Published in final edited form as:

Mov Disord. 2017 June ; 32(6): 853–864. doi:10.1002/mds.26987.

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Gunter U. Hoglinger, MD[1,2,*], **Gesine Respondek, MD**[1,2], **Maria Stamelou, MD**[3], **Carolin Kurz, MD**[4], **Keith A. Josephs, MD, MST, MSc**[5], **Anthony E. Lang, MD**[6], **Brit Mollenhauer, MD**[7], **Ulrich Muller, MD**[8], **Christer Nilsson, MD**[9], **Jennifer L. Whitwell, PhD**[10], **Thomas Arzberger, MD**[2,4,11], **Elisabet Englund, MD**[12], **Ellen Gelpi, MD**[13], **Armin Giese, MD**[11], **David J. Irwin, MD**[14], **Wassilios G. Meissner, MD, PhD**[15,16,17], **Alexander Pantelyat, MD**[18], **Alex Rajput, MD**[19], **John C. van Swieten, MD**[20], **Claire Troakes, PhD, MSc**[21], **Angelo Antonini, MD**[22], **Kailash P. Bhatia, MD**[23], **Yvette Bordelon, MD, PhD**[24], **Yaroslau Compta, MD, PhD**[25], **Jean-Christophe Corvol, MD, PhD**[26], **Carlo Colosimo, MD, FEAN**[27], **Dennis W. Dickson, MD**[28], **Richard Dodel, MD**[29], **Leslie Ferguson, MD**[19], **Murray Grossman, MD**[14], **Jan Kassubek, MD**[30], **Florian Krismer, MD, PhD**[31], **Johannes Levin, MD**[2,32], **Stefan Lorenzl, MD**[33,34,35], **Huw R. Morris, MD**[36], **Peter Nestor, MD**[37], **Wolfgang H. Oertel, MD**[38], **Werner Poewe, MD**[31], **Gil Rabinovici, MD**[39], **James B. Rowe, MD**[40], **Gerard D. Schellenberg, PhD**[41], **Klaus Seppi, MD**[31], **Thilo van Eimeren, MD**[42], **Gregor K. Wenning, MD, PhD**[31], **Adam L. Boxer, MD, PhD**[39], **Lawrence I. Golbe, MD**[43], and **Irene Litvan, MD**[44] **for the Movement Disorder Society–endorsed PSP Study Group**

[1]Department of Neurology, Technische Universitat Munchen, Munich, Germany [2]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany [3]Second Department of Neurology, Attikon University Hospital, University of Athens, Athens, Greece [4]Department of Psychiatry, Ludwig-Maximilians-Universitat, Munich, Germany [5]Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA [6]Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital, Toronto, Canada [7]Paracelsus-Elena Klinik, Kassel, Germany, and University Medical Center Gottingen, Institute of Neuropathology, Gottingen, Germany [8]Institute of Human Genetics, Giessen, Germany [9]Department of Clinical Sciences, Division of Neurology, Lund University, Lund, Sweden [10]Department of Radiology, Mayo Clinic, Rochester, Minnesoya, USA [11]Center for Neuropathology and Prion Research, Ludwig-Maximilians-Universitat, Munich, Germany [12]Department of Clinical Sciences, Division of Oncology and Pathology, Lund University, Lund, Sweden [13]Neurological Tissue Bank of the Biobank - Hospital Clínic de Barcelona, Universitat de Barcelona, IDIBAPS, Barcelona, Spain [14]Frontotemporal Degeneration Center, Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, USA [15]Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France [16]CNRS, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France [17]Service de

[*]Correspondence to: Prof. Dr. Gunter U. Hoglinger, Department of Translational Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), Feodor-Lynen Straβe 17, D-81677 Munich, Germany; guenter.hoeglinger@dzne.de. Drs. Hoglinger, Respondek, Stamelou, Golbe, Boxer, and Litvan made an equal contribution.

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Neurologie, Hôpital Pellegrin, CHU de Bordeaux, Bordeaux, France [18]Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA [19]Division of Neurology, Royal University Hospital, University of Saskatchewan, Saskatoon, SK, Canada [20]Department of Neurology, Erasmus Medical Centre, Rotterdam, The Netherlands [21]London Neurodegenerative Diseases Brain Bank, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, United Kingdom [22]Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, and Department of Neurosciences, Padova University, Padova, Italy [23]Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, United Kingdom [24]Department of Neurology, University of California, Los Angeles, California, USA [25]Parkinson's Disease & Movement Disorders Unit, Neurology Service, Hospital Clinic/IDIBAPS/University of Barcelona, Barcelona, Catalonia, Spain [26]Sorbonne Universités, UPMC Univ Paris 06; and INSERM UMRS_1127, CIC_1422; and CNRS UMR_7225; and AP-HP; and ICM, Hôpital Pitié-Salpêtrière, Département des maladies du système nerveux, Paris, France [27]Department of Neurology, Santa Maria University Hospital of Terni, Terni, Italy [28]Mayo Clinic, Jacksonville, Florida, USA [29]Department of Geriatric Medicine, University Hospital Essen, Essen, Germany [30]Department of Neurology, University of Ulm, Ulm, Germany [31]Department of Neurology, Medical University Innsbruck, Innsbruck, Austria [32]Department of Neurology, Ludwig-Maximilians-Universitat, Munich, Germany [33]Institute of Nursing Science and Practice, Paracelsus Medical University, Salzburg, Austria [34]Department of Neurology, Hospital Agatharied, Agatharied, Germany [35]Department of Palliative Medicine, Munich University Hospital, LMU Munich, Munich, Germany [36]Department of Clinical Neuroscience, UCL Institute of Neurology, London, United Kingdom [37]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany [38]Department of Neurology, Philipps Universitat, Marburg, Germany [39]Memory and Aging Center, Department of Neurology, University of California, San Francisco, California, USA [40]Department of Clinical Neurosciences, Cambridge University, Cambridge, United Kingdom [41]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA [42]Departments of Nuclear Medicine and Neurology, University of Cologne, Cologne, Germany [43]Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA [44]Department of Neurology, University of California, San Diego, California, USA

Abstract

Background—PSP is a neuropathologically defined disease entity. Clinical diagnostic criteria, published in 1996 by the National Institute of Neurological Disorders and Stroke/Society for PSP, have excellent specificity, but their sensitivity is limited for variant PSP syndromes with presentations other than Richardson's syndrome.

Objective—We aimed to provide an evidence- and consensus-based revision of the clinical diagnostic criteria for PSP.

Methods—We searched the PubMed, Cochrane, Medline, and PSYCInfo databases for articles published in English since 1996, using postmortem diagnosis or highly specific clinical criteria as the diagnostic standard. Second, we generated retrospective standardized clinical data from patients with autopsy-confirmed PSP and control diseases. On this basis, diagnostic criteria were

drafted, optimized in two modified Delphi evaluations, submitted to structured discussions with consensus procedures during a 2-day meeting, and refined in three further Delphi rounds.

