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"Sensitivity and Specificity of Diagnostic Criteria for Progressive Supranuclear Palsy"

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Abstract

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Background: In 2017, the Movement Disorders Society put forward new clinical criteria for the diagnosis of PSP recognizing diverse PSP phenotypes.

Objectives: In this study, we compare the sensitivity and specificity of the new criteria to the National Institutes of Neurological Disease and Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria at different time points.

Methods: Patients with clinical parkinsonism, clinical and/or neuropathological diagnosis of PSP were identified from the Society for Progressive Supranuclear Palsy (SPSP) brain bank. All patients had neuropathologic diagnoses and detailed clinical examination performed by a neurologist at one of the three Mayo Clinic sites located in Florida, Arizona and Minnesota. Clinical symptoms and signs were abstracted retrospectively in a blinded fashion and used to determine whether or not patients met either diagnostic criterion. Patients were divided into early and late disease stage groups using a 3-year cut off.

Results: A total of 129 patients were included of which 66 (51%) had PSP pathology. The remainder had other neurodegenerative diseases. The overall sensitivity of the Movement Disorders Society criteria was 87.9% compared to 45.5% for National Institutes of Neurological Disease and Society for Progressive Supranuclear Palsy criteria, whereas the specificity of the Movement Disorders Society criteria probable PSP criteria was 85.7% and 90.5% for National Institutes of Neurological Disease criteria. Individual patients were noted to have features of multiple PSP phenotypes.

Conclusion: The Movement Disorders Society criteria recognize several phenotypes of PSP and hence have a higher sensitivity than the previous criteria.

Keywords

Progressive supranuclear palsy; PSP diagnostic criteria; MDS-PSP; NINDS-SPSP

Introduction

Progressive supranuclear palsy (PSP) is a tauopathy characterized by a tau isoform bearing 4 conserved repeats (4R) in the microtubule binding domain. At present, PSP can only be definitively diagnosed based on neuropathological examination of the brain. Microscopically, the hallmark of PSP includes neuronal and glial (both astrocytic and oligodendroglia) lesions composed of hyperphosphorylated 4R tau. Tau pathology affects the neostriatum, globus pallidus, substantia nigra, subthalamic nucleus, brainstem nuclei, as well as motor cortex. In affected white matter, tau immunoreactive oligodendroglial coiled bodies are frequent, while tufted astrocytes are frequent in motor cortex, neostriatum and midbrain tectum. On gross examination there is atrophy of the subthalamic nucleus, midbrain and superior cerebellar peduncle with depigmentation of substantia nigra as well as atrophy and discoloration of the cerebellar dentate nucleus. [1, 2]

Clinical diagnosis of PSP is challenging, but overall diagnostic accuracy approaches 80%.[3] The original description of PSP is now referred to as classic PSP or Richardson syndrome (PSP-RS).[4] These patients were described as having remarkable postural instability, falls, vertical supranuclear gaze palsy (VSGP) and axial rigidity as a result of subcortical and

brainstem tau pathology.[5] The National Institutes of Neurological Disease and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) diagnostic criteria for PSP recognized this phenotype as a sporadic onset progressive disorder in adults over age 40. Patients with asymmetric parkinsonism and cortical signs were excluded. “Possible PSP” was defined as patients with either vertical supranuclear gaze palsy (VSGP) or slow saccades along with postural instability, whereas “probable PSP” required both VSGP and postural instability (supplementary Table 1). [5]. Criteria for “possible PSP” had sensitivity (true positive rate) of 54–83% and specificity (true negative rate) of 85–93% whereas the criteria for “probable PSP” had a sensitivity of 21–54% and fairly high specificity of almost 100%. [5–7] Frequent early falls and VSGP are most consistently predictive of PSP neuropathology. [8, 9] Subsequent analysis of SPSP brain bank showed a 24% false positive rate [3] and an analysis of cases from the Queen Square Brain bank revealed a 22% false positive rate in clinically diagnosed PSP [10]. Multiple system atrophy (MSA), Lewy body disease (LBD) and corticobasal degeneration (CBD) were some of the neuropathologic substrates of PSP-RS. [3, 10] This illustrates the important point that several neurodegenerative proteinopathies can have overlapping symptoms.

