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RESEARCH ARTICLE

CME

Which Ante Mortem Clinical Features Predict Progressive Supranuclear Palsy Pathology?

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Members of the Movement Disorder Society-Endorsed PSP Study Group are listed in the Appendix.

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ABSTRACT: Background: Progressive supranuclear palsy (PSP) is a neuropathologically defined disease presenting with a broad spectrum of clinical phenotypes.

Objective: To identify clinical features and investigations that predict or exclude PSP pathology during life, aiming at an optimization of the clinical diagnostic criteria for PSP.

Methods: We performed a systematic review of the literature published since 1996 to identify clinical features and investigations that may predict or exclude PSP pathology. We then extracted standardized data from clinical charts of patients with pathologically diagnosed PSP and relevant disease controls and calculated the sensitivity, specificity, and positive predictive value of key clinical features for PSP in this cohort.

Results: Of 4166 articles identified by the database inquiry, 269 met predefined standards. The literature review identified clinical features predictive of PSP, including features of the following 4 functional domains: ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction. No biomarker or genetic feature was found reliably validated to predict definite PSP. High-quality original natural history data were available from 206 patients with pathologically diagnosed PSP and from 231 pathologically diagnosed disease controls (54 corticobasal degeneration, 51 multiple system atrophy with predominant parkinsonism, 53 Parkinson's disease, 73 behavioral variant frontotemporal dementia). We identified clinical features that predicted PSP pathology, including phenotypes other than Richardson's syndrome, with varying sensitivity and specificity.

Conclusions: Our results highlight the clinical variability of PSP and the high prevalence of phenotypes other than Richardson's syndrome. The features of variant phenotypes with high specificity and sensitivity should serve to optimize clinical diagnosis of PSP. © 2017 International Parkinson and Movement Disorder Society

Key Words: Progressive supranuclear palsy; clinical features; diagnosis; clinico-pathological series; systematic review

Progressive supranuclear palsy (PSP) is a neurodegenerative disease first described by Steele and colleagues in 1964.[1] Its prevalence was estimated from a clinical perspective to be 3 to 6 per 100,000.[2,3] Age at symptom onset is 65 years, and the disease duration to death is 6 to 9 years, on average.[2,4] Neuropathological examination provides the gold standard for diagnosis, defining the disease entity.[5-7] The National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria for the clinical diagnosis of PSP[7] are commonly applied as ante mortem diagnostic standard. A diagnosis of "probable" PSP requires the presence of vertical supranuclear gaze palsy (vSNP) plus postural instability (PI) and falls within 1 year of disease. For a diagnosis of "possible" PSP, either vSNP or a combination of slow vertical saccades and PI with falls within 1 year need to be present.[7] This clinical manifestation of PSP with predominant ocular motor dysfunction and PI is called Richardson's syndrome (PSP-RS). The NINDS-SPSP criteria have excellent specificity,[8,9] but low sensitivity early in the clinical course[9-12] because typical features of PSP-RS are either absent or become apparent only after several years in a significant proportion of PSP patients.[4,9,10,13-34] A recent analysis of autopsy-confirmed patients suggested that 60% to 75% of patients with ascertained PSP pathology have variant PSP syndromes (vPSP) other than PSP-RS.[4] Too often, patients with vPSP, but also with PSP-RS, are diagnosed only after several years or never during their

TABLE 1. Key questions of the systematic literature review

Key Question
1. How effective are clinical diagnostic criteria to predict or exclude neuropathologically defined PSP?
2. Which signs/symptoms/syndromes predict or exclude neuropathologically defined PSP?
3. How effective is acute/chronic levodopa/apomorphine testing to predict or exclude PSP?
4. How effective is objective autonomic function testing to exclude PSP?
5. How effective is neuropsychological testing to predict or exclude PSP?
6. How effective is clinical or quantitative oculomotor analysis to predict or exclude PSP?
7. How effective is genetic testing to predict or exclude PSP?
8. Is there a biomarker for PSP?

lifetime.[4] However, early diagnosis is urgently warranted because disease-modifying treatments are being developed and would ideally be initiated before relevant cognitive or motor impairment is present.[35,36]

Therefore, the International Parkinson and Movement Disorder Society-endorsed PSP Study Group (MDS-PSPSG) aimed to optimize clinical diagnostic criteria for PSP. To identify clinical features and investigations that reliably predict or exclude PSP pathology, we first performed a systematic literature review. We then verified the diagnostic value of the suggested features in the largest clinico-pathological cohort of PSP reported thus far in comparison to relevant disease controls (corticobasal degeneration [CBD], multiple system atrophy with predominance of parkinsonism [MSA-P], PD, or frontotemporal lobar degeneration [from any underlying non-PSP/CBD proteinopathy] presenting with a behavioral variant frontotemporal dementia [FTLD-bvFTD]).