Results—Defined clinical, imaging, laboratory, and genetic findings serve as mandatory basic features, mandatory exclusion criteria, or context-dependent exclusion criteria. We identified four functional domains (ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction) as clinical predictors of PSP. Within each of these domains, we propose three clinical features that contribute different levels of diagnostic certainty. Specific combinations of these features define the diagnostic criteria, stratified by three degrees of diagnostic certainty (probable PSP, possible PSP, and suggestive of PSP). Clinical clues and imaging findings represent supportive features.

Conclusions—Here, we present new criteria aimed to optimize early, sensitive, and specific clinical diagnosis of PSP on the basis of currently available evidence.

Keywords

progressive supranuclear palsy; evidence-based; consensus-based; clinical diagnostic criteria

PSP was first described in 1964 on the basis of a small case series as an adult-onset, rapidly progressive neurodegenerative disease with the leading feature of vertical supranuclear gaze palsy and nerve cell degeneration mainly in the brain stem.[1]

Since then, major advances have led PSP to be defined by intracerebral aggregation of the microtubule-associated protein tau, predominantly involving isoforms with four microtubule-binding repeats (4R-tau), in neurofibrillary tangles, oligodendrocytic coils, and, specifically, astrocytic tufts.[2–4] Thus, a definite diagnosis of PSP currently requires neuropathological examination.[2,5]

The clinical criteria proposed by the National Institute of Neurological Disorders and Stroke and Society for PSP (NINDS-SPSP) are currently the most widely used criteria for the ante mortem diagnosis of PSP.[5] They rely on the demonstration of a vertical supranuclear gaze palsy plus postural instability and falls within the first year of symptom onset to diagnose “probable” PSP. “Possible” PSP is diagnosed in the presence of either supranuclear gaze palsy or a combination of slow vertical saccades and postural instability with falls within the first year.

The NINDS-SPSP criteria, as validated by autopsy, have excellent specificity, around 95% to 100% for probable PSP and around 80% to 93% for possible PSP.[6–8] The combination of early onset postural instability and falls with vertical ocular motor dysfunction is now usually referred to as Richardson’s syndrome (PSP-RS)[9] and is well captured by the NINDS-SPSP criteria.[10] However, the criteria’s sensitivity for PSP overall is limited (median, 24%; range, 14%–83%) at the first clinical visit.[5,7,8,11–13] Diagnosis is typically made 3 to 4 years after onset of first symptoms, when the cardinal features, that is falls and supranuclear gaze palsy, have become unequivocally apparent.[13] Whereas inadequate ocular motor examinations may partly explain the low sensitivity early in the disease course, the NINDS-SPSP criteria also have low sensitivity for PSP patients presenting with variant PSP syndromes syndromes other than PSP-RS.[10]

Patients with autopsy-confirmed PSP have been reported with variant PSP clinical presentations, including initial predominance of ocular motor dysfunction (PSP-OM),[10,14] postural instability (PSP-PI),[10,15] Parkinsonism resembling idiopathic Parkinson's disease (PSP-P),[9,11,16] frontal lobe cognitive or behavioral presentations (PSP-F), including behavioral variant frontotemporal dementia (bvFTD),[14,17–19] progressive gait freezing (PSP-PGF),[20–22] corticobasal syndrome (PSP-CBS),[23–26] primary lateral sclerosis (PSP-PLS),[27,28] cerebellar ataxia (PSP-C),[29–32] and speech/language disorders (PSP-SL), including nonfluent/agrammatic primary progressive aphasia (nfaPPA) and progressive apraxia of speech (AOS).[33–36] Patients with presentations other than PSP-RS occurred in 76% of autopsy-confirmed PSP cases in a recent series and met the NINDS-SPSP criteria at significantly lower frequencies and longer latencies from symptom onset.[10]

Thus, early and reliable diagnosis of PSP remains a major clinical challenge, but is justifiably demanded by patients and their carers and is highly important for estimation of prognosis, appropriate allocation to therapeutic trials, and development of new diagnostic tools. Therefore, the International Parkinson and Movement Disorder Society (MDS)-endorsed PSP Study Group set out to provide an evidence- and consensus-based revision of the NINDS-SPSP criteria. We aimed at improving the clinical detection of underlying PSP pathology by maintaining high diagnostic sensitivity for PSP-RS, improving sensitivity for early and variant PSP presentations, and achieving high specificity versus alternative diagnoses such as Parkinson's disease (PD), MSA with predominant parkinsonism (MSA-P), corticobasal syndrome (CBS) attributed to corticobasal degeneration (CBD) or alternative proteinopathies, and frontotemporal lobar degeneration (from any underlying non-PSP/CBD proteinopathy) presenting as bvFTD (FTLD-bvFTD).

Here, we propose official MDS clinical diagnostic criteria for PSP (MDS-PSP criteria) for use in research and clinical practice.

Methodology of Criteria Generation

The MDS-PSP criteria were generated by the MDS-PSP study group in a three-step approach.

First, we performed a systematic literature review covering the time since publication of the NINDS-SPSP criteria. In brief, the steering committee (G.U.H., M.S., A.L.B., L.I.G., and I.L.) assembled expert working groups for specific questions relevant to the diagnosis of PSP. We searched the PubMed, Cochrane, Medline, and PSYCInfo databases for articles, systematic reviews, and meta-analyses published in English from 1996 to 2015, applying either postmortem diagnosis or the NINDS-SPSP criteria. Study group members were encouraged to add relevant articles to be considered throughout the project period (end of 2016), particularly those published after 2015. The literature was analyzed following the Scottish Intercollegiate Guidelines Network recommendations.[37] From N = 5,903 identified articles, N = 462 met the inclusion standards. The literature-based evidence was then summarized by the working groups for imaging and clinical aspects and is published in detail in accompanying papers in this issue of *Movement Disorders*.[38,39]

Second, we collected the largest autopsy-confirmed case series reported so far for PSP and disease controls (CBD, MSA-P, PD, and FTLD-bvFTD) from nine brain banks with a proven track record of a close collaboration with tertiary clinical referral centers, both with excellent experience in neurodegenerative diseases (Amsterdam, Netherlands; Baltimore, MD; Barcelona, Spain; Bordeaux, France; London, UK; Lund, Sweden; Munich, Germany; Philadelphia, PA; and Saskatchewan, Canada). High-quality original natural history data were available from patients with autopsy-confirmed PSP (N = 206), CBD (N = 54), MSA-P (N = 51), PD (N = 53), and FTLD-bvFTD (N = 73). We extracted demographic data and predefined clinical features (absence/presence/onset) in a standardized manner locally from the clinical records and collected them centrally. These data were used to estimate and stratify the diagnostic value of the clinical items selected from a comprehensive literature review and are reported in detail in an accompanying paper.[38]

Third, on the basis of the evidence obtained in the first two steps, the steering committee drafted an initial proposal of the criteria, which was distributed to the MDS-PSP study group members. They provided written feedback to the process coordinator (G.U.H.), who incorporated the comments into optimized criteria in two modified Delphi rounds. In March 2016, the group convened for a 2-day consensus meeting in Munich to present and discuss all aspects of the criteria (structure, basic features, exclusion criteria, core functional domains, operationalized clinical features, supportive findings, imaging, biomarkers, and genetics). For each of these items, the data obtained in the first two steps were presented by the subgroup coordinators. Thereafter, the written draft of the criteria was discussed stepwise. Modifications were integrated until the entire group unanimously agreed to the items under discussion. After the meeting, the written document was circulated again and optimized in three further Delphi rounds, in particular, dealing with precise wording, operationalized definition of clinical examination guidelines, and newly evolving aspects, such as tau PET imaging. After final approval, the current manuscript was written (G.U.H.) and circulated to incorporate final modifications.