Among patients with PSP neuropathology, symptoms vary widely due to differences in severity and neuroanatomical distribution of pathology. Morris et al described patients with PSP who resembled idiopathic Parkinson’s disease (PSP-P). [11] Other PSP variants/ phenotypes with a predominantly subcortical burden of tau pathology have been recognized and include primary progressive freezing of gait (PGF),[12] PSP with postural instability (PSP-PI)[13] and PSP with predominant cerebellar ataxia (PSP-C).[14] Recognition of these diverse phenotypes in autopsy proven cohorts [15] led to the development of the Movement Disorders Society (MDS) criteria for diagnosis of PSP (supplementary Table 1). [16] The criteria seek to improve upon the low sensitivity of the NINDS-SPSP criteria and enhance early, reliable detection of PSP. The criteria were formulated by a panel of PSP experts based on detailed analysis of an autopsy cohort consisting of PSP (n=206), CBD (n=54), MSA-Parkinsonism (n=51), Parkinson’s disease (PD) (n=53) and behavioral variant frontotemporal lobar degeneration (FTLD-bvFTD) (n=73). Four domains of symptoms are defined according to these criteria, including ocular motor (O), postural instability (P), akinesia (A) and cognitive dysfunction (C). Within each domain, signs and symptoms are assigned levels of confidence based on how strongly they predict PSP neuropathology. For example, freezing of gait is assigned a higher level of confidence than asymmetric parkinsonism. Based on the combination of qualifying symptoms and signs, patients are assigned PSP phenotypes with different levels of confidence, such as probable, possible and suggestive. Phenotypes recognized include PSP-RS, PSP-PGF, PSP-P, a frontal dysexecutive syndrome (PSP-F), PSP with predominant ocular motor abnormalities (PSP-OM), corticobasal syndrome (PSP-CBS), and speech/language disorders characterized by progressive apraxia of speech and non-fluent aphasia (PSP-SL). “Clinical clues” and “imaging findings” are also listed as supportive features. PSP-CBS and PSP-SL are recognized as “probable 4R tauopathies.” as both CBD and PSP neuropathology may lead to CBS, progressive apraxia of speech (AOS) and aphasia.[17–21] Richardson syndrome like phenotype is recognized as a manifestation of CBD by the most recent criteria.[22]

In this study we establish the sensitivity and specificity of the new MDS-PSP criteria in a neuropathologically defined cohort. We describe clinical features of patients in the early and late disease stages and compare it to the NINDS-SPSP criteria.

Methods

Patients with clinical parkinsonism who had neuropathological diagnoses available were identified from the SPSP brain bank. The SPSP brain bank was established over 2 decades ago and includes patients that are evaluated by clinicians from all 50 states. For this study, patients with clinical or neuropathological diagnosis of PSP were included. We also included patients with clinical diagnosis of parkinsonism who had neuropathological diagnosis available, so as to ascertain sensitivity and specificity. We selected patients who had been evaluated by a Mayo Clinic specialist in movement disorders or behavioral neurology at any of three Mayo Clinic sites located in Florida, Arizona and Minnesota. All patients had detailed clinical examinations performed, and medical records accessible within the Mayo Clinic electronic health record system. All neuropathologic examinations were conducted by an expert neuropathologist (DWD) maintaining uniformity. A movement disorders neurologist (FA), who was blinded to the neuropathologic diagnoses, performed a retrospective review of clinical symptoms and neurological examination findings as documented by the evaluating neurologist. For this study the following signs and symptoms by category were recorded: ocular motor findings (vertical supranuclear gaze palsy, apraxia of eyelid opening, slow saccades), postural instability (spontaneous falls, fall on pull test or more than 3 steps on pull test), parkinsonism (freezing of gait, axial predominant rigidity, asymmetric parkinsonism with tremor) and cognitive dysfunction (apraxia of speech, non-fluent aphasia, frontal/behavioral cognitive presentation and corticobasal syndrome). Definitions set by the MDS-PSP criteria were used to screen for clinical signs and symptoms. [16] The symptoms were then assigned the appropriate level of confidence for each category, namely; O (ocular motor), P (postural instability), A (akinesia) and C (cognitive dysfunction). When multiple symptoms were present, the one with highest level of confidence was used.

Symptoms that met the definitions set by the NINDS-SPSP criteria for slowed saccades, VSGP and postural instability were recorded separately. If on rare occasion a key feature was not listed in the evaluating physicians note, this feature was designated “not documented”.

Clinical signs and symptoms for each patient were recorded independently for the first and final neurological evaluation at one of the three Mayo Clinic sites. The first and final visits were treated as two separate time points if they were over 6 months apart, based on the assumption that clinically meaningful progression of disease is unlikely to occur in less than 6 months.

Patients were divided into two subgroups. The “early disease stage” subgroup included anyone with a neurological evaluation within 3 years of symptom onset whereas the “late disease stage” subgroup included every patient who had an evaluation greater than 3 years from symptom onset. Only the initial and final evaluation at Mayo Clinic was used to gather

data on symptoms in the early and late disease subgroups respectively as defined by the 3-year cut off as the number of visits was highly variable between patients. The 3-year split was based on the temporal cut-off for development of falls and extraocular movement abnormalities employed by the MDS-PSP diagnostic criteria.