Methods

Systematic Literature Review

The MDS-PSPSG steering committee (G.U.H., A.L.B., I.L., L.I.G., M.S.) assembled working groups of key experts to conduct a systematic review of published literature on specific aspects relevant to the diagnosis of PSP. Members of the groups defined key questions (Table 1) and search terms (Supplemental Table 1). Literature was searched on PubMed, Cochrane, Medline, and PSYCInfo databases for entries from 1996 until 2015 using the search terms for each key question and for PSP ("Progressive Supranuclear Palsy" OR "Progressive Supranuclear Ophthalmoplegia" OR "Steele Richardson Olszewski syndrome"). Study group members were encouraged to add relevant articles for consideration throughout the project period (end of 2016), particularly those published after 2015. All titles and abstracts of identified articles were reviewed independently by 2 investigators (G.H., C.K.) to select research articles, systematic reviews, and meta-analyses published in English using either a postmortem diagnosis or the highly specific NINDS-SPSP criteria as diagnostic standard. Three independent members of the consortium (G.U.H., G.R., C.K.) analyzed methodology (internal validity, overall assessment, description) of these articles using the checklist of the Scottish Intercollegiate Guidelines Network (SIGN, www.sign.ac.uk)[37] and rated their methodological quality as "very reliable," "OK," or "insufficient." "Insufficient" articles were excluded from further analysis. For each included article, 2 independent experts collated standardized information on (1) study design, (2) evidence level, (3) patient characteristics, (4) key test or feature, (5) key findings, and (6) diagnostic value. Written summaries were provided to all MDS-PSPSG members. Evidence was summarized for each key question by the working groups (Supplemental Table 1).

Clinico-Pathological Case Series

This work was approved by the ethics committee of the Technical University of Munich and the participating centers. Autopsied cases with detailed clinical information and a definite diagnosis of PSP,[5,6,38] CBD,[5,39] MSA-P,[40] PD,[41] and a clinical syndrome of bvFTD[42] with frontotemporal lobar degeneration (FTLD) from any underlying non-PSP/CBD proteinopathy (ie, FTLD with Tau pathology (FTLD-Tau), including frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) or Pick's disease, FTLD with transactive response DNA-binding protein pathology (FTLD-TDP), or FTLD with fused in sarcoma protein pathology (FTLD-FUS))[43] were recruited from 9 brain banks with expertise in neurodegenerative diseases (Ludwig-Maximilians-University, Munich, Germany; University Hospital of Bordeaux, France; King's College, London, UK; University of Lund, Lund, Sweden; Erasmus Medical Center, Rotterdam, the Netherlands; Hospital Clinic–IDIBAPS, Barcelona, Spain; University of Saskatchewan, Canada; Johns Hopkins University, Baltimore, Maryland; University of Pennsylvania, Philadelphia, Pennsylvania). Before death, all donors had given written informed consent according to the Declaration of Helsinki for the scientific use of their brains and medical records. Although cases with minor age-related copathology, such as amyloid-beta pathology, primary age-ralated tauopathy, argyrophilic grain disease, and aging-related tau-astrogliopathy were included in the analysis, cases with more than 1 pathological diagnosis were excluded. Clinical data were acquired as described previously.[4] In short, demographic data, age at disease onset and death, disease duration, initial clinical diagnosis, final clinical diagnosis, and 37 clinical features (Supplemental Table 2), including year of onset, were abstracted from clinical records using a standardized template by

local physicians. Features not specifically mentioned in the records were considered absent.

Statistics

Demographic and clinical data of groups were compared with analysis of variance and post hoc Fisher's least significant difference test. $P < .05$ was considered statistically significant. Prevalence, positive predictive value (PPV), and specificity of clinical features was calculated for PSP versus all control cases.

Results

Systematic Literature Review

The 2 key questions on radiological biomarkers of PSP are reported in detail in an accompanying article in this issue of *Movement Disorders*.[44] The literature research for the 8 nonimaging key questions (Table 1) is reported herein. From the identified 4166 abstracts, 1035 publications met the criteria for full review. The methodology of 269 articles was considered "very reliable" or "OK." Evidence pertinent to the diagnosis of PSP for each key question is shown in detail in Supplemental Table 1 and summarized in the following paragraphs.