Here, we present the MDS clinical diagnostic criteria for PSP.

Basic Features

Basic features need to be present in a patient in order to be considered for the diagnosis of PSP of any phenotype and at any stage (Table 1). Mandatory inclusion criteria (Table 1, B1) indicate the presence of a sporadic, adult-onset, gradually progressive neurodegenerative disease. Mandatory exclusion criteria (Table 1, B2) rule out PSP and need to be applied in any patient. Context-dependent exclusion criteria (Table 1, B3) also rule out PSP, but should be applied only in patients presenting with suggestive, unusual clinical features justifying further investigation.

Core Features

We propose four core functional domains as characteristic clinical manifestations of PSP (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]; Table 2). In each domain, we propose three characteristic core clinical

features, stratified by presumed levels of certainty (1 [highest], 2 [mid], and 3 [lowest]) that they contribute to the diagnosis of PSP (Table 2).

Supportive Features

Supportive features (Table 3) are those having positive predictive values insufficient to qualify them as diagnostic features, but sufficient to provide helpful ancillary evidence to increase informal diagnostic confidence. These are classified as clinical clues (CC1–CC4) and imaging findings (IF1, IF2).

Operationalized Definitions

The core clinical features, supportive clinical clues, and supportive imaging findings were operationalized in an attempt to standardize the application of the MDS-PSP criteria (Table 4).

Certainty Levels

Four levels of diagnostic certainty are proposed (Table 5). Definite PSP is the neuropathological gold standard defining the disease entity, regardless of its clinical presentation. Probable PSP is diagnosed in the presence of a combination of clinical features with high specificity. Possible PSP is diagnosed in the presence of clinical features considered to substantially increase the sensitivity for PSP. Clinical syndromes suggestive of PSP have features that alone or in combination may constitute early, subtle evidence for PSP with modest, but still useful, positive predictive value. Additional presence of imaging findings (IF1 or IF2) qualifies for the label imaging supported diagnosis.

Predominance Types

Clinical predominance types are determined based on the combination of clinical features (Table 5). These include PSP-RS, PSP-OM, PSP-PI, PSP-P, PSP-F, PSP-PGF, PSP-CBS, and PSP-SL, per our literature analysis reported in an accompanying article.[38] Patients with possible PSP-SL or PSP-CBS also qualify for the diagnosis of a probable 4R-tauopathy.

Discussion

Here, we propose new MDS-PSP criteria, which are aimed to optimize early, sensitive, and specific clinical diagnosis of PSP on the basis of currently available evidence. They are intended for use in both clinical practice and research, including the diagnosis of early and variant PSP for clinical trials.

The new diagnostic criteria accept the neuropathological examination as the gold standard to define PSP as a disease entity.[2–4,40] The appropriateness of this definition is demonstrated by the unique morphological (e.g., tufted astrocytes, globose tangles),[3,4] biochemical (e.g., straight filaments, 4R-tauopathy),[3,4] and genetic features (e.g., the statistically robust findings obtained in a genome-wide association study)[41] obtained in patients on the basis of this disease definition.

The development of the MDS-PSP clinical criteria was based on the NINDS-SPSP criteria, which are known to be very specific for the clinical prediction of pathologically defined PSP.[7,8,13] For this reason, NINDS-SPSP "possible" and "probable" cases are now jointly classified as probable PSP-RS, as proposed previously,[42] thus allowing comparability with the past published literature.

The mandatory inclusion criteria of the NINDS-SPSP criteria were largely maintained. We still consider PSP as a sporadic, not as a monogenic disease, because clinical or pathological phenocopies resulting from rare genetic variants (mutations) in *MAPT* do not share an identical etiology to sporadic PSP. Because sporadic occurrence does not ultimately rule out underlying monogenic inheritance, particularly in small families, *MAPT* sequencing may be considered, where higher certainty is warranted. We continue to set the minimum age at onset as 40, given that no autopsy-confirmed case has been demonstrated to manifest earlier, whereas some PSP look-alikes (e.g., Niemann-Pick disease, type C) may do so. We also specified the onset of PSP-related symptoms as including neurological, cognitive, or behavioral deficits to reflect current knowledge of the broad clinical spectrum over which PSP may range. Inclusion and exclusion criteria have been carefully adapted to the current state of knowledge, as presented in accompanying papers.[38,39]

Whereas the NINDS-SPSP criteria focused on two core functional domains (ocular motor dysfunction, postural instability), the MDS-PSP criteria added two further domains (akinesia, cognitive dysfunction). This accounts for the results obtained by hypothesis-free cluster analyses in two independent large clinicopathological series of definite PSP patients, identifying these four domains as most representative of characteristic disease manifestations.[9,10] Within each domain, we specified three characteristic clinical features, stratified by levels of certainty for the diagnosis of PSP. These were identified through the systematic literature review, validated quantitatively in the clinicopathological cohort, and specified where required by expert consensus. Of note, these levels may coincide with a typical temporal evolution of symptoms in some (e.g., ocular motor dysfunction, postural instability), but not in other domains (e.g., akinesia, cognitive dysfunction). Using this 12-unit grid, we were able to allocate most symptoms considered as characteristic for the spectrum displayed by autopsy-confirmed PSP patients.

These 12 clinical features help to diagnose PSP with differing sensitivity and specificity[38]:

- high sensitivity and high specificity, for example, vertical supranuclear palsy, frequently observed in PSP with high diagnostic relevance;
- high sensitivity, but reduced specificity, for example, parkinsonism, with tremor and/or asymmetry and/or levodopa responsiveness, representing conditions that help to identify PSP patients, but depend on presence of other PSP-specific features to qualify for the diagnosis;
- low sensitivity, but high specificity, for example, progressive gait freezing within 3 years of symptom onset, representing a very rare condition, however with a very high positive predictive value for the diagnosis of PSP; and

- low sensitivity and low specificity, for example, CBS, which is observed regularly in specialized centers and needs to be considered as a possible manifestation of PSP as one of several possible underlying pathologies.

