Published in final edited form as:

Mov Disord. 2019 August ; 34(8): 1228–1232. doi:10.1002/mds.27666.

How to Apply the Movement Disorder Society Criteria for Diagnosis of Progressive Supranuclear Palsy

Max-Joseph Grimm[#1,2], **Gesine Respondek, MD**[#1,2], **Maria Stamelou, MD**[3], **Thomas Arzberger, MD**[2,4,5], **Leslie Ferguson, MD**[6], **Ellen Gelpi, MD**[7,8], **Armin Giese, MD**[4], **Murray Grossman, MD**[9], **David J. Irwin, MD**[9], **Alexander Pantelyat, MD**[10], **Alex Rajput, MD**[6], **Sigrun Roeber, MD**[4], **John C. van Swieten, MD**[11], **Claire Troakes, PhD, MSc**[12], **Angelo Antonini, MD, PhD**[13], **Kailash P. Bhatia, MD**[14], **Carlo Colosimo, MD, FEAN**[15], **Thilo van Eimeren, MD**[16], **Jan Kassubek, MD**[17], **Johannes Levin, MD**[2,18], **Wassilios G. Meissner, MD, PhD**[19,20,21], **Christer Nilsson, MD**[22], **Wolfgang H. Oertel, MD**[23], **Ines Piot**[1,2], **Werner Poewe, MD**[24], **Gregor K. Wenning, MD, PhD**[24], **Adam Boxer, MD, PhD**[25], **Lawrence I. Golbe, MD**[26], **Keith A. Josephs, MD, MST, MSc**[27], **Irene Litvan, MD**[28], **Huw R. Morris, MD**[29], **Jennifer L. Whitwell, PhD**[30], **Yaroslau Compta, MD**[31], **Jean-Christophe Corvol, MD, PhD**[32], **Anthony E. Lang, MD**[33], **James B. Rowe, MD**[34], **Günter U. Höglinger, MD**[1,2,*] **Movement Disorder Society-endorsed PSP Study Group**

[1]Department of Neurology, Technische Universität München, 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]Center for Neuropathology and Prion Research, Ludwig- Maximilians-Universität, Munich, Germany [5]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany [6]Division of Neurology, Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada [7]Neurological Tissue Bank and Neurology Department, Hospital Clinic de Barcelona, Universitat de Barcelona, IDIBAPS, CERCA, Barcelona, Catalonia, Spain [8]Institute of Neurology, Medical University of Vienna, Vienna, Austria [9]Frontotemporal Degeneration Center, Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, USA [10]Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA [11]Department of Neurology, Erasmus Medical Centre, Rotterdam, The Netherlands [12]London Neurodegenerative Diseases Brain Bank, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK [13]Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, and Department of Neurosciences, Padova University, Padova, Italy [14]Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, UK [15]Department of Neurology, Santa Maria University Hospital of Terni, Terni, Italy [16]Departments of Nuclear Medicine and Neurology, University of Cologne, Cologne, Germany [17]Department of Neurology, University of Ulm, Ulm, Germany [18]Department of Neurology, Ludwig-Maximilians-Universität, Munich, Germany [19]Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France [20]Service de Neurologie, Hôpital Pellegrin, CHU de Bordeaux,

[*]**Correspondence to:** Prof. Dr. Günter U. Höglinger, Dept. of Translational Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), Feodor-Lynen Str. 17, D-81677 Munich, Germany. Phone: +49-89-4400-46464, Fax: +49-89-4400-46565; guenter.hoeglinger@dzne.de.

Relevant conflicts of interest/financial disclosures: None.

Bordeaux, France [21]Dept. Medicine, University of Otago, Christchurch, and New Zealand Brain Research Institute, Christchurch, New Zealand [22]Department of Clinical Sciences, Division of Neurology, Lund University, Lund, Sweden [23]Department of Neurology, Philipps Universität, Marburg, Germany [24]Department of Neurology, Medical University Innsbruck, Innsbruck, Austria [25]Memory and Aging Center, Department of Neurology, University of California, San Francisco, California, USA [26]Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA [27]Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA [28]Department of Neurology, University of California, San Diego, California, USA [29]Department of Clinical Neuroscience, UCL Institute of Neurology, Queen Square, London, UK [30]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA [31]Parkinson's Disease & Movement Disorders Unit, Hospital Clínic/IDIBAPS/CIBERNED/ European Reference Network for Rare Neurological Diseases (ERN-RND)/Institut de Neurociéncies, Universitat de Barcelona, Barcelona, Catalonia, Spain [32]Sorbonne Université, INSERM, CNRS, Assistance Publique Hôpitaux de Paris, ICM, Hôpital Pitié- Salpêtriére, Department of Neurology, Paris, France [33]The Edmond J Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada [34]Department of Clinical Neurosciences and Cambridge Centre for Parkinson-Plus, Cambridge University, Cambridge, UK

[#] These authors contributed equally to this work.