Patients were then assigned a possible or probable level of diagnostic confidence if they met the NINDS-SPSP or MDS-PSP criteria, with an additional “suggestive” designation as recognized by the MDS-PSP criteria, for both the initial and last visit. PSP phenotype that best described the patient’s most predominant clinical syndrome, as defined by the MDS-PSP diagnostic criteria was also recorded. When patients had prominent symptoms of more than one phenotype, all symptoms were recorded and are presented in the results section (Figure 1A and 1B), however the overall diagnostic level (possible, probable and suggestive) was assigned based on the phenotype with the highest level of confidence.

Medical records were screened for exclusion criteria per NINDS-SPSP and MDS-PSP guidelines. These were recorded independently for both first and final evaluations.

Statistical analysis was performed using R (version 3.5.1), a statistical package for descriptive statistics and construction of data tables. We calculated the sensitivity and specificity of both diagnostic criteria in the early and late disease groups. Details of demographics, clinical features, level of diagnostic certainty, and phenotypes were plotted against neuropathological diagnoses for both early and late stage groups.

Results

Demographics and clinical diagnosis according to NINDS-SPSP and MDS-PSP criteria are shown in Table 1. One-hundred and twenty-nine patients with the following neuropathologic diagnoses were identified; PSP (n=66), CBD (N=35), LBD (n=20), MSA (n=4), globular glial tauopathy (GGT) (n=3) and FTLD-TDP (n=1). All patients in the Lewy body pathology group were clinically diagnosed as Parkinson’s disease. Of the entire cohort 50% were male (n=65). Forty-five percent (n=58) were clinically suspected to have PSP at some point during the disease course, including 71% (n=47) of the PSP group, 20% (n=7) of CBD group, and all GGT (n=3) and FTLD-TDP (n=1) cases. Follow up, defined as a second visit over 6 months from the initial visit was available for 86 (66.7%) of the patients.

The first reported symptom and median duration from symptom onset to death are summarized in supplementary table 2. The median duration between symptom onset and the first neurological evaluation at Mayo Clinic was 2.4 years (IQR 1.2–3.9), whereas the last evaluation occurred a median of 6.0 (IQR 3.5–8.2) years from symptom onset (see table 2 for classification of follow up time by neuropathological diagnosis).

Forty-five PSP patients had a neurological evaluation within 3 years of symptom onset. Of these 69% (n=31) did not meet NINDS-SPSP criteria, whereas 84% (n=38) met suggestive, possible or probable levels of MDS-PSP criteria (see Table 2). Five patients with non-PSP neuropathological diagnoses (false positives) met NINDS-SPSP criteria for probable PSP. When MDS-PSP criteria were applied, 25 patients with non-PSP neuropathology met PSP

criteria, 16 of whom had CBD pathology and met criteria for “suggestive PSP,” and 5 of whom had CBD pathology and met criteria for “probable-PSP.”

There were 37 patients in the “late disease stage” group, of whom 24 (65%) met NINDS-SPSP criteria, and all met the MDS-PSP criteria (see Table 2). A patient with a PSP-RS like phenotype, but CBD neuropathology accounted for the only false positive case per the NINDS-SPSP criteria, whereas 24 patients with non-PSP pathology met MDS-PSP criteria at this late evaluation.

These data were used to calculate sensitivity and specificity of both criteria (Table 3A). Overall, the probable PSP criteria according to MDS had a sensitivity of 47% and specificity of 86%, whereas NINDS-SPSP criteria had a sensitivity of 33% and specificity of 90%. Possible-PSP criteria according to MDS had a sensitivity of 52% and specificity of 84%, whereas NINDS-SPSP possible-PSP criteria had a sensitivity of 46% and specificity of 90%. Addition of the “suggestive” category improved the sensitivity of MDS-PSP criteria to 88% but resulted in a lower specificity of 40%. Sensitivity and specificity calculations were also performed for both the early and late stage groups separately. At both the early and late disease stage evaluations (Table 3B and 3C), sensitivity of the MDS-PSP criteria was superior (84% and 100%, respectively) compared to the NINDS-SPSP criteria (31% and 65%, respectively). NINDS-SPSP probable criteria were marginally more specific at both early and late stages (87% and 97%, respectively) as compared to the MDS-PSP criteria (82% and 91%, respectively).