We also propose a list of supportive clinical clues to increase diagnostic confidence. We are aware of several other clinical signs that have been proposed to indicate the diagnosis of PSP, for example, retropulsion with spontaneous backward falls, falling back into a chair when precipitously attempting to rise from it without attributed caution ("rocket sign"), clumsily and unsteadily walk ("drunken sailor gait"), nuchal dystonia with retrocollis, raised eyebrows attributed to frontalis muscle overactivity ("astonished facies"), vertical wrinkles in the glabella region attributed to procerus muscle overactivity ("procerus sign"), low frequency of blinking ("Mona Lisa gaze"), and "messy-tie sign" attribute to an inability to look down when eating. Whereas these signs may indeed be helpful to raise suspicion about PSP, we found no clear evidence suggesting that they would indeed contribute reliable information to substantiate the diagnosis of PSP.

Until now, there have been no uniformly accepted clinical diagnostic criteria available for the variant PSP manifestations of neuropathologically defined PSP other than PSP-RS. Therefore, most of these cases were not identified early (or at all) for the purposes of routine clinical care, standardized acquisition of natural history data, or inclusion in therapeutic trials. Our proposed criteria overcome these limitations by providing evidence- and consensus-based guidelines to diagnose PSP-OM,[10,14] PSP-PI,[10,15] PSP-P,[9,11,16] PSP-F,[14,17–19] PSP-CBS,[23–26] PSP-PGF,[20–22] and PSP-SL.[33–36]

We did not attempt to provide criteria for PSP-PLS[27,28] and PSP-C,[29–32] although we do acknowledge the existence of these manifestations. This decision reflects the very rare occurrence of PSP-PLS and PSP-C and the sparse published clinicopathological evidence, which was not perceived to delineate features specific enough to allow ante mortem diagnosis. The study group declined to risk including patients with predominant PLS or cerebellar ataxia, because this would have weakened the distinction of PSP from motor neuron disease and MSA-C and other adult-onset sporadic cerebellar ataxias, respectively.

The MDS-PSP clinical diagnostic criteria are stratified by diagnostic certainty and may therefore be used for different purposes. The concept underlying this stratification has been described in detail elsewhere.[43] The following diagnostic categories are proposed:

- "Definite PSP" can only be diagnosed by neuropathological examination at present. Currently, no other biomarker, imaging, or genetic finding with close to 100% sensitivity and specificity is available.
- "Probable PSP" is diagnosed in the presence of a combination of clinical features that may not be very sensitive for PSP, but are considered to be highly specific, thus being ideally suited for therapeutic and biological studies, where it is important to exclude non-PSP from the subject group.
- "Possible PSP" is diagnosed in the presence of clinical features that substantially increase sensitivity, but at the possible cost of decreased specificity. This category is therefore suitable for descriptive epidemiologic studies and clinical

care, where it is important not to exclude any cases of true PSP. With the addition of biomarkers to increase diagnostic specificity, these individuals might also be reasonably included in a therapeutic study.

- Conditions "suggestive of PSP" represent subtle early signs of PSP, but do not meet the threshold for possible or probable PSP, and are suitable for early identification of individuals in whom the diagnosis may be confirmed as the disease evolves, thereby justifying close clinical follow-up examinations, especially in longitudinal observational studies to further characterize the natural history of PSP with the overall goal of improving diagnosis of patients in early-stage disease. This diagnostic category has been newly introduced in the MDS-PSP criteria in analogy to other progressive neurological diseases, in which defined conditions have been identified with predictable risk of converting to the established disease of interest (e.g., rapid eye movement sleep behavior disorder for PD, mild cognitive impairment for Alzheimer's disease [AD], or clinically isolated syndrome for multiple sclerosis). From a scientific perspective, this new category appears highly relevant for the prospective development of new clinical diagnostic tools and biomarkers permitting a diagnosis of PSP at an earlier stage. This diagnostic category would also be highly relevant for the development of disease-modifying therapies that would ideally be initiated in the very early course, before extensive neurodegeneration has occurred.

For the first time, we also introduce a new category for "probable 4R-tauopathies," comprising patients with possible PSP-SL or PSP-CBS. By introducing this category, we acknowledge that these clinically defined conditions have a high likelihood of underlying PSP or CBD pathology, provided that the corresponding context-dependent exclusion criteria to rule out AD and genetic forms of FTLD-TDP are applied. PSP and CBD are two primary tauopathies with predominant aggregation of four-repeat tau isoforms, which are very difficult to differentially diagnose without neuropathological examination. Their joint ante mortem recognition as probable 4R-tauopathies, however, may offer opportunities for neurobiological investigations of shared pathological mechanisms (e.g., previous works[41,44] or rational disease-modifying interventions. Obviously, all "probable" PSP categories are also probable 4R-tauopathies, however, with high probability of underlying PSP, but not CBD pathology.

We carefully evaluated the added diagnostic value obtained by supportive investigations, the results of which are presented in accompanying papers.[38,39] In short, we adapted the following conclusions for the MDS-PSP criteria:

- Genetic analyses do not help to support the clinical diagnosis of PSP, but known rare genetic variants (mutations) in some genes are exclusion criteria, because they may mimic aspects of PSP clinically, but differ neuropathologically. Furthermore, *MAPT* H2 haplotype homozygosity renders the diagnosis unlikely, but is not an exclusion criterion.
- Established fluid biomarkers do not help to support the clinical diagnosis of PSP, but can rule out alternative non-neurodegenerative diagnoses in patients with similar clinical presentations (Table 1, B3). Cerebrospinal fluid (CSF)

biomarkers for AD may be useful in research investigations and help exclude patients with underlying AD neuropathology in CBS, which has a high frequency of patients with primary AD neuropathology (~20%) that can mimic PSP-CBS[25,45]; however, caution should be used in interpretation of these results in other forms of clinical PSP syndromes, given that secondary age-associated AD neuropathology can influence levels of CSF tau and β-amyloid in patients with PSP pathology.[46]

- Brain imaging is relevant to rule out alternative diagnoses. Demonstration of predominant midbrain atrophy or hypometabolism and/or postsynaptic striatal dopaminergic degeneration increases the diagnostic confidence in patients diagnosed on the basis of clinical features and qualifies for the label of "imaging supported diagnosis." However, only limited data are currently available, which would suggest that current imaging techniques may eventually help to anticipate or strongly consolidate the diagnosis as compared to diagnoses based on clinical features alone, given that most imaging studies have not been performed at a time point preceding the clinical diagnosis and have not been evaluated against the neuropathological gold standard. Tau-PET may evolve as an in vivo modality supportive of the pathological PSP diagnosis at the individual patient level.[47,48] However, the currently available evidence with regard to its sensitivity and specificity, as assessed against the neuropathological gold standard, is too limited to draw firm diagnostic conclusions.