Abstract

Background: The Movement Disorder Society criteria for progressive supranuclear palsy define diagnostic allocations, stratified by certainty levels and clinical predominance types. We aimed to study the frequency of ambiguous multiple allocations and to develop rules to eliminate them.

Methods: We retrospectively collected standardized clinical data by chart review in a multicenter cohort of autopsy-confirmed patients with progressive supranuclear palsy, to classify them by diagnostic certainty level and predominance type and to identify multiple allocations.

Results: Comprehensive data were available from 195 patients. More than one diagnostic allocation occurred in 157 patients (80.5%). On average, 5.4 allocations were possible per patient. We developed four rules for Multiple Allocations eXtinction (MAX). They reduced the number of patients with multiple allocations to 22 (11.3%), and the allocations per patient to 1.1.

Conclusions: The proposed MAX rules help to standardize the application of the Movement Disorder Society criteria for progressive supranuclear palsy.

Keywords

autopsy; diversity; phenotype; progressive supranuclear palsy

---

The clinical manifestations of progressive supranuclear palsy (PSP) reflect the distribution of lesions, comprising ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction.[1-3]

The International Movement Disorder Society introduced new diagnostic criteria (MDS-PSP criteria) to cover this clinical spectrum.[4] A validation study demonstrated higher sensitivity and a small reduction in specificity compared with prior criteria.[5]

Although the MDS-PSP criteria[4] have been widely accepted as a step forward in research and care, their application has revealed a new problem: many individuals qualify for more than one diagnostic category (predominance type, diagnostic certainty) at the same time.[5] Moreover, a patient meeting one category at disease onset may come to meet additional categories as the disease progresses. Although the evolution of different diagnoses through the disease course provides the most accurate description of patients' syndromes, in many circumstances (therapeutic trials, epidemiology), it is essential to have a single primary diagnosis. Here, we aimed to quantify the frequency of multiple diagnostic allocations when using the MDS-PSP criteria and to introduce Multiple Allocations eXtinction (MAX) rules.

Methods

Patients

This work was approved by the ethics committees of the Technical University Munich and participating centers. Patients with definite PSP and detailed clinical information were identified from brain banks experienced in PSP (Ludwig-Maximilians-University, Munich, Germany; University Hospital, Bordeaux, France; King's College, London, UK; Lund University, Sweden; Erasmus Medical Center, Rotterdam, the Netherlands; Hospital Clinic-IDIBAPS, Barcelona, Spain; University of Saskatchewan, Canada; Johns Hopkins University, Baltimore, MD; University of Pennsylvania, Philadelphia, PA). All donors had given written informed consent for the scientific use of their brains and medical records. The cohort has been reported previously in a different project.[3]

Data Analysis

Local physicians associated with the brain banks (G.R., L.F., E.G., D.J.I., A.P., J.C.S., C.T., W.G.M., C.N., Y.C., J.B.R.) extracted demographic and clinical data from patient charts, as reported elsewhere.[6] Of this extensive data set, the onset of the 12 core clinical features in 4 functional domains, defined in the MDS-PSP criteria[4] (OPAC classification), were used for our analysis:

- Ocular motor dysfunction: O1, vertical supranuclear gaze palsy; O2, slow velocity of vertical saccades; O3, frequent macro square wave jerks or "eyelid opening apraxia."
- Postural instability: P1, repeated unprovoked falls within 3 years; P2, tendency to fall on the pull-test within 3 years; P3, more than 2 steps backward on the pull-test within 3 years.
- Akinesia: A1, progressive gait freezing within 3 years; A2, parkinsonism, akinetic-rigid, predominantly axial, and levodopa-resistant; A3, parkinsonism, with tremor and/or asymmetric and/or levodopa-responsive.

- Cognitive dysfunction: C1, speech/language disorder, that is, nonfluent/agrammatic primary progressive aphasia or progressive apraxia of speech; C2, frontal cognitive/behavioral presentation; C3: corticobasal syndrome. Note bene: in the definition of C3, “limb dystonia” was unintentionally omitted in the original publication[4] and shall be considered as the fourth qualifying movement disorder sign for corticobasal syndrome.