The NINDS-SPSP criteria were found to be very specific, but not sensitive in the early clinical course.[9-12,45] Alternative clinical diagnostic criteria were not better for early diagnosis.[9,11] Major challenges are absence of features specific for PSP-RS, particularly ocular motor dysfunction in some patients with PSP, and clinical overlap with other diseases (particularly PD, MSA-P, CBD, and FTD).

Two large clinico-pathological series of PSP patients identified 3 coherent clusters of symptoms by hypothesis-free cluster analysis.[4,33] These were (1) vSNP and falls, (2) parkinsonian signs/symptoms, and (3) cognitive symptoms. We considered these functional domains most relevant to the clinical manifestation of definite PSP.

The literature from the past 20 years emphasizes vPSP syndromes other than PSP-RS: definite PSP patients were reported in small series with initial predominance of ocular motor dysfunction,[4] PI, [4,46] parkinsonism resembling idiopathic PD,[10,33] frontal lobe cognitive or behavioral presentations,[18,23,24] progressive gait freezing,[16,19,34,47] speech/language disorders, including nonfluent/agrammatic variant of primary progressive aphasia (nfaPPA),[15,22,31] and progressive apraxia of speech (AOS),[22,48] corticobasal syndrome,[14,27,49] primary lateral sclerosis,[32] or cerebellar ataxia.[50,51]

A broad spectrum of diseases other than PSP have been clinically reported to present similarly to PSP (PSP look-alikes) and need to be considered as differential diagnosis (Supplemental Table 1).

Available studies on neuropsychological testing are limited by lack of autopsy confirmation and the inclusion of mostly PSP-RS cases. The few studies with autopsy confirmation revealed that PSP may present with features classically attributed to FTD, such as bvFTD[18,23,24] and nfaPPA.[31] The typical frontal syndrome of PSP appears to comprise apathy, bradyphrenia (ie, slowness of thinking), executive dysfunction, reduced phonemic verbal fluency, impulsivity, disinhibition, and perseveration.[52-56]

Studies addressing ocular motor analysis in autopsy-confirmed cases reported a high specificity of vSNP and reduced vertical saccade velocity for PSP.[57,58] Further studies reported eyelid-opening apraxia,[59-61] frequent macro square wave jerks,[62] and nonspecific ocular symptoms (diplopia,[28,60] blurred vision,[28,60] burning eye sensation,[28] photophobia,[28,60,63] blepharospasm,[59,64] and reduced blinking rate[65]) as characteristics for PSP.

The literature on genetics of PSP confirms that PSP is generally sporadic. However, non-Mendelian family histories for neurodegenerative diseases were found in up to 33% of PSP index patients.[66,67] Homozygosity for the H1 haplotype of microtubule-associated protein tau (*MAPT*) and polymorphisms at syntaxin 6 (*STX6*), myelin-associated oligodendrocyte basic protein (*MOBP*), and eukaryotic translation initiation factor 2 alpha kinase 3 (*EIF2AK3*) represent risk factors for sporadic PSP.[68] Mendelian inheritance of PSP-like syndromes occurs rarely as a result of *MAPT* mutations,[69,70] but the similarity to PSP-RS is only partial. Mutations in other genes can present as PSP-like syndromes, but they have either no or an uncertain relationship to definite PSP (Supplemental Table 1).

Studies on fluid biomarkers in PSP lack sufficient sample numbers, homogeneity (clinical phenotype, comorbidities, comedication, etc.), and autopsy confirmation, but also suffer technical shortcomings (heterogeneous sample processing, assay limitations, lack of independent confirmation). It is established, however, that CSF concentrations of total and phosphorylated tau are not increased in PSP patients, unlike in Alzheimer's disease (AD).[71]

Clinico-Pathological Case Series

Detailed clinical data were available for autopsy confirmed cases of PSP (n = 206), CBD (n = 54), MSA-P (n = 51), PD (n = 53), and FTLD-bvFTD (n = 73). Characteristics of 100/206 PSP patients have been described previously.[4] A subset of control patients (CBD, MSA-P, PD, FTLD-bvFTD) has been published previously in disease-specific studies, but not in systematic comparative evaluations of PSP features. Their demographic data, as shown in Table 2, are consistent with previously published data.[4,72-75] No PSP patient had a symptom onset prior to 41 years of