In summary, we propose the MDS clinical diagnostic criteria for PSP, incorporating the advances in knowledge about PSP and its differential diagnoses from the past 20 years. The MDS-PSP study group aims to develop a web-based tool to facilitate the broad implementation of the new criteria in clinical practice and a video-based tutorial to facilitate standardized application. The study group is engaged in international activities to validate these criteria prospectively in clinicopathological studies. We acknowledge that the MDS-PSP criteria will require continuous, adaptive modification as our understanding of PSP advances.

Acknowledgments

We thank all brain donors and their families for their generous donation allowing to advance our knowledge about PSP, clinicians for providing reliable clinical data, Ina B. Kopp for guidance in the methods of evidence-based medicine, and Judith Dams for conducting the database inquiry. G.U.H. was supported by the Deutsche Forschungsgemeinschaft (DFG; HO2402/6-2). W.H.O. is senior research professor of the charitable Hertie Foundation, Frankfurt/Main, Germany. J.L.W. and K.A.J. were supported by NIH grants R01-NS89757 and R01-DC12519. Y.C. is supported by CERCA Programme/Generalitat de Catalunya, Catalonia, Spain. Autopsy patient data from the University of Pennsylvania was obtained through NIH-funded program projects P01-AG017586, P50-NS053488, and P30-AG010124. The London Neurodegenerative Diseases Brain Bank, King's College London was supported by the MRC and Brains for Dementia Research—jointly funded by the Alzheimer's Society and Alzheimer's Research UK. H.R.M. is supported by the PSP Association and CBD-Solutions. J.B.R. is supported by the Wellcome Trust (103838) The project was supported by the Bischof Dr. Karl Golser Stiftung, CurePSP, Deutsche Forschungsgemeinschaft (DFG; HO 2402/11-1), German Center for Neurodegenerative Diseases e.V. (DZNE), German PSP Gesellschaft, Tau Consortium, UK PSP Association, and the International Parkinson and Movement Disorder Society.

Funding agencies: The project was supported by the Bischof Dr. Karl Golser Stiftung, CurePSP, Deutsche Forschungsgemeinschaft (DFG, HO 2402/11-1), German Center for Neurodegenerative Diseases e.V. (DZNE),

German PSP Gesellschaft, Tau Consortium, UK PSP Association, and the International Parkinson and Movement Disorder Society.

References

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol. 1964; 10:333–359. [PubMed: 14107684]
2. Litvan I, Hauw JJ, Bartko JJ, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supra-nuclear palsy and related disorders. J Neuropathol Exp Neurol. 1996; 55:97–105. [PubMed: 8558176]
3. Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. J Neurol. 1999; 246(Suppl 2):II6–II15. [PubMed: 10525997]
4. Kovacs GG. Neuropathology of tauopathies: principles and practice. Neuropathol Appl Neurobiol. 2015; 41:3–23. [PubMed: 25495175]
5. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996; 47:1–9. [PubMed: 8710059]
6. Litvan I, Campbell G, Mangone CA, et al. Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? A clinicopathological study. Brain. 1997; 120:65–74. [PubMed: 9055798]
7. Lopez OL, Litvan I, Catt KE, et al. Accuracy of four clinical diagnostic criteria for the diagnosis of neurodegenerative dementias. Neurology. 1999; 53:1292–1299. [PubMed: 10522887]
8. Osaki Y, Ben-Shlomo Y, Lees AJ, et al. Accuracy of clinical diagnosis of progressive supranuclear palsy. Mov Disord. 2004; 19:181–189. [PubMed: 14978673]
9. Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005; 128:1247–1258. [PubMed: 15788542]
10. Respondek G, Stamelou M, Kurz C, et al. The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. Mov Disord. 2014; 29:1758–1766. [PubMed: 25370486]
11. Birdi S, Rajput AH, Fenton M, et al. Progressive supranuclear palsy diagnosis and confounding features: report on 16 autopsied cases. Mov Disord. 2002; 17:1255–1264. [PubMed: 12465065]
12. Sakamoto R, Tsuchiya K, Mimura M. Clinical heterogeneity in progressive supranuclear palsy: problems of clinical diagnostic criteria of NINDS-SPSP in a retrospective study of seven Japanese autopsy cases. Neuropathology. 2010; 30:24–35. [PubMed: 19508347]
13. Respondek G, Roeber S, Kretzschmar H, et al. Accuracy of the National Institute for Neurological Disorders and Stroke/Society for Progressive Supranuclear Palsy and neuroprotection and natural history in Parkinson plus syndromes criteria for the diagnosis of progressive supranuclear palsy. Mov Disord. 2013; 28:504–509. [PubMed: 23436751]
14. Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1996; 60:615–620. [PubMed: 8648326]
15. Kurz C, Ebersbach G, Respondek G, Giese A, Arzberger T, Hoglinger GU. An autopsy-confirmed case of progressive supranuclear palsy with predominant postural instability. Acta Neuropathol Commun. 2016; 4:120. [PubMed: 27842578]
16. Williams DR, Lees AJ. What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-parkinsonism (PSP-P)? Mov Disord. 2010; 25:357–362. [PubMed: 20108379]
17. Donker Kaat L, Boon AJ, Kamphorst W, Ravid R, Duivenvoorden HJ, van Swieten JC. Frontal presentation in progressive supranuclear palsy. Neurology. 2007; 69:723–729. [PubMed: 17709703]
18. Han HJ, Kim H, Park JH, et al. Behavioral changes as the earliest clinical manifestation of progressive supranuclear palsy. J Clin Neurol. 2010; 6:148–151. [PubMed: 20944816]

