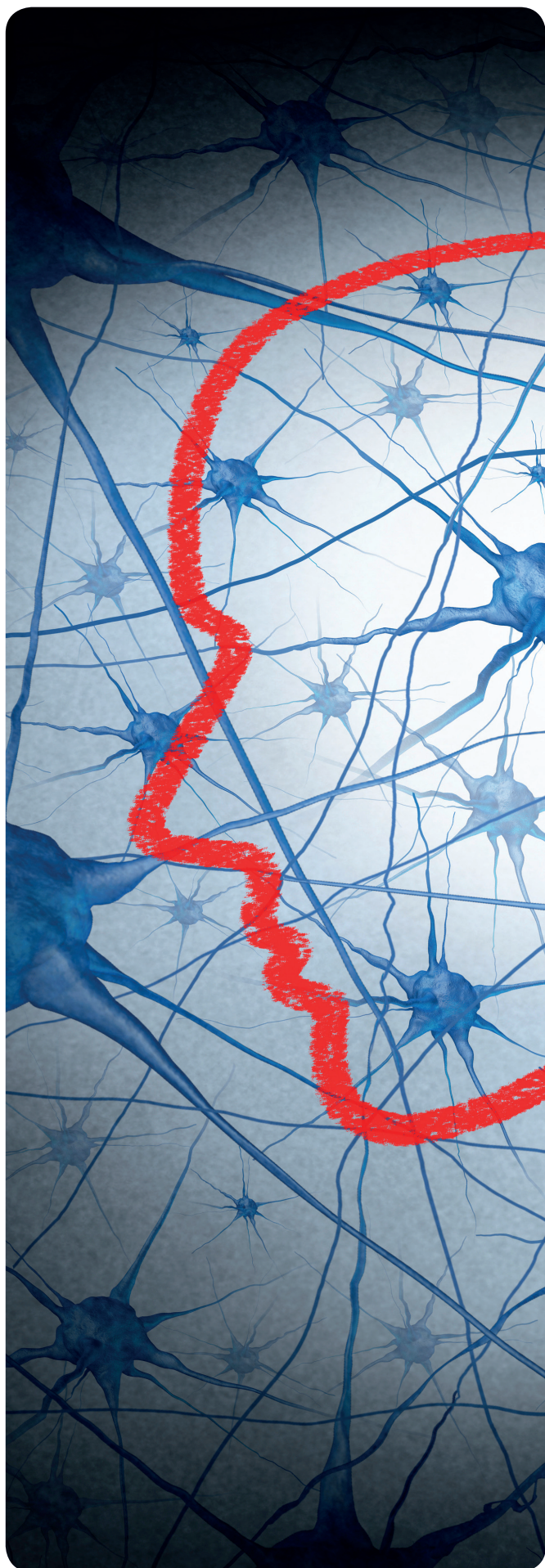
A study of autopsy-confirmed PSP cases<sup>3</sup> casts doubt on the above clinical proportions and supports an even greater degree of clinical heterogeneity than has been clinically appreciated to date. The post mortem data

suggest that only 24 % of the cases present as pure PSP-RS, with a large proportion of patients having overlapping neuropathological features of several predefined phenotypes, (PSP-P; PSP-CGS; PSP-bvFTD) or features not fitting proposed classification criteria (atypical) for PSP phenotypes. Importantly, most phenotypes were rare in their pure form and almost 40 % of patients could not be classified into any one specific phenotype, most often due to an absence of specific clinical features but also due to the presence of important exclusion criteria. Adding to the confounding nature of an accurate diagnosis, is the fact that mixed PSP pathologies may be found in patients with late-adult onset neurodegenerative diseases. In a contemporary study evaluating 64 cases of pathologically confirmed PSP, 36 % also had concomitant Alzheimer's disease, 20 % PD, 1 % dementia with Lewy bodies, 44 % argyrophilic grains, 52 % cerebral white matter rarefaction and 25 % cerebral amyloid angiography.<sup>4</sup>