TABLE 2. Demographic data of the pathology confirmed cohort

	PSP	CBD	MSA-P	PD	FTLD-bvFTD
N	206	54	51	53	73
Age at onset	66.2 ± 0.6 [41-91]	63.3 ± 1.3* [42-81]	59.3 ± 1.3*** [40-80]	58.8 ± 1.5*** [40-80]	57.1 ± 1.0*** [35-74]
Age at death	74.0 ± 0.6 [54-94]	69.8 ± 1.2** [49-85]	66.8 ± 1.2*** [51-90]	73.1 ± 1.2 [56-90]	63.8 ± 1.2*** [41-84]
Disease duration	7.9 ± 0.3 [2-27]	6.8 ± 0.4 [3-12]	7.2 ± 0.4 [2-15]	14.6 ± 1.0*** [3-34]	6.7 ± 0.5 [1-20]

Demographic data of definite PSP, CBD, MSA, PD, and FTD patients. Data are mean ± SD [range]. ANOVA followed by post hoc LSD test: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. PSP. Abbreviations: PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; MSA-P, multiple system atrophy with predominance of parkinsonism; FTLD, frontotemporal lobar degeneration; bvFTD, behavioral variant of frontotemporal dementia.

age, nor a Mendelian inheritance pattern or a known *MAPT* mutation. FTLD cases had varying pathology (75% transactive response DNA-binding (TDP)-43, 21% Tau [other than PSP or CBD], 4% fused in sarcoma (FUS)); 34% (n = 25) were hereditary, 5% (n = 4) with *MAPT* mutations, 29% (n = 21) with known

TABLE 3. Initial and final clinical diagnosis in pathologically diagnosed patients

	PSP, % (n/n)	CBD, % (n/n)	MSA-P, % (n/n)	PD, % (n/n)	FTLD-bvFTD, % (n/n)
Initial clinical diagnosis					
PSP	**25.4 (31/122)**	6.7 (2/30)	6.3 (2/32)	0.0 (0/34)	1.9 (1/52)
CBS	1.6 (2/122)	**0.0 (0/30)**	0.0 (0/32)	0.0 (0/34)	0.0 (0/52)
MSA	0.0 (0/122)	3.3 (1/30)	**6.3 (2/32)**	2.9 (1/34)	0.0 (0/52)
PD	23.0 (28/122)	3.3 (1/30)	71.9 (23/32)	**82.4 (28/34)**	0.0 (0/52)
FTD	9.8 (12/122)	33.3 (10/30)	0.0 (0/32)	0.0 (0/34)	**76.9 (40/52)**
FTD-MND	0.0 (0/122)	0.0 (0/30)	0.0 (0/32)	0.0 (0/34)	**7.7 (4/52)**
MND	0.8 (1/122)	0.0 (0/30)	0.0 (0/32)	0.0 (0/34)	1.9 (1/52)
Parkinsonism	11.5 (13/122)	13.3 (4/30)	0.0 (0/32)	2.9 (1/34)	0.0 (0/52)
LBD	1.6 (2/122)	0.0 (0/30)	0.0 (0/32)	0.0 (0/34)	0.0 (0/52)
NPH	0.0 (0/122)	0.0 (0/30)	3.1 (1/32)	0.0 (0/34)	0.0 (0/52)
AD	1.6 (2/122)	6.7 (2/30)	0.0 (0/32)	0.0 (0/34)	0.0 (0/52)
Dementia	2.5 (3/122)	6.7 (2/30)	0.0 (0/32)	0.0 (0/34)	3.8 (2/52)
Cerebral vasculopathy	2.5 (3/122)	3.3 (1/30)	0.0 (0/32)	0.0 (0/34)	0.0 (0/52)
Essential tremor	0.8 (1/122)	0.0 (0/30)	0.0 (0/32)	2.9 (1/34)	0.0 (0/52)
Depression	4.1 (5/122)	0.0 (0/30)	0.0 (0/32)	0.0 (0/34)	0.0 (0/52)
Mixed	7.4 (9/122)	10.0 (3/30)	6.3 (2/32)	5.9 (2/34)	5.8 (3/52)
Other	8.2 (10/122)	18.8 (6/30)	6.3 (2/32)	2.9 (1/34)	1.9 (1/52)
Final clinical diagnosis					
PSP	**62.6 (114/182)**	13.7 (7/51)	5.9 (3/51)	7.8 (4/51)	1.4 (1/69)
CBS	1.6 (3/182)	**27.5 (14/51)**	2.0 (1/51)	0.0 (0/51)	2.9 (2/69)
MSA	1.6 (3/182)	0.0 (0/51)	**70.6 (36/51)**	3.9 (2/51)	0.0 (0/69)
PD	9.9 (18/182)	0.0 (0/51)	11.8 (6/51)	**80.4 (41/51)**	0.0 (0/69)
FTD	3.3 (6/182)	29.4 (15/51)	0.0 (0/51)	0.0 (0/51)	**65.2 (45/69)**
FTD-MND	0.0 (0/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	**10.1 (7/69)**
MND	0.5 (1/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	4.3 (3/69)
Parkinsonism	2.7 (4/182)	3.9 (2/51)	2.0 (1/51)	3.9 (2/51)	0.0 (0/69)
LBD	0.5 (1/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)
NPH	0.0 (0/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)
AD	3.8 (7/182)	3.9 (2/51)	0.0 (0/51)	0.0 (0/51)	5.8 (4/69)
Dementia	2.2 (4/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)
Cerebral vasculopathy	0.5 (1/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)
Essential tremor	0.0 (0/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)
Depression	0.0 (0/182)	0.0 (0/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)
Mixed	8.2 (15/182)	17.6 (9/51)	7.8 (4/51)	3.9 (2/51)	10.1 (7/69)
Other	2.7 (5/182)	3.9 (2/51)	0.0 (0/51)	0.0 (0/51)	0.0 (0/69)