19. Hassan A, Parisi JE, Josephs KA. Autopsy-proven progressive supranuclear palsy presenting as behavioral variant frontotemporal dementia. Neurocase. 2012; 18:478–488. [PubMed: 22181323]
20. Compta Y, Valldeoriola F, Tolosa E, Rey MJ, Marti MJ, Valls-Sole J. Long lasting pure freezing of gait preceding progressive supranuclear palsy: a clinicopathological study. Mov Disord. 2007; 22:1954–1958. [PubMed: 17724746]
21. Facheris MF, Maniak S, Scaravilli F, Schule B, Klein C, Pramstaller PP. Pure akinesia as initial presentation of PSP: a clinicopathological study. Parkinsonism Relat Disord. 2008; 14:517–519. [PubMed: 18325816]
22. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord. 2007; 22:2235–2241. [PubMed: 17712855]
23. Tsuboi Y, Josephs KA, Boeve BF, et al. Increased tau burden in the cortices of progressive supranuclear palsy presenting with corticobasal syndrome. Mov Disord. 2005; 20:982–988. [PubMed: 15834857]
24. Josephs KA, Petersen RC, Knopman DS, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology. 2006; 66:41–48. [PubMed: 16401843]
25. Ling H, de Silva R, Massey LA, et al. Characteristics of progressive supranuclear palsy presenting with corticobasal syndrome: a cortical variant. Neuropathol Appl Neurobiol. 2014; 40:149–163. [PubMed: 23432126]
26. Ling H, O'Sullivan SS, Holton JL, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain. 2010; 133:2045–2057. [PubMed: 20584946]
27. Josephs KA, Katsuse O, Beccano-Kelly DA, et al. Atypical progressive supranuclear palsy with corticospinal tract degeneration. J Neuropathol Exp Neurol. 2006; 65:396–405. [PubMed: 16691120]
28. Nagao S, Yokota O, Nanba R, et al. Progressive supranuclear palsy presenting as primary lateral sclerosis but lacking parkinsonism, gaze palsy, aphasia, or dementia. J Neurol Sci. 2012; 323:147–153. [PubMed: 23026537]
29. Kanazawa M, Shimohata T, Toyoshima Y, et al. Cerebellar involvement in progressive supranuclear palsy: a clinicopathological study. Mov Disord. 2009; 24:1312–1318. [PubMed: 19412943]
30. Iwasaki Y, Mori K, Ito M, Tatsumi S, Mimuro M, Yoshida M. An autopsied case of progressive supranuclear palsy presenting with cerebellar ataxia and severe cerebellar involvement. Neuropathology. 2013; 33:561–567. [PubMed: 23320789]
31. Kanazawa M, Tada M, Onodera O, Takahashi H, Nishizawa M, Shimohata T. Early clinical features of patients with progressive supranuclear palsy with predominant cerebellar ataxia. Parkinsonism Relat Disord. 2013; 19:1149–1151. [PubMed: 23916652]
32. Koga S, Josephs KA, Ogaki K, et al. Cerebellar ataxia in progressive supranuclear palsy: an autopsy study of PSP-C. Mov Disord. 2016; 31:653–662. [PubMed: 26841329]
33. Boeve B, Dickson D, Duffy J, Bartleson J, Trenerry M, Petersen R. Progressive nonfluent aphasia and subsequent aphasic dementia associated with atypical progressive supranuclear palsy pathology. Eur Neurol. 2003; 49:72–78. [PubMed: 12584413]
34. Mochizuki A, Ueda Y, Komatsuzaki Y, Tsuchiya K, Arai T, Shoji S. Progressive supranuclear palsy presenting with primary progressive aphasia—clinicopathological report of an autopsy case. Acta Neuropathol. 2003; 105:610–614. [PubMed: 12669238]
35. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain. 2006; 129:1385–1398. [PubMed: 16613895]
36. Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. Curr Opin Neurol. 2008; 21:688–692. [PubMed: 18989114]
37. Scottish Intercollegiate Guidelines Network. A Guideline Developer's Handbook. Edinburgh, UK: Edinburgh Elliott House; 2008. SIGN 50.
38. Respondek G, Kurz C, Arzberger T, et al. Which ante-mortem clinical features predict progressive supranuclear palsy pathology? Mov Disord. (submitted).

39. Whitwell JL, Hoglinger GU, Antonini A, et al. Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? Mov Disord. (submitted).
40. Hauw JJ, Daniel SE, Dickson D, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology. 1994; 44:2015–2019. [PubMed: 7969952]
41. Hoglinger GU, Melhem NM, Dickson DW, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011; 43:699–705. [PubMed: 21685912]
42. Litvan I, Bhatia KP, Burn DJ, et al. SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord. 2003; 18:467–486. [PubMed: 12722160]
43. Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Hoglinger GU. Targeting tau therapeutics to PSP: support from new diagnostic criteria and biomarkers. Lancet Neurol. (submitted).
44. Kouri N, Ross Owen A, et al. Genome-wide association study identifies microtubule-associated protein tau (MAPT) and myelin-associated oligodendrocytic basic protein (MOBP) as shared genetic risk factors for corticobasal degeneration and progressive supranuclear palsy. Nat Commun. 2015; 6:7247. [PubMed: 26077951]
45. Lee SE, Rabinovici GD, Mayo MC, et al. Clinicopathological correlations in corticobasal degeneration. Ann Neurol. 2011; 70:327–340. [PubMed: 21823158]
46. Toledo JB, Brettschneider J, Grossman M, et al. CSF biomarkers cutoffs: the importance of coincident neuropathological diseases. Acta Neuropathol. 2012; 124:23–35. [PubMed: 22526019]
47. Marquié M, Normandin MD, Meltzer AC, et al. Pathologic correlations of [F-18]-AV-1451 imaging in non-Alzheimer tauopathies. Ann Neurol. 2017; 81:117–128. [PubMed: 27997036]
48. Passamonti L, Vázquez Rodríguez P, Hong YT, et al. [18F]AV-1451 positron emission tomography in Alzheimer's disease and progressive supranuclear palsy. Brain. 2017 Jan 24. pii: aww340. Epub ahead of print. doi: 10.1093/brain/aww340
49. Wood EM, Falcone D, Suh E, et al. Development and validation of pedigree classification criteria for frontotemporal lobar degeneration. JAMA Neurol. 2013; 70:1411–1417. [PubMed: 24081456]
50. Otero-Millan J, Serra A, Leigh RJ, Troncoso XG, Macknik SL, Martinez-Conde S. Distinctive features of saccadic intrusions and microsaccades in progressive supranuclear palsy. J Neurosci. 2011; 31:4379–4387. [PubMed: 21430139]

Appendix. The MDS Endorsed PSP Study Group

Adam L. Boxer, Alex Rajput, Alexander Pantelyat, Angelo Antonini, Anthony E. Lang, Armin Giese, Brit Mollenhauer, Carlo Colosimo, Caroline Kurz, Christer Nilsson, Claire Troakes, David J. Irwin, Dennis W. Dickson, Ellen Gelpi, Florian Krismer, Gerard D. Schellenberg, Gesine Respondek, Gil Rabinovici, Gregor K. Wenning, Gunter U. Hoglinger, Huw R. Morris, Irene Litvan, James B. Rowe, Jan Kassubek, Jean-Christophe Corvol, Jennifer L. Whitwell, Johannes Levin, John van Swieten, Kailash P. Bhatia, Keith A. Josephs, Klaus Seppi, Lawrence I. Golbe, Maria Stamelou, Murray Grossman, Peter Nestor, Richard Dodel, Stefan Lorenzl, Thilo van Eimeren, Thomas Arzberger, Ulrich Muller, Wassilios G. Meissner, Werner Poewe, Wolfgang H. Oertel, Yaroslau Compta, and Yvette Bordelon.