PSP phenotypes were analyzed for all neuropathologic diagnoses at the first and last visit (Table 4, also see Table 2A for details of time between onset and evaluation). Clinical symptoms were defined using the MDS-PSP criteria. At the initial visit, 22 of 129 patients had prominent features of more than one PSP phenotype, whereas 33 patients were not classifiable into a specific phenotype according to the MDS-PSP criteria. At first visit, 11 patients had apraxia of speech, 2 had aphasia, 13 patients met criteria for both apraxia of speech and aphasia, 8 patients with CBS also had prominent apraxia of speech and aphasia, 2 patients with PSP-RS had features of CBS whereas 5 patients with PSP-RS had prominent behavioral symptoms as defined by PSP-F. Neuropathologies and clinical phenotypes for the initial visits are shown in Table 4 and Figure 1A. Eighty-six patients had a subsequent visit more than 6 months from the first visit (Table 4 and Figure 1B). Of this group, 26 met criteria for multiple phenotypes, whereas 15 were not classifiable into a specific phenotype according to the MDS-PSP criteria. Ten patients met criteria for both apraxia of speech and aphasia, 15 patients with CBS also had apraxia of speech and/or aphasia. Among patients with PSP-RS 2 had features of CBS, 3 had a speech/ language disorder, 6 had prominent behavioral symptoms as defined by PSP-F. Richardson syndrome was most predictive of PSP neuropathology, but other 4R tauopathies occasionally led to this phenotype. PSP-SL was associated with CBD more often than PSP. Alpha synucleinopathies, such as LBD and MSA, never qualified for more than “suggestive” of PSP-P. Patients with PSP pathology were more likely to have additional extraocular motor abnormalities and postural instability.

Exclusion criteria for NINDS-SPSP and MDS-PSP are shown in Supplementary Tables 3 and 4. Asymmetric parkinsonism and cortical signs were common reasons for exclusion of

true PSP cases by the NINDS-SPSP criteria. The MDS criteria led to exclusion of one PSP case due to prominent ataxia at onset and 2 cases due to amnestic dementia.

Of all available clinical encounters, 2% of the data was missing due to lack of documentation and was evenly spread out hence did not contribute to bias.

Discussion

Progressive supranuclear palsy is a neuropathologically defined entity. Clinical antemortem diagnosis is challenging. Richardson syndrome was most commonly associated with PSP after recognition by the NINDS-SPSP criteria in 1996. [5] Since then, however, several phenotypes have been associated with PSP, which ultimately led to the publication of the MDS-PSP criteria in 2017. [16, 23] The MDS-PSP criteria aim to improve the clinical recognition of PSP by including several phenotypes of PSP as well as adding a suggestive category. Our results show that these criteria are far more sensitive and will likely lead to better detection of PSP for natural history and biomarker discovery studies. The improved detection of PSP was associated with a small reduction in specificity. Overall, the MDS-PSP criteria perform very favorably in comparison to other criteria for clinical diagnosis of other neurodegenerative disorders. For comparison, a recent study of the PD criteria, found an 11.5% false positive rate, sensitivity of 94.5% and specificity of 88.5%. [24] Sensitivity of the clinical diagnosis of Alzheimer's disease ranges from 70.9–87.3% and specificity 44.3–70.8%. [25] Similarly, criteria for "possible bvFTD" have sensitivity of 95% and specificity of 82% whereas "probable bvFTD" have sensitivity of 85% and specificity of 95%. [26]

False positives result from overlapping symptoms in patients with other tauopathies, such as CBD and GGT. This overlap occurs to a much lesser extent with alpha-synucleinopathies that are more likely to have distinguishing clinical features such as anosmia, dream enactment behavior and hallucinations. [27] This is an important step with the advent of tau directed therapies, as the criteria are very effective at detecting 4R tauopathies. However, discerning between PSP and CBD remains challenging and may become important if therapeutics have different efficacy or side effect profiles among various 4R tauopathies. [27] MDS-PSP criteria appropriately identify overlapping clinical presentations of CBD and PSP as "4R tauopathies".[16]

Some clinical phenotypes highlight this overlap between tauopathies. For example, the PSP-RS phenotype is more commonly seen in PSP, but it is well recognized that CBD may present with a very similar phenotype. [22, 28]Similarly, CBS is a pathologically diverse entity that poses diagnostic challenges. [1, 17, 29] CBS can be a manifestation of both CBD and PSP, [16, 22] although patients with PSP-CBS are less likely to develop VSGP and postural instability compared to PSP-RS. [30] PSP and CBD overlap clinically and 4R tau inclusion formation is common to both, but they are pathologically and biochemically distinguishable. [31, 32] A third clinical phenotype that highlights the overlap between tauopathies is the speech and language spectrum disorders. Degenerative AOS, occurring either in isolation or with aphasia,[33, 34] can be associated with both PSP and CBD.[35] In addition, patients may present with progressive aphasia or AOS and then evolve to develop motor symptoms suggestive of either CBD or PSP.[18, 35, 36] In our cohort, patients meeting criteria for PSP-SL were more

likely to have CBD than PSP. More research is needed in order to determine whether there are distinct speech and language characteristics that may be more predictive of PSP than CBD. Non-language cognitive symptoms occurred commonly among PSP patients. A rare minority present with amnestic symptoms (2 cases in our cohort) that would be excluded by either diagnostic criteria. On the other hand, a significant number developed variable degrees of frontal dysexecutive symptoms (49% at last visit, see Supplementary Table 5), infrequently severe enough to meet criteria for bvFTD. [37]