Initial and final clinical diagnosis of autopsy-confirmed patients with PSP, CBD, MSA-P, PD, and FTLD-bvFTD. Data are % (n with specific clinical diagnosis/n with any record of clinical diagnosis) of patients per group. Values in bold indicate the correct clinical diagnosis. AD, Alzheimer's dementia; bvFTD, behavioral variant of frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; FTD, frontotemporal dementia; FTD-MND, frontotemporal dementia with motor neuron disease; FTLD, frontotemporal lobar degeneration; bvFTD, behavioral variant of frontotemporal dementia; LBD, Lewy body dementia; MSA, multiple system atrophy; MSA-P, multiple system atrophy with predominant parkinsonism; NPH, normal pressure hydrocephalus; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

TABLE 4. Sensitivity, positive predictive value, and specificity of clinical features for PSP, in percentages

Clinical features	Sensitivity for					PPV for PSP	Spec. for PSP
	PSP	CBD	MSA-P	PD	FTLD-bvFTD		
Ocular motor dysfunction							
Vertical supranuclear gaze palsy	70.9	14.8	7.8	11.3	2.7	88	91
Vertical supranuclear gaze palsy within 3 years	29.6	9.3	2.0	3.8	0	88	97
Abnormal saccades	65.5	25.9	21.6	7.5	6.8	80	85
Abnormal saccades within 3 years	30.6	13.0	7.8	1.9	2.7	82	94
Nonspecific ocular symptoms	35.9	11.1	2.0	5.7	5.5	84	94
Postural instability							
Postural instability	82.0	48.1	90.2	75.5	16.4	58	46
Postural instability within 3 years	53.9	20.1	45.1	11.3	5.5	72	81
Postural instability within 1 year	44.7	13	23.5	5.7	1.4	74	90
Falls	78.6	37.0	66.7	66.0	8.2	64	59
Falls within 3 years	51.0	16.7	29.4	7.5	5.5	77	86
Falls within 1 year	37.4	11.1	13.7	3.8	0	84	94
Akinesia							
Parkinsonism, akinetic-rigid, predominantly axial, & levodopa-resistant	28.6	7.4	9.8	7.5	8.2	76	92
Parkinsonism, with tremor and/or asymmetric and/or levodopa-responsive	44.2	38.9	78.4	86.8	21.9	43	47
Progressive gait freezing within 3 years	1.9	0	0	0	0	100	100
Cognitive dysfunction							
Nonfluent/agrammatic primary progressive aphasia	18.9	27.8	0	1.9	16.4	58	88
Nonfluent/agrammatic primary progressive aphasia within 3 years	9.2	20.4	0	0	12.3	49	91
Apraxia of speech	4.4	18.5	0	3.8	2.7	39	94
Apraxia of speech within 3 years	1.0	7.4	0	0	2.7	25	97
Frontal dysfunction	57	66.7	21.6	28.3	86.8	50	46
Frontal dysfunction within 3 years	30	40.7	3.9	7.5	79.5	45	63
Corticobasal syndrome							
At least one of limb rigidity/akinesia/dystonia/myoclonus + at least 1 of apraxia/cortical sensory deficit/alien limb	12.6	22.2	2.0	1.9	2.7	62	93
Bulbar dysfunction							
Dysarthia	69.4	35.2	66.7	66.0	26.0	57	54
Dysarthia within 3 years	32.5	14.8	21.6	11.3	17.8	64	84
Dysphagia	65.0	37.0	62.7	43.4	41.1	56	55
Dysphagia within 3 years	23.8	11.1	11.8	5.7	20.5	62	87

Sensitivity, PPV, and specificity of selected symptoms in the clinico-pathological cohort of patients with PSP, CBD, MSA-P, and FTLD-bvFTD. PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; MSA-P, multiple system atrophy with predominant parkinsonism; PD, Parkinson's disease; FTLD, frontotemporal lobar degeneration; bvFTD, behavioral variant of frontotemporal dementia; PPV, positive predictive value; Spec., specificity.

mutations other than *MAPT*; 23% (n = 17) were associated with motor neuron disease.