TABLE 1

Basic features

B1: Mandatory inclusion criteria	**1**	Sporadic occurrence *
	2	Age 40 or older at onset ** of first PSP-related symptom ***
	3	Gradual progression of PSP-related symptoms ***
B2: Mandatory exclusion criteria[a]	Clinical findings	
	1	Predominant, otherwise unexplained impairment of episodic memory, suggestive of AD
	2	Predominant, otherwise unexplained autonomic failure, e.g., orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing ≥30 mm Hg systolic or ≥15 mm Hg diastolic), suggestive of multiple system atrophy or Lewy body disease
	3	Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness, suggestive of dementia with Lewy bodies
	4	Predominant, otherwise unexplained multisegmental upper and lower motor neuron signs, suggestive of motor neuron disease (pure upper motor neuron signs are *not* an exclusion criterion)
	5	Sudden onset or step-wise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
	6	History of encephalitis
	7	Prominent appendicular ataxia
	8	Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction, severe spasticity, or lower motor neuron syndrome
	Imaging findings	
	1	Severe leukoencephalopathy, evidenced by cerebral imaging
	2	Relevant structural abnormality, e.g., normal pressure or obstructive hydrocephalus; basal ganglia, diencephalic, mesencephalic, pontine or medullary infarctions, hemorrhages, hypoxic-ischemic lesions, tumors, or malformations
B3: Context dependent exclusion criteria[a,b]	Imaging findings	
	1	In syndromes with sudden onset or step-wise progression, exclude stroke, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or severe cerebral amyloid angiopathy, evidenced by diffusion-weighted imaging (DWI), fluid attenuated inversion recovery, or T2 *-MRI
	2	In cases with very rapid progression, exclude cortical and subcortical hyperintensities on DWI-MRI suggestive of prion disease
	Laboratory findings	
	1	In patients with PSP-CBS, exclude primary AD pathology (typical CSF constellation [i.e., both elevated total tau/phospho-tau protein and reduced β-amyloid 42] or pathological β-amyloid PET imaging)
	2	In patients aged <45 years, exclude
		a. Wilson's disease (e.g., reduced serum ceruloplasmin, reduced total serum copper, increased copper in 24 hour urine, and Kayser-Fleischer corneal ring)
		b. Niemann-Pick disease, type C (e.g., plasma cholestan-3β,5a,6β-triol level, filipin test on skin fibroblasts)
		c. Hypoparathyroidism
		d. Neuroacanthocytosis (e.g., Bassen-Kornzweig, Levine Critchley, McLeod disease)
		e. Neurosyphilis
	3	In rapidly progressive patients, exclude
		a. Prion disease (e.g., elevated 14-3-3, neuron-specific enolase, very high total tau protein [>1,200 pg/mL], or positive real-time quaking-induced conversion in CSF)

b. Paraneoplastic encephalitis (e.g., anti-Ma1, Ma2 antibodies)

4 In patients with suggestive features (i.e., gastrointestinal symptoms, arthralgias, fever, younger age, and atypical neurological features such as myorhythmia), exclude Whipple's disease (e.g., T. Whipplei DNA polymerase chain reaction in CSF)

Genetic findings[c]

1 *MAPT* rare variants (mutations) are no exclusion criterion, but their presence defines inherited, as opposed to sporadic PSP.

2 *MAPT* H2 haplotype homozygosity is not an exclusion criterion, but renders the diagnosis unlikely.

3 *LRRK2* and *Parkin* rare variants have been observed in patients with autopsy confirmed PSP, but their causal relationship is unclear so far.

4 Known rare variants in other genes are exclusion criteria, because they may mimic aspects of PSP clinically, but differ neuropathologically; these include

a. Non-*MAPT* associated frontotemporal dementia (e.g., *C9orf72, GRN, FUS, TARDBP, VCP, CHMP2B*)

b. PD (e.g., *SYNJ1, GBA*)

c. AD (*APP, PSEN1, PSEN2*)

d. Niemann-Pick disease, type C (*NPC1, NPC2*)

e. Kufor-Rakeb syndrome (*ATP13A2*)

f. Perry syndrome (*DCTN1*)

g. Mitochondrial diseases (*POLG*, mitochondrial rare variants)

h. Dentatorubral pallidoluysian atrophy (*ATN1*)

i. Prion-related diseases (*PRNP*)

j. Huntington's disease (*HTT*)

k. Spinocerebellar ataxia (*ATXN1, 2, 3, 7, 17*)

---

[*] MAPT rare variants (mutations) may lead to inherited phenocopies of the sporadic disease with a Mendelian trait pattern.

[**] MAPT rare variants carriers may have earlier disease onset.

[***] Consider any new onset neurological, cognitive, or behavioral deficit that subsequently progresses during the clinical course in absence of other identifiable cause as a PSP-related symptom.

[a] Suggestive of other conditions, which may mimic aspects of PSP clinically.

[b] Need to be verified only if suggestive clinical findings are present.

[c] Perform genetic counseling and testing, if at least one first- or second-degree relative has a PSP-like syndrome with a Mendelian inheritance trait or known rare variants; high-risk families may be identified as described elsewhere[49]; the list of genes proposed reflects current knowledge and will evolve with time.

TABLE 2

Core clinical features

	Functional Domain			
Levels of Certainty	**Ocular Motor Dysfunction**	**Postural Instability**	**Akinesia**	**Cognitive Dysfunction**
Level 1	**O1**: Vertical supranuclear gaze palsy	**P1**: Repeated unprovoked falls within 3 years	**A1**: Progressive gait freezing within 3 years	**C1**: Speech/language disorder, i.e., nonfluent/ agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	**O2**: Slow velocity of vertical saccades	**P2**: Tendency to fall on the pull-test within 3 years	**A2**: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2**: Frontal cognitive/behavioral presentation
Level 3	**O3**: Frequent macro square wave jerks or “eyelid opening apraxia”	**P3**: More than two steps backward on the pull-test within 3 years	**A3**: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	**C3**: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in Table 4.

TABLE 3

Supportive features

Clinical Clues	Imaging Findings
CC1: Levodopa-resistance	**IF1**: Predominant midbrain atrophy or hypometabolism
CC2: Hypokinetic, spastic dysarthria	**IF2**: Postsynaptic striatal dopaminergic degeneration
CC3: Dysphagia	
CC4: Photophobia	

TABLE 4

Operationalized definitions of core clinical features, supportive clinical clues, and supportive imaging findings