Combinations of these features, defined by the MDS-PSP criteria,[4] specified the diagnosis, stratified by

- Predominance type: PSP-RS, Richardson syndrome; PSP-PI, predominant postural instability; PSP-OM, predominant ocular motor dysfunction; PSP-P, predominant parkinsonism; PSP-PGF, progressive gait freezing; PSP-CBS, predominant corticobasal syndrome; PSP-F, predominant frontal presentation; PSP-SL, predominant speech/language disorder; and
- Diagnostic certainty: suggestive of, possible, or probable PSP to predict the neuropathological diagnosis (definite PSP).

Diagnoses were recorded as follows: Initial/interim/ final clinical diagnosis (time): diagnostic certainty, predominance type (OPAC classification), for example, initial clinical diagnosis (December 2018), suggestive of PSP-P (O_3, P_2, A_3, C_0), with indexed 0 indicating absence of clinical features from the corresponding domain. Data are shown as mean ± standard error (range).

Results

Data with sufficient details were available for n = 195 patients. Their age was 66.3 ± 0.6 years (range, 41-91 years) at symptom onset and 74.1 ± 0.6 years (range, 54-94 years) at death. Disease duration was 7.7 ± 0.3 years (range, 0-27 years). Ninety-three (47.7%) were female.

Table 1 shows the evolution of features of 1 representative patient. The MDS-PSP criteria would have allowed the following diagnoses:

- Initial diagnosis (1st year): suggestive of PSP-PI (O_0, $P_{1,2}$, A_0, C_2).
- Interim diagnosis (5th year): suggestive of PSP-PI and PSP-SL (O_0, $P_{1,2}$, A_0, $C_{1,2}$).
- Interim diagnosis (7th year): suggestive of PSP-PI, PSP-SL, and PSP-P (O_0, $P_{1,2}$, A_3, $C_{1,2}$).
- Final clinical diagnosis (8th year): suggestive of PSP-PI, PSP-SL, PSP-P, and PSP-OM; possible PSP-OM and PSP-SL; probable PSP-F, PSP-P, and PSP-RS ($O_{1,2}$, $P_{1,2}$, $A_{2,3}$, $C_{1,2}$).

Table 2 shows the diagnoses in the entire cohort by the MDS-PSP criteria, based on final antemortem records. On average, 5.4 ± 0.2 diagnoses (range, 0-11 diagnoses) were justified per patient.

Therefore, the study group developed the following MAX rules:

MAX 1 (Diagnostic Certainty): Probable > Possible > Suggestive of

While moving to higher levels of diagnostic certainty of the MDS-PSP criteria, patients still formally qualify for the lower levels. Because specificity increases with a higher level of certainty,[5] the allocations to lower levels should be disregarded.

MAX 2 (Temporal Order): 1st > 2nd > 3rd Diagnosis

Predominance types occurring earlier in time shall be retained as a diagnosis over those arising later in time. Clinicians should be able to neglect this rule, if later features come to clearly dominate the clinical picture.

MAX 3 (Phenotypic Hierarchy): PSP-RS > PSP-OM/PSP-PI > Other Predominance Types

The MDS-PSP criteria propose to record the predominance type that best describes the prevailing clinical features when formally more than 1 predominance type is possible. *Only when this is not possible,* a phenotypic hierarchy may be considered. Postural instability within 3 years after symptom onset (P_1, P_2, P_3) and ocular motor dysfunction (O_1, O_2, O_3) have high sensitivity and specificity for PSP.[4,5] Therefore, these domains in combination (PSP-RS), or less so in isolation (PSP-PI, PSP-OM), are considered particularly characteristic of PSP.[4] Thus, PSP-RS shall be ranked higher than PSP-OM and PSP-PI. If postural instability and/or ocular motor dysfunction dominates the clinical picture, including symptom frequency, severity and impact on quality of life, then PSP-RS, PSP-OM, or PSP-PI is considered the principal diagnosis above the other predominance types. Importantly, postural instability developing later than 3 years after onset does not qualify for PSP-RS or PSP-PI.

MAX 4 (MAX Hierarchy): MAX 1 > MAX 2 > MAX 3

When more than 1 of the above rules applies, MAX 1 shall be considered stronger than MAX 2 and MAX 2 stronger than MAX 3.

Applying these rules, the representative patient (Table 1) has unequivocal diagnostic allocations:

- Initial diagnosis (1st year): suggestive of PSP-PI (O_0, $P_{1,2}$, A_0, C_2).
- Interim diagnosis (5th year): suggestive of PSP-PI (O_0, $P_{1,2}$, A_0, $C_{1,2}$); PSP-SL ruled out by MAX 2.
- Interim diagnosis (7th year): suggestive of PSP-PI (O_0, $P_{1,2}$, A_3, $C_{1,2}$); PSP-SL and PSP-P ruled out by MAX 2.
- Final clinical diagnosis (8th year): probable PSP-RS ($O_{1,2}$, $P_{1,2}$, $A_{2,3}$, $C_{1,2}$); other diagnoses ruled out by MAX 1 and MAX 3.