Table 3 lists the diagnoses made at initial and final ante mortem clinical evaluation. For 122 (59%) and 182 (88%) of 206 PSP patients, initial and final diagnoses were recorded, respectively. PSP was correctly diagnosed in 31 of 122 cases (25%) initially and in 114 of 182 patients (63%) at final visit. PD was the most common clinical misdiagnosis in PSP patients (28/122 [23%] initially, 18/182 [10%] at final visit).

The frequency of 37 clinical features throughout the disease course is shown in Supplemental Table 3. Based on the literature review we selected symptoms of putative diagnostic value and calculated their sensitivity, PPV, and specificity in our clinico-pathological cohort (Table 4).

Ocular Motor Dysfunction

The presence of vSNP throughout the disease had a specificity of 91% for definite PSP, increasing to 97% when present within 3 years after disease onset; sensitivity was 71% throughout, but only 30% within 3 years. Because the retrospective analysis did not provide reliable data on slowing of saccades for many patients, the term was generalized to *abnormal saccades*. These were recorded in 66% of PSP patients throughout the disease, yielding a specificity of 85%. When present within 3 years, sensitivity for PSP decreased to 31%, but specificity increased to 94%. Nonspecific ocular symptoms (defined as any of painful eyes, dry eyes, visual blurring, diplopia, blepharospasm, ptosis, reduced blinking rate, or "apraxia of eyelid opening") were recorded in 36% of PSP patients throughout the

disease, but only 2% to 11% in control groups, yielding a high specificity (94%).

PI

PI throughout the disease course was the most frequent symptom in PSP (82%), but had low specificity (46%), also being common in CBD, MSA-P, and PD. PI within 3 years was observed in only 54% of PSP patients, but had considerably better specificity (81%). PI within 1 year had even higher specificity (90%), but lower sensitivity (45%).

Falls throughout the disease course had moderate sensitivity (79%) and specificity (59%) for PSP. Falls within 3 years had reduced sensitivity (51%), but improved specificity (86%). Falls within 1 year resulted in even lower sensitivity (37%) and only slightly improved specificity (94%).

Akinesia and Gait Freezing

Akinetic-rigid, predominantly axial, and levodopa-resistant parkinsonism distinguished PSP with a sensitivity of only 29% and specificity of 92%. Parkinsonism with tremor and/or asymmetry and/or levodopa-responsiveness identified PSP with higher sensitivity (44%), but lower specificity (47%). The most specific symptom for PSP (100%) was progressive gait freezing within 3 years, defined as gait freezing or start hesitation in absence of limb rigidity, tremor, or dementia and without response to levodopa[34]; however, it was only present in very few PSP patients (2%).

Cognitive Dysfunction

nfaPPA was present in 19% of definite PSP cases. nfaPPA also occurred in FTLD-bvFTD (16%) and in CBD (28%). Specificity of nfaPPA for PSP in our cohort was 88%. When noted within 3 years, nfaPPA had lower sensitivity (9%), but higher specificity (91%) for PSP. AOS had low sensitivity (4%) but high specificity (94%) for PSP. When considering AOS within 3 years only, sensitivity was even lower (1%), and specificity higher (97%). However, it should be noted that only cases of FTLD-bvFTD patients were included in our study, and thus including FTLD-PPA cases could have reduced specificity of these findings for PSP.

Frontal dysfunction was defined as presence of at least 1 of the following: personality change, frontal behavior, social dysfunction, executive dysfunction, and frontal physical signs. Information on the type of frontal dysfunction was too limited for differential analysis. The presence of frontal dysfunction throughout the course had a sensitivity for PSP of 57% and a specificity of 46%. When present within 3 years, sensitivity was only 30% and specificity was 63%.

Corticobasal syndrome (CBS), defined as at least 1 cortical and 1 movement disorder sign,[76] occurred in 13% of our PSP cases, yielding a specificity of 93% for PSP. As expected, CBD was the most relevant differential diagnosis.