Domain	Feature	Definition
Ocular motor dysfunction		
O1	Vertical supranuclear gaze palsy	A clear limitation of the range of voluntary gaze in the vertical more than in the horizontal plane, affecting both up- and downgaze, more than expected for age, which is overcome by activation with the vestibulo-ocular reflex; at later stages, the vestibulo-ocular reflex may be lost, or the maneuver prevented by nuchal rigidity.
O2	Slow velocity of vertical saccades	Decreased velocity (and amplitude) of vertical greater than horizontal saccadic eye movements; this may be established by quantitative measurements of saccades, such as infrared oculography, or by bedside testing; gaze should be assessed by command ("Look at the flicking finger") rather than by pursuit ("Follow my finger"), with the target >20 degrees from the position of primary gaze; to be diagnostic, saccadic movements are slow enough for the examiner to see their movement (eye rotation), rather than just initial and final eye positions in normal subjects; a delay in saccade initiation is not considered slowing; findings are supported by slowed or absent fast components of vertical optokinetic nystagmus (i.e., only the slow following component may be retained).
O3	Frequent macro square wave jerks or "eyelid opening apraxia"	Macro square wave jerks are rapid involuntary saccadic intrusions during fixation, displacing the eye horizontally from the primary position, and returning it to the target after 200 to 300 milliseconds; most square wave jerks are <1 degree in amplitude and rare in healthy controls, but up to 3 to 4 degrees and more frequent (>10/min) in PSP.[50] "Eyelid opening apraxia" is an inability to voluntarily initiate eyelid opening after a period of lid closure in the absence of involuntary forced eyelid closure (i.e., blepharospasm); the term is written in quotation marks because the inability to initiate eyelid opening is often attributed to activation of the pretarsal component of the orbicularis oculi (i.e., pretarsal blepharospasm) rather than failure to activate the levator palpebrae.
Postural instability		
P1	Repeated unprovoked falls within 3 years	Spontaneous loss of balance while standing, or history of more than one unprovoked fall, within 3 years after onset of PSP-related features.
P2	Tendency to fall on the pull-test within 3 years	Tendency to fall on the pull-test if not caught by examiner, within 3 years after onset of PSP-related features. The test examines the response to a quick, forceful pull on the shoulders with the examiner standing behind the patient and the patient standing erect with eyes open and feet comfortably apart and parallel, as described in the MDS-UPDRS item 3.12.
P3	More than two steps backward on the pull-test within 3 years	More than two steps backward, but unaided recovery, on the pull-test, within 3 years after onset of PSP-related features.
Akinesia		
A1	Progressive gait freezing within 3 years	Sudden and transient motor blocks or start hesitation are predominant within 3 years after onset of PSP-related symptoms, progressive and not responsive to levodopa; in the early disease course, akinesia may be present, but limb rigidity, tremor, and dementia are absent or mild.
A2	Parkinsonism, akinetic-rigid, predominantly axial and levodopa resistant	Bradykinesia and rigidity with axial predominance, and levodopa resistance (see Clinical Clue CC1 for operationalized definition).
A3	Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	Bradykinesia with rigidity and/or tremor, and/or asymmetric predominance of limbs, and/or levodopa responsiveness (see Clinical Clue CC1 for operationalized definition).
Cognitive dysfunction		
C1	Speech/language disorder	Defined as at least one of the following features, which has to be persistent (rather than transient): 1. Nonfluent/agrammatic variant of primaryLoss of grammar and/or telegraphic speech or writing progressive aphasia (nfaPPA) or 2. Progressive apraxia of speech (AOS) — Effortful, halting speech with inconsistent speech sound errors and distortions or slow syllabically segmented prosodic speech patterns with spared single-word comprehension, object knowledge, and word retrieval during sentence repetition.

Domain	Feature	Definition		
C2	Frontal cognitive/behavioral presentation	Defined as at least three of the following features, which have to be persistent (rather than transient):		
		1. Apathy		Reduced level of interest, initiative, and spontaneous activity; clearly apparent to informant or patient.
		2. Bradyphrenia		Slowed thinking; clearly apparent to informant or patient.
		3. Dysexecutive syndrome		E.g., reverse digit span, Trails B or Stroop test, Luria sequence (at least 1.5 standard deviations below mean of age- and education-adjusted norms).
		4. Reduced phonemic verbal fluency		E.g., “D, F, A, or S” words per minute (at least 1.5 standard deviations below mean of age- and education-adjusted norms).
		5. Impulsivity, disinhibition, or perseveration		E.g., socially inappropriate behaviors, overstuffing the mouth when eating, motor recklessness, applause sign, palilalia, echolalia.
C3	CBS	Defined as at least one sign each from the following two groups (may be asymmetric or symmetric):		
		1. Cortical signs	**a.**	Orobuccal or limb apraxia.
			b.	Cortical sensory deficit.
			c.	Alien limb phenomena. (more than simple levitation).
		2. Movement disorder signs	**a.**	Limb rigidity.
			b.	Limb akinesia.
			c.	Limb myoclonus.
Clinical clues				
CC1	Levodopa resistance			Levodopa resistance is defined as improvement of the MDS-UPDRS motor scale by ≤30%; to fulfill this criterion patients should be assessed having been given at least 1,000 mg (if tolerated) at least 1 month OR once patients have received this treatment they could be formally assessed following a challenge dose of at least 200 mg.
CC2	Hypokinetic, spastic dysarthria			Slow, low volume and pitch, harsh voice.
CC3	Dysphagia			Otherwise unexplained difficulty in swallowing, severe enough to request dietary adaptations.
CC4	Photophobia			Intolerance to visual perception of light attributed to adaptative dysfunction.
Imaging findings				
IF1	Predominant midbrain atrophy or hypometabolism			Atrophy or hypometabolism predominant in midbrain relative to pons, as demonstrated, e.g., by MRI or [^{18}F]DG-PET.
IF2	Postsynaptic striatal dopaminergic degeneration			Postsynaptic striatal dopaminergic degeneration, as demonstrated, e.g., by [^{123}I]IBZM-SPECT or [^{18}F]-DMFP-PET.

TABLE 5

Degrees of diagnostic certainty, obtained by combinations of clinical features and clinical clues

Diagnostic Certainty	Definition	Combinations	Predominance Type	Abbreviation
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
	Suitable for therapeutic and biological studies	(O1 or O2) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(O1 or O2) + C2	PSP with predominant frontal presentation	prob. PSP-F
Possible PSP	Substantially more sensitive, but less specific for PSP	O1	PSP with predominant ocular motor dysfunction	poss. PSP-OM
	Suitable for descriptive epidemiological studies and clinical care	O2 + P3	PSP with Richardson's syndrome	poss. PSP-RS
		A1	PSP with progressive gait freezing	poss. PSP-PGF
		(O1 or O2) + C1	PSP with predominant speech/language disorder[a]	poss. PSP-SL
		(O1 or O2) + C3	PSP with predominant CBS[a]	poss. PSP-CBS
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP	O2 or O3	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
	Suitable for early identification	O3 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (O3, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (O3 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

The basic features B1+B2+B3 (see Table 1) apply for all probable, possible, and suggestive criteria. Core clinical features are defined by their functional domain (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]), and stratified by presumed levels of certainty (1 [highest], 2 [mid], 3 [lowest]) they contribute to the diagnosis of PSP (see Table 2). Supportive clinical clues (CC) are presented in Table 3. Operationalized definitions of clinical features and clinical clues are given in Table 4.

[a]Probable 4R-tauopathy (i.e., either PSP or CBD).