Applying these rules to the entire cohort reduced the number of patients with multiple allocations from 157 (80.5%) to 22 (11.3%) and the number of allocations per patient from 5.4 to 1.1 (Table 2).

Discussion

The MDS-PSP criteria operationalized clinical features to establish the diagnosis of PSP, stratified by predominance type and diagnostic certainty. Applying the criteria retrospectively to a cohort of 195 definite PSP patients, we observed patients frequently qualifying for more than 1 diagnostic category. The question of how to deal with multiple diagnostic allocations becomes particularly relevant when patients accumulate a broader spectrum of clinical features with increasing disease duration.

Recording multiple diagnoses per patient may be of value for research studies, specifically to raise awareness of nonmotor features of PSP. In most clinical care and research settings, however, a single lead diagnosis is used. Therefore, the MDS-PSP study group developed 4 simple MAX rules, which allow for nearly complete elimination of equivocal diagnostic allocations.

MAX 1 proposes to prioritize categories of higher diagnostic certainty over those with lower certainty. Although this principle is spelled out here explicitly, this simple rule is implicitly used in most disease areas to acknowledge the growing confidence in the clinical diagnosis as more convincing pieces of a diagnostic puzzle emerge in a given patient.

MAX 2 proposes to maintain the initial predominance type as diagnosis, even if additional features qualifying for other predominance types add to the clinical picture of the patient. Because the initial manifestation is suspected to yield relevant insights into the characteristic disease features of a given patient (eg, anatomical topography of brain damage, prognosis for future disease course, hypothetical tau strains), we recommend maintaining a record of the initial manifestation. However, clinicians should be able to override MAX 2 if the most prominent clinical features (ie, with the highest impact on the patient's daily life) suggest a different predominance type. The initial manifestation may also be of prognostic value. For example, the clinical course may be dramatically different between patients with an initial PSP-RS manifestation and patients with initial variant manifestation who develop clinical features qualifying for PSP-RS only later on.

MAX 3 proposes a phenotypic hierarchy of PSP-RS over PSP-OM and PSP-PI, because the combination of postural instability and ocular motor dysfunction is more predictive of PSP than each feature in isolation.[4] Of course, the MDS-PSP criteria aim to remain open to the phenotypic evolution of all predominance types, avoiding the introduction of bias by a priori definitions. Therefore, MAX 3 emphasizes the need to consider the clinically dominant features of the illness, including motor and nonmotor aspects. When formally more than one predominance type is justified by the MDS- PSP criteria, the one that best describes the predominant clinical features by judgment of the experienced physician should be recorded. Only when this is not possible, for example, because of a balanced presentation of several clinical features or because available data do not allow the identification of one predominating feature, the MDS-PSP study group recommends considering a phenotypic hierarchy prioritizing PSP-RS, PSP-PI, and PSP-OM over other predominance types.

MAX 4 ranks the rules 1-3, when more than one of them applies. This situation occurred 66 times in the current cohort.

These guidelines are mainly based only on expert opinion rather than on any objective "gold standards" for defining PSP subgroups. Biomarkers (eg, genetic, epigenetic, or biochemical attributes) and imaging support[7] currently only serve to support a diagnosis of PSP and to exclude differential diagnoses.[4,7] Biomarkers and imaging may become available in the near future to define PSP subgroups on a neurobiological basis. Future insights in these areas may allow us to revise our proposed guidelines and maybe even the overall MDS-PSP criteria. Although not yet tested prospectively, application of these MAX rules to our retrospective cohort strikingly reduced the number of patients with multiple diagnostic allocations. Thus, it is hoped that they will help to simplify and standardize the use of the MDS-PSP criteria for both research and clinical care. This work also demonstrated the usefulness of recording the temporal evolution of the core clinical features of PSP patients in a standardized manner using the OPAC code, predominance type, and diagnostic certainty.

Acknowledgments

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 & Movement Disorder Society.