Other Features

Dysarthria and dysphagia throughout the disease course had limited specificity for PSP (54% and 55%, respectively). Specificity increased markedly for both symptoms if these were present within 3 years of disease (84% and 87%, respectively).

A total of 10 PSP cases (5%) and 55 control cases (24%) had clinical features considered to be supportive for diagnoses other than PSP. These were (1) impairment of episodic memory within 1 year, suggestive of AD (3 PSP, 8 CBD, 2 PD, 1 FTLD); (2) unexplained autonomic failure within 1 year, suggestive of MSA (5 PSP, 10 MSA-P, 1 PD, 1 CBD); (3) unexplained visual hallucinations within 1 year, suggestive of dementia with Lewy bodies (1 PSP); (4) unexplained multisegmental upper and lower motor neuron signs, suggestive of motor neuron disease (17 FTLD); (5) appendicular ataxia (1 PSP, 2 MSA-P); and (6) hereditary cases with mutations other than *MAPT* (21 FTLD).

Discussion

In this article, we sought to identify ante mortem clinical features that individually predict PSP pathology by analyzing retrospective clinical data from a large autopsy cohort of PSP, CBD, MSA-P, PD, and FTLD patients. For the same purpose, we conducted an extensive systematic literature review on features relevant for the diagnosis of PSP published since 1996. The need for this work is apparent from the low rate of correct clinical diagnoses observed in this very cohort. Clinical diagnosis of PSP was correct in only 25% of cases at first visit, and in 63% at last visit, highlighting that PSP is underdiagnosed. One reason for the clinical underdiagnosis of pathologically defined PSP is its phenotypic variability.[9-12,45] In vPSP syndromes other than PSP-RS, key features may be missing, especially early in the disease course. Indeed, of the PSP patients reported here, 33% never developed vSNP, and 23% did not have PI and falls, similar to previous observations.[4,9,10,33,46] This explains suboptimal sensitivity of the NINDS-SPSP clinical diagnostic criteria, as confirmed in our literature review.[9-11] The results of this study should serve as a framework to develop new clinical diagnostic criteria for PSP.

As demonstrated in our clinic-pathological analysis, key features of PSP-RS are highly specific for PSP pathology. vSNP, abnormal saccades, PI, and falls

were highly specific for PSP, in agreement with previous reports.[7,28,38] Notably, CBS was also very specific for PSP (93%). A limited specificity of CBS for CBD was reported previously,[26] challenging the concept of CBS as the hallmark of CBD. Other features with high specificity for PSP included progressive gait freezing within 3 years (100% specificity)[16,34] as well as AOS and nfaPPA.[15,17,20] However, because only FTLD-bvFTD was included in our cohort, the high specificity of the latter features must be interpreted with caution. The addition of cases with FTLD-PPA would have reduced specificity of PPA features for PSP. Thus, in patients with AOS and nfaPPA, a diagnosis of PSP should be suspected; however, additional PSP-specific features should be present to reliably predict PSP pathology, as evident in the literature.[15,22,31,48] Interestingly, predominantly axial and levodopa-resistant parkinsonism, a feature not mentioned in the NINDS-SPSP criteria, was reasonably specific for PSP pathology. Thus, to diagnose PSP with high specificity, the aforementioned features should be considered when designing new criteria.

A major shortcoming of the NINDS-SPSP criteria is low sensitivity.[9-11] With regard to key features of PSP-RS, expanding the time window for onset of PI and falls from 1 year (as required in the NINDS-SPSP criteria) to 3 years after disease onset resulted in improved sensitivity for a diagnosis of PSP (falls, from% 37 to 51%; PI, from 45% to 54%). Similarly, presence of frontal dysfunction, dysarthria and/or dysphagia, and parkinsonism with tremor and/or asymmetry and/or levodopa response had good sensitivity; however, the specificity of these findings for PSP was, as expected, limited. Frontal dysfunction was also common in CBD and bvFTD, and dysphagia and dysarthria were frequently present in MSA-P and bvFTD, often early in the disease course. In summary, the results of this cohort study show that (1) there are a variety of features that may be acknowledged to increase sensitivity of diagnosing PSP and (2) not unexpectedly, this increase in sensitivity comes at the expense of specificity.