The MDS-PSP criteria define distinct phenotypes and levels of confidence for certain combinations of symptoms. Not all patients demonstrate typical features until later in the disease course. For example, extraocular motor abnormalities are required for all probable PSP phenotypes. In our cohort, 41% of PSP patients did not have eye movement abnormalities at their first visit (Supplementary Table 5). This is not necessarily surprising since many of the PSP variants, including PSP-P, PSP-PGF and PSP-SL may not have extraocular movement abnormalities until later in the disease course and some may never develop classic VSGP. Some phenotypes were uncommon in this cohort, such as a single patient with prominent cerebellar ataxia at presentation, who was excluded by both MDS-PSP and NINDS criteria. There were no cases of PSP-PLS.

Another important observation in this cohort was that patients did not always fit precisely into a single predefined syndrome and instead their symptoms spanned multiple phenotypes. For example, we noted co-occurrence of corticobasal syndrome, aphasia and apraxia of speech, and co-occurrence of PSP-RS and significant frontal dysexecutive symptoms in patients with either CBD or PSP pathology. These “hybrid-phenotypes” have been described previously. [38]

Although clinical criteria are important to standardize phenotypes, they are imperfect as diagnostic biomarkers. This has led to the development of several imaging-based biomarkers. However, neuroimaging biomarkers in PSP have their own limitations. Midbrain atrophy correlates with the clinical syndrome of PSP-RS, but is not predictive of neuropathology.[39] Development of tau-specific radio ligands has advanced PET neuroimaging of AD,[40, 41]and uptake has also been reported in PSP, especially in the midbrain, thalamus, subthalamic nucleus and pallidum.[42–45] Tau-PET imaging in PSP needs to be interpreted with caution due to poor binding of all available radio ligands to 4R tau as compared to much higher binding with paired helical filaments of 3R+4R tau as in AD.[46] A recent review of the neuroimaging modalities in PSP [47]concluded that none are definitively diagnostic of PSP pathology[47]. The NINDS-SPSP criteria did not include imaging criteria however the MDS-PSP criteria recognizes imaging findings that are supportive of a diagnosis of PSP. This includes midbrain atrophy by MRI, midbrain hypometabolism by ^{18}FDG-PET and post-synaptic striatal dopaminergic degeneration as demonstrated by ^{123}I-IBZM-SPECT or ^{18}F-DMFP-PET. [16] In summary, despite the importance of clinical criteria in the diagnosis and detection of PSP, our ability to predict neuropathology in vivo is highly limited and molecular biomarkers are sorely lacking currently.

Concomitant proteinopathies affect neuropathological and clinical manifestations of any neurodegenerative disorder. It was recently shown that 45% of CBD cases have concomitant

TDP-43 pathology, and when located in the midbrain tegmentum can lead to VSGP and a PSP-RS like phenotype.[48] Concomitant proteinopathies are also well recognized in all forms of parkinsonism.[49] The burden and characteristics of co-pathology may depend on age, *APOE* ε4, and may be independently influenced by presence of tau versus alpha synuclein.[50] Detailed analysis of concomitant pathologies that may influence clinical syndrome was beyond the scope of this article and have not been accounted for by the MDS-PSP criteria. Another limitation of our study is the routine use of a single hemisphere for neuropathological examination which is sufficient for diagnosis, but in cases with asymmetric neuropathology may affect the findings. Due to the retrospective nature of this study, not all phenotypes recognized by the MDS-PSP criteria were available and documented clinical data was limited to that recorded by evaluating physicians potentially affecting the findings. Prospective enrollment of PSP patients according to the MDS-PSP criteria may be more accurate.