Given this overlap of concomitant illnesses, the numerous clinical phenotypes and large clinical heterogeneity of PSP, it is easy to appreciate that one of the greatest challenges to current trials designed to assess PSP treatments is the accurate diagnosis and inclusion of an appropriate PSP patient sample. In an effort to improve diagnostic accuracy, the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) criteria have been proposed for use in clinical trials.<sup>5</sup> These criteria define three diagnostic categories of increasing certainty: possible, probable, and definite. The diagnosis of possible and probable PSP depends primarily on the presence of specific clinical features (gradual progressive disorder with an age of onset over 40 years, falls within the first year, signs of vertical supranuclear gaze palsy or slowing of vertical saccades), as well as on meeting salient exclusion criteria (i.e. cortical sensory loss; psychosis not related to dopaminergic therapy). A definite diagnosis requires a typical PSP neuropathological lesion distribution pattern with cellular inclusions that are tau-positive. Although these diagnostic criteria have been used widely in the research community, there is still disagreement as to their value. Validation of these criteria in independent populations of patients demonstrated a high positive predictive value, albeit low sensitivity particularly during the early course of the disease.<sup>6</sup> Specifically, the NINDS-SPSP criteria appear to be adequate at clinically defining the PSP-RS phenotype, whereas all other variable phenotypic presentations of PSP, especially those described after the development of these criteria (1996), have not been characterised in a reliable manner. Further, it has been estimated that the NINDS-SPSP criteria accurately detect only 50–75 % of PSP-RS patients within three years of disease onset. Although evidence-based revised clinical criteria for diagnosis of PSP are currently being developed by the Movement Disorders Society (MDS) PSP research group, there are currently no accepted diagnostic guidelines for the clinical diagnosis of other phenotypic presentations of PSP available to clinical trialists.

Given this lack of diagnostic accuracy and the broad clinical heterogeneity of PSP, both diagnostic and predictive biomarkers such as magnetic resonance imaging (MRI) and tau imaging will undoubtedly play an increasingly important role for inclusion criteria in clinical trials assessing disease-modifying drugs. Ultimately the biomarkers with the best utility are likely to be some combination of imaging markers designed to exclude specific pathologies (e.g. Alzheimer's or PD) and to define the presence of specific 4R tauopathy. For example, volumetric MRI imaging may show midbrain atrophy, a finding that differentiates patients with PSP from healthy controls and those with PD and other disorders with symptoms of atypical Parkinsonism. Interestingly, the midbrain atrophy seen on mid-sagittal scans characteristically resembles a penguin or hummingbird silhouette in up to two-thirds of patients with PSP-RS, but unfortunately, can also be seen in patients with multisystem atrophy (MSA) and spinocerebellar ataxia (SCA), therefore confounding differential diagnosis.<sup>7</sup> Diffusion-weighted imaging (DWI) has shown significantly higher rADC (regional apparent diffusion coefficient) values in both the putamen and globus pallidus in patients with PSP than in those with PD, but this pattern can also be seen in patients with MSA.<sup>8</sup> Diffusion tensor imaging (DTI) studies have suggested that white matter tract degeneration especially in the superior cerebellar peduncles and superior longitudinal fasciculus is characteristic of patients with PSP-RS.<sup>9</sup> Focal midbrain hypometabolism on fluorodeoxyglucose (FDG)-positron emission tomography (PET) has also been consistently identified in patients with PSP-RS.<sup>10</sup> This is especially important as PET tau imaging agents have shown considerable promise in both differentiating PSP from other Parkinsonian conditions and other subtypes of PSP, and in serving as a possible marker of disease progression.<sup>11</sup> There are several tau selective tracers in development, but the most widely utilised to date are [18F]AV-1451, a series of [18F]-labelled arylquinoline derivatives ([18F]-THK) compounds, and 2-((1E,3E)-4-(6-(11C-methylamino)pyridin-3-yl)buta-1,3-dienyl) benzo[d]thiazol-6-ol ([11C]-PBB3). A better understanding of what targets these tau imaging agents are actually binding to, as well as the best reference region and analyses methods, is urgently required to optimise their use in disease-modifying clinical trials.