Ideally, diagnostic investigations should be added to the clinical diagnostic criteria of PSP to increase both specificity and sensitivity. In this context, neuroimaging merits a separate discussion and is addressed in detail in a comprehensive review of the MDS-PSPSG in an accompanying paper.[44] In short, brain imaging is useful in differential diagnosis (Supplemental Table 1) and may be useful to support a clinical diagnosis of PSP-RS.[44] Although midbrain atrophy among other markers reliably discriminates PSP-RS from disease controls, this does not seem to be the case for other PSP phenotypes.[44] Imaging markers for atypical PSP phenotypes, for example, to predict PSP pathology in CBS and FTD would be most desirable, but studies with autopsy confirmation are missing so far.[44]

Our literature review on other diagnostic investigations highlights the lack of any in vivo investigation that reliably predicts PSP pathology and might be useful for the clinical diagnostic criteria. Although autopsy confirmation was available in a reasonable number of retrospective studies that reported on the natural history of PSP, it was missing in most studies related to additional diagnostic investigations, including autonomic testing, neuropsychological testing, oculomotor analysis, and biomarker assessments. In these studies, only PSP-RS patients were evaluated, and the use/extent of additional diagnostic investigations in a more challenging diagnostic context is unclear. With regard to genetic testing, homozygosity for the *MAPT* H1 haplotype polymorphism is frequent in but not diagnostic for PSP. Homozygosity for the *MAPT* H2 haplotype polymorphism is very rare in PSP, but does not exclude the diagnosis. Rare *MAPT* mutations can cause a PSP-like presentation, albeit obviously with a distinct etiology than the sporadic disease. However, genetic testing, as well as CSF biomarkers, can be helpful to identify PSP look alikes, including prion disease, hereditary spinocerebellar ataxias, Perry syndrome, Kufor-Rakeb disease, Whipple's disease, Niemann-Pick disease type C, Gaucher's disease, progressive encephalomyelitis with rigidity and myoclonus, and AD. AD rarely presents clinically as PSP-RS or levodopa-resistant parkinsonism, but can clinically mimic other PSP phenotypes, most notably CBS (in up to 25% of cases), but also nfaPPA and bvFTD; thus AD biomarkers (CSF Aβ and tau, amyloid PET) may be indicative of primary AD pathology in these syndromes. Research should be encouraged to identify investigations useful for early clinical diagnosis of PSP, as is the case in other neurodegenerative disorders such as AD.[77] It remains to be seen whether tau-PET imaging will qualify as a useful ancillary test.

Last, we were unable to identify specific features that could convincingly describe a characteristic prodromal phase of PSP, although individual reports clearly described speech/language, behavioral, or cognitive features as premotor manifestations in patients diagnosed with PSP on follow-up or autopsy. Early clinical features of PSP are yet poorly addressed in the literature. It will be crucial to prospectively study putative PSP patients presenting with nonspecific, albeit suggestive features in a prospective setting, starting at the earliest clinical stages of the disease course.

There are several limitations of our work. Data were obtained from clinical charts and may be incomplete as in any retrospective clinico-pathological study. The numbers of cases per diagnosis did not present relative frequencies expected in the general population. To our knowledge, the only community-based autopsy series focusing on pathologically defined diseases of interest for our study found the following

relative frequencies in 233 autopsy cases: 19% PD, 13% TDP-43 proteinopathy, 3% PSP (including anatomically restricted forms), 0.9% PSP sensu stricto, 0.9% MSA, and 0.4% CBD.[78] Any approach to mimic the population-based prevalence of diseases would have required introducing a massive distortion of brain bank frequencies. Hence, the relatively low numbers of PD cases included in this cohort introduces a bias that needs to be recognized when interpreting PPV and specificity. A selection bias overrepresenting cases with unusual clinical features cannot be excluded either. Thus PPV and specificity of clinical features for PSP might be underestimated in this cohort. The presence of some features, such as slowing of vertical saccades, may not have been documented or missed entirely. However, the presented data were extracted from the largest clinico-pathological cohort of PSP published to date and compared with a substantial number of pathologically confirmed patients with the most relevant differential diagnoses. In the future, multivariate statistical models may increase diagnostic accuracy by considering clinical variables jointly, rather than singly, but such models are less easy to apply in the clinical setting.

In conclusion, our work provides a strong rationale for developing new diagnostic criteria for PSP. The various phenotypes and symptoms from 4 functional domains (ocular motor dysfunction, postural instability, akinesia, cognitive dysfunction), each with its characteristic clinical features, should be considered when conceptualizing new criteria. Different levels of diagnostic certainty will need to be incorporated into the criteria to allow for inclusion of symptoms with differing sensitivity and specificity, including features that are nonspecific, but relevant for early and sensitive diagnosis of PSP. ■

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Appendix: The MDS-Endorsed PSP Study Group

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.