In this study we compare clinical signs and symptoms of patients with neurodegenerative pathologies and apply both NINDS-SPSP and the MDS-PSP criteria for PSP diagnosis at different time points to calculate sensitivity and specificity. Our study has several strengths, including the large number of autopsy confirmed cases, all of whom were examined by a single expert neuropathologist (DWD). Patients were evaluated by experts in movement disorders and behavioral neurology, suggesting high internal reliability. The fact that our cases were all seen at a single institution, with three sites in geographically diverse regions, allowed us to sample a broader demographic while still having highly uniform clinical data available. This is the first study to our knowledge to assess the sensitivity and specificity of the new MDS-PSP criteria and our results will inform future studies that rely on these criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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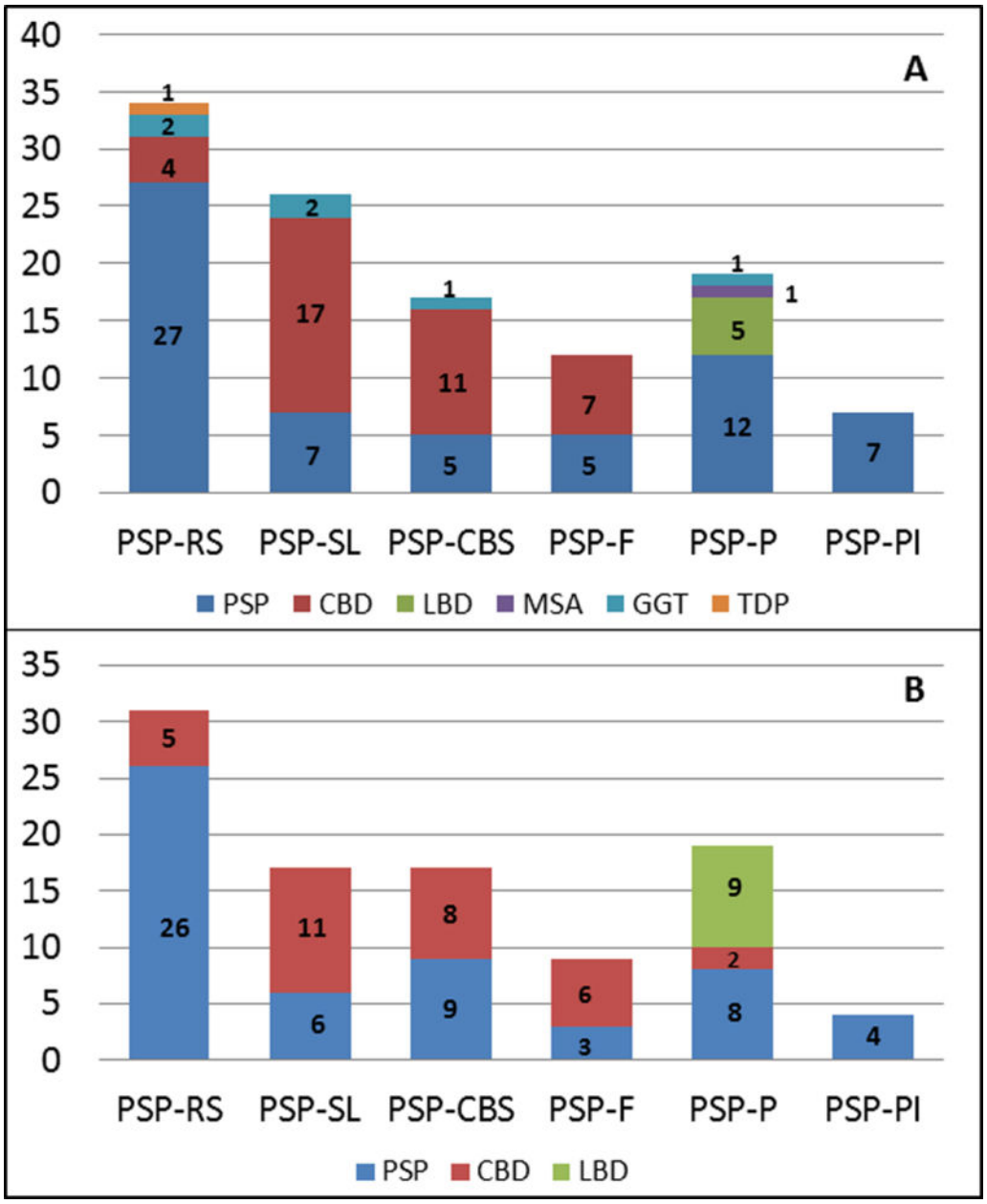

Figure 1.

Clinical phenotypes (identified in text) by neuropathology at first (A) and last visit (B).

CBD: Corticobasal degeneration, GGT: Globular glial tauopathy, MSA: Multiple systems atrophy, LBD: Lewy body Disease, PSP: Progressive supranuclear palsy, TDP: Transactive DNA binding protein-43.