In one of the first registration studies of a disease-modification agent, as well as one of the largest Phase II/III studies PSP studies conducted to date, 313 PSP-RS patients were randomised in a double-blind fashion to Davunetide 30 mg or placebo administered intranasally twice daily for 52 weeks.<sup>12</sup> Patients all met modified National Neuroprotection in Parkinson's Plus (NNIPPS) criteria for possible or probable PSP and were assessed via co-primary endpoints of change from baseline in PSP Rating Scale (PSPRS) and Schwab and England activities of daily living (SEADL) scale which measure overall disability/function and the ability of patients to function independently, respectively. Approximately 78 % of



the patients completed this trial which concluded that Davunetide was well tolerated but regrettably not an effective treatment for PSP.<sup>7</sup> Despite the lack of positive findings, this study suggested that clinical trials of disease-modifying therapy are indeed feasible in PSP and should be pursued, utilising other promising tau-directed therapies.

Importantly, this trial garnered essential information regarding the utility of various outcome measures and data on potential predictive and surrogate biomarkers for use in future PSP disease-modification trials. Boxer and team<sup>12</sup> reported a mean annual rate of decline on the PSP rating scale (PSPRS which rates overall PSP symptoms<sup>1</sup>) of 11.0 (9.9-12.3) points and a survival rate of approximately 93.1% over approximately one year; which is slightly higher than predicted from the PSPRS validation study (86.9%) based on the mean baseline PSPRS score of 40.<sup>12</sup> For the co-primary endpoint, the SEADL, an annual rate of decline of 17 per cent<sup>15-19</sup> was shown. This information can be used to determine clinical relevance for slope differences between treatment groups in future disease-modification trials. Boxer *et al.*<sup>12</sup> also reported a mean annual brain atrophy rate of 1%; a mean annual ventricular volume expansion rate of approximately 9.4%; a midbrain atrophy rate of 3.6%; and a 7.3% annual rate of superior cerebellar peduncle atrophy – all useful for future disease-modification studies powered on tissue sparing/salvage.

A more recent review of this data, which also included numerous exploratory cognitive assessments and CSF measures (in a subset of patients) in addition to volumetric MRI measurements, reported that shorter PSP disease duration, more severe depression, and poorer cognitive performance overall at baseline were all associated with faster progression of PSP symptoms on the PSPRS for those 243 patients who completed the 52-week trial.<sup>13</sup> When those patients who dropped out of the study were included in the analyses, these same cognitive measures of executive function and activities of daily living had a significant effect on PSPRS trajectory, further supporting that baseline cognitive status and depression influence the rate of disease progression in PSP-RS. Conversely, patients with longer disease duration at baseline had a relatively slower rate of progression and thus would require a longer treatment duration in order to show significant changes associated with treatment. This slower rate of decline might be attributed to the inclusion of patients who had variant forms of PSP such as PAGF or PSP-P preceding their progression to Richardson's syndrome. Of note is that multivariate models that included baseline clinical and MR imaging variables were no better at explaining variance in annual PSPRS progression than simple univariate models of individual variables. These data suggest that patient samples could be readily enriched for more rapid progression in disease-modification trials using a few crucial baseline variables and these researchers identified cut-off values that could be used to identify patients with a more rapid or

predictable disease progression..

In summary, the above-mentioned studies suggest that the diagnostic criteria for PSP are suitable, if not optimal, for recruiting mild to moderately impaired PSP patients into multicentre trials, and that once enrolled, such patients follow a highly predictable rate of clinical- and biomarker-related decline that can be used to power future trials of disease-modifying drugs in a reliable manner. Furthermore, these patient populations can be enriched on progression in order to save time and money in disease-modifying trials which are relatively lengthy and have larger sample sizes than comparative trials of symptomatic drugs. Finally, it is possible that, like many of the failed disease-modifying trials in Alzheimer's disease, it may have been too late in the course of the PSP to show any reliable and consistent changes in symptomatology associated with disease-modifying treatments such as Davunetide. Rather, it has been proposed that it may be better to evaluate potential disease-modifying therapies in PSP patients much earlier in the disease process and researchers have emphasised the value of PET tau imaging as a promising biomarker that may not only help to demonstrate target engagement but also permit identification of PSP patients at earlier stages of the disease when tau directed therapeutics are more likely to be effective.<sup>13</sup>

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