APPENDIX

The MDS-Endorsed PSP Study Group

Adam L. Boxer, Alex Rajput, Alexander Pantelyat, Angelo Antonini, Anthony E. Lang, Armin Giese, Carlo Colosimo, Christer Nilsson, Claire Troakes, David J. Irwin, Dennis W. Dickson, Ellen Gelpi, Gesine Respondek, Gregor K Wenning, Günter U. Höglinger, Huw R. Morris, Ikuko Aiba, Irene Litvan, James B. Rowe, Jan Kassubek, Jean-Christophe Corvol, Jennifer L. Whitwell, Johannes Levin, John van Swieten, Kailash P. Bhatia, Keith A. Josephs, Lawrence I. Golbe, Maria Stamelou, Murray Grossman, Thilo van Eimeren, Thomas Arzberger, Ulrich Muller, Wassilios G. Meissner, Werner Poewe, Wolfgang H. Oertel, Yaroslau Compta.

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. Kovacs GG. Neuropathology of tauopathies: principles and practice. Neuropathol Appl Neurobiol 2015;41:3–23. [PubMed: 25495175]
3. Respondek G, Kurz C, Arzberger T, et al., for the Movement Disorder Society-endorsed PSP Study Group. Which ante-mortem features predict progressive supranuclear palsy? Mov Disord 2017;32(7): 995–1005. [PubMed: 28500752]
4. Höglinger GU, Respondek G, Stamelou M, et al., for the Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy — the Movement Disorder Society Criteria. Mov Disord 2017;32(6):853–864. [PubMed: 28467028]
5. Ali F, Martin P, Botha H, et al. Sensitivity and specificity of diagnostic criteria for progressive supranuclear palsy. Move Disord 2019; doi: 10.1002/mds.27619.

6. 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]

7. Whitwell JL, Höglinger GU, Antonini A, et al., Movement Disorder Society-endorsed PSP Study Group. Radiological biomarkers for diagnosis in PSP: Where are we and where do we need to be? Mov Disord 2017;32(7):955–971. [PubMed: 28500751]

TABLE 1.

Clinical features and diagnoses of a representative patient with definite PSP

Clinical features				
Level of certainty	**Ocular motor dysfunction**	**Postural instability**	**Akinesia**	**Cognitive dysfunction**
Level 1	01 (year 8)	P1 (year 1)	A1 (n.r.)	C1 (year 5)
Level 2	02 (year 8)	P2 (year 1)	A2 (year 8)	C2 (year 1)
Level 3	03 (n.r.)	P3 (n.r.)	A3 (year 7)	C3 (n.r.)
MDS-PSP diagnoses				
Disease duration	**Suggestive of**	**Possible**	**Probable**	**Definite**
Year 1	**PSP-PI**			
Year 5	**PSP-PI**, PSP-SL			
Year 7	**PSP-PI**, PSP-SL, PSP-P			
Year 8	PSP-PI, PSP-SL, PSP-P, PSP-0M	PSP-0M PSP-SL	PSP-F, PSP-P, **PSP-RS**	
Year 10	PSP-PI, PSP-SL, PSP-P, PSP-0M	PSP-0M PSP-SL	PSP-F, PSP-P, **PSP-RS**	**PSP**

Aged 66, this male patient developed postural instability (P2), unprovoked falls (P1), and mild frontal cognitive dysfunction (C2). Five years later, nonfluent agrammatic variant of primary progressive aphasia (C1) was recorded. After 7 years, Parkinson's disease was diagnosed with asymmetric, levodopa-responsive parkinsonism (A3). After 8 years, parkinsonism became levodopa-resistant (A2), and slowing of vertical saccades (O2) and supranuclear gaze palsy (O1) occurred. He died after 10 years without clear clinical diagnosis and was diagnosed PSP on autopsy. The table shows the onset of clinical features in years after symptom onset. n.r., Not reported throughout the entire clinical course.

The resulting MDS-PSP diagnostic allocations are reported in the lower half of the table. Diagnoses prioritized after application of the MAX rules are in boldface.

TABLE 2.

MDS-PSP diagnoses without and with Multiple Allocations extinction (MAX) rules

	Without MAX rules	With MAX rules
Total number of definite PSP patients	195	195
Patients with clinical MDS-PSP diagnosis	182	182
Patients without clinical MDS-PSP diagnosis	13	13
Total number of MDS-PSP diagnoses	984	207
Probable MDS-PSP diagnosis	319	160
Possible MDS-PSP diagnosis	196	5
Suggestive of MDS-PSP diagnosis	469	42
Patients with >1 MDS-PSP diagnoses	157	22
MDS-PSP diagnoses per patient	5.4	1.1

The table shows the clinical diagnoses using the MDS-PSP criteria without and with application of the Multiple Allocations eXtinction (MAX) rules in definite PSP patients at their final antemortem record.