Table 1

Demographics and diagnostic level by neuropathology

	CBD (N=35)	FTLD-TDP (N=1)	GGT (N=3)	MSA (N=4)	LBD (N=20)	PSP (N=66)	Total (N=129)
CLINICALLY SUSPECTED PSP							
No	28 (80.0%)	0	0	4 (100.0%)	20 (100.0%)	19 (28.8%)	71 (55.0%)
Yes	7 (20.0%)	1 (100.0%)	3 (100.0%)	0	0	47 (71.2%)	58 (45.0%)
Male sex							
No	16 (45.7%)	1 (100.0%)	2 (66.7%)	3 (75.0%)	10 (50.0%)	32 (48.5%)	64 (49.6%)
Yes	19 (54.3%)	0	1 (33.3%)	1 (25.0%)	10 (50.0%)	34 (51.5%)	65 (50.4%)
NINDS-SPSP first visit							
Does not meet criteria	31 (88.6%)	0	2 (66.7%)	4 (100.0%)	20 (100.0%)	36 (54.5%)	93 (72.1%)
Possible	0	0	0	0	0	8 (12.1%)	8 (6.2%)
Probable	4 (11.4%)	1 (100.0%)	1 (33.3%)	0	0	22 (33.3%)	28 (21.7%)
NINDS-SPSP last visit							
Does not meet criteria	18 (81.8%)	0	0	1 (100.0%)	19 (100.0%)	19 (40.4%)	57 (64.0%)
Possible	0	0	0	0	0	5 (10.6%)	5 (5.6%)
Probable	4 (18.2%)	0	0	0	0	23 (48.9%)	27 (30.3%)
MDS-PSP first visit							
Not classifiable	5 (14.3%)	0	0	3 (75.0%)	17 (85.0%)	8 (12.1%)	33 (25.6%)
Suggestive	23 (65.7%)	0	1 (33.3%)	1 (25.0%)	3 (15.0%)	24 (36.4%)	52 (40.3%)
Possible	1 (2.9%)	0	0	0	0	3 (4.5%)	4 (3.1%)
Probable	6 (17.1%)	1 (100.0%)	2 (66.7%)	0	0	31 (47.0%)	40 (31.0%)
MDS-PSP last visit							
Not classifiable	3 (14.3%)	0	0	1 (100.0%)	10 (52.6%)	1 (2.2%)	15 (17.4%)
Suggestive	11 (52.4%)	0	0	0	9 (47.4%)	8 (17.8%)	28 (32.6%)
Possible	2 (9.5%)	0	0	0	0	4 (8.9%)	6 (7.0%)
Probable	5 (23.8%)	0	0	0	0	32 (71.1%)	37 (43.0%)

Demographics and diagnostic level according to NINDS-SPSP and MDS-PSP criteria by neuropathological category. *CBD: Corticobasal degeneration, GGT: Globular Glial Tauopathy, FTLD-TDP: Fronto-temporal lobar degeneration TDP-43, LBD: Lewy body disease, MSA: Multiple systems atrophy, PSP: Progressive supranuclear palsy.*

Table 2

Section A: Time between symptom onset, first and last clincial evaluation

	CBD (N=35)	FTLD-TDP (N=1)	GGT (N=3)	MSA (N=4)	LBD (N=20)	PSP (N=66)	Total (N=129)
Symptom onset to first visit							
Median years (Q1, Q3)	2.54 (1.55, 3.38)	1.62 (1.62, 1.62)	2.92 (2.68, 3.57)	3.13 (2.57, 3.35)	4.30 (1.57, 5.78)	1.98 (1.06, 3.61)	2.43 (1.24, 3.86)
Symptom onset to last visit							
Median years (Q1, Q3)	5.18 (3.56, 6.89)	NA	NA	2.40 (2.40, 2.40)	11.03 (7.08, 14.48)	5.05 (3.38, 6.58)	6.03 (3.53, 8.23)

Section B: Dignoses for "early disease stage" group. First evaluation within 3 years of symptom onset.

	CBD (N=25)	FTLD-THP (N=1)	GGT (N=2)	MSA (N=1)	LBD (N=9)	PSP (N=45)	Total (N=83)
Onset to first visit (years)							
Median (Q1, Q3)	1.82 (1.24, 2.58)	1.62 (1.62, 1.62)	2.68 (2.56, 2.80)	1.01 (1.01, 1.01)	1.53 (0.50, 1.70)	1.33 (0.93, 2.07)	1.53 (0.98, 2.36)
NINDS-SPSP first visit							
Does not meet criteria	22 (88.0%)	0	1 (50.0%)	1 (100.0%)	9 (100.0%)	31 (68.9%)	64 (77.1%)
Possible	0	0	0	0	0	5 (11.1%)	5 (6.0%)
Probable	3 (12.0%)	1 (100.0%)	1 (50.0%)	0	0	9 (20.0%)	14 (16.9%)
MDS-PSP first visit							
Not classifiable	4 (16.0%)	0	0	1 (100.0%)	8 (88.9%)	7 (15.6%)	20 (24.1%)
Suggestive	16 (64.0%)	0	1 (50.0%)	0	1 (11.1%)	21 (46.7%)	39 (47.0%)
Possible	0	0	0	0	0	2 (4.4%)	2 (2.4%)
Probable	5 (20.0%)	1 (100.0%)	1 (50.0%)	0	0	15 (33.3%)	22 (26.5%)

Section C: Dignoses for "late disease stage" group. Evaluation over 3 years of symptom onset.

	CBD (N=18)	LBD (N=17)	PSP (N=37)	Total (N=72)
Onset to last visit (years)				
Median (Q1, Q3)	6.04 (4.41, 7.96)	11.05 (10.02, 15.31)	6.09 (4.31, 6.94)	6.40 (4.87, 9.08)
NINDS-SPSP last visit				
Does not meet criteria	17 (94.4%)	17 (100.0%)	13 (35.1%)	47 (65.3%)
Possible	0	0	5 (13.5%)	5 (6.9%)
Probable	1 (5.6%)	0	19 (51.4%)	20 (27.8%)
MDS-PSP last visit				

Section C: Dignoses for “late disease stage” group. Evaluation over 3 years of symptom onset.				
	CBD (N=18)	LBD (N=17)	PSP (N=37)	Total (N=72)
Not classifiable	2 (11.1%)	9 (52.9%)	0	11 (15.3%)
Suggestive	11 (61.1%)	8 (47.1%)	4 (10.8%)	23 (31.9%)
Possible	2 (11.1%)	0	3 (8.1%)	5 (6.9%)
Probable	3 (16.7%)	0	30 (81.1%)	33 (45.8%)

A: Time from disease onset to first and last visit by neuropathology. B and C: Diagnoses and level of confidence in the early and late disease stage group. NA: Follow up at >6 months from initial visit was not available.

Table 3

Section A: Sensitivity and specificity for the entire cohort

Criteria	Designation	Clinical PSP	PSP pathology	Sensitivity (%)	No clinical PSP	Non-PSP pathology	Specificity (%)
MDS	Probable	31	66	47.0	9	63	85.7
	Possible	3	66	51.5	1	63	84.1
	Suggestive	24	66	87.9	28	63	39.7
NINDS	Probable	22	66	33.3	6	63	90.5
	Possible	8	66	45.5	0	63	90.5

Section B: Sensitivity and specificity at initial evaluation within 3 years of symptom onset "early stage" group

		Clinical PSP	PSP pathology	Sensitivity (%)	PPV (%)	No clinical PSP	Non-PSP pathology	Specificity (%)	NPV (%)
MDS	Probable	15	45	33.3	68.2	7	38	81.6	50.8
	Possible	2	45	37.8	70.8	0	38	81.6	52.5
	Suggestive	21	45	84.4	60.3	18	38	34.2	65.0
NINDS	Probable	9	45	20.0	64.3	5	38	86.8	47.8
	Possible	5	45	31.1	73.7	0	38	86.8	51.6

Section C: Sensitivity and specificity at evaluation over 3 years of symptom onset "late stage" group

		Clinical PSP	PSP pathology	Sensitivity (%)	PPV (%)	No clinical PSP	Non-PSP pathology	Specificity (%)	NPV (%)
MDS	Probable	30	37	81.1	86.5	3	35	91.4	73.5
	Possible	3	37	89.2	83.7	2	35	85.7	79.1
	Suggestive	4	37	100.0	62.0	19	35	31.4	93.3
NINDS	Probable	19	37	51.4	85.2	1	35	97.1	61.3
	Possible	5	37	64.9	87.5	0	35	97.1	66.7

Sensitivity, specificity positive and negative predictive values divided by "early disease stage", and "late disease stage". *MDS: Movement Disorders Society, NINDS: National Institutes of Neurological* Diseases and Stroke, NPV: negative predictive value, PSP: Progressive Supranuclear Palsy, PPV: Positive predictive value.

Table 4

Phenotypes by MDS-PSP criteria at first and last visit

First Visit						
	PSP-RS	**PSP-PI**	**PSP-P**	**PSP-SL**	**PSP-F**	**PSP-CBS**
robable	34	0	3	2*	7	2*
Possible	0	0	0	1	1*	4
Suggestive	0	7	13	23	3	11
Last Visit						
Probable	31	0	3	4*	5	5*
Possible	0	0	0	2	0	6
Suggestive	0	4	16	11	4	6

Relative level of diagnostic confidence by phenotype for patients with features of multiple phenotypes. *PSP: Progressive supranuclear palsy, CBS: Corticobasal syndrome, F: Frontal, RS: Richardson Syndrome, PI: Postural instability, P: Parkinsonism, SL: speech language.*