

RESEARCH ARTICLE

Prospective Multicenter Evaluation of the MDS “Suggestive of PSP” Diagnostic Criteria

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ABSTRACT: Background: The recent Movement Disorders Society (MDS)-progressive supranuclear palsy (PSP) diagnostic criteria conceptualized three clinical diagnostic certainty levels: “suggestive of PSP” for sensitive early diagnosis based on subtle clinical signs, “possible PSP” balancing sensitivity and specificity, and “probable PSP” highly specific for PSP pathology.

Objective: The aim of this study was to prospectively validate the criteria against long-term clinical follow-up and characterize the diagnostic certainty increase over time.

Methods: Patients with “possible PSP” or “suggestive of PSP” diagnosis and clinical follow-up were recruited in two German multicenter longitudinal observational studies (ProPSP and DescribePSP). The cumulative percentage of patients longitudinally increasing diagnostic certainty was assessed over up to 2.5 years of follow-up. The sample size per arm required to detect 30%

attenuated rate in diagnostic certainty increase in trials was estimated over multiple time intervals.

Results: Of 254 patients with available longitudinal data, 61 patients had low diagnostic certainty at baseline (48 suggestive of PSP, 13 possible PSP) and multiple clinical visits (median: 3, range: 2–4). The cumulative percentage of patients increasing diagnostic certainty progressed with follow-up duration (30.4% at 6 months, 51.7% at 1 year, 80.4% at 2.5 years). The sample size required to detect 30% reduction in diagnostic certainty increase rate within 1 year was 163, slightly smaller than that required using the PSP rating scale.

Conclusions: Most “suggestive of PSP” patients increased diagnostic certainty upon longitudinal follow-up, providing the first prospective multicenter validation of MDS-PSP diagnostic criteria. Our data support the design of trials tailored for these early-stage patients, suggesting the PSP rating scale and the diagnostic

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Relevant conflicts of interest/financial disclosures: G.U.H. participated in industry-sponsored research projects from AbbVie, Biogen, Biohaven, Novartis, Roche, Sanofi, and UCB; has ongoing research collaborations with Roche, UCB, and AbbVie; serves as a consultant for AbbVie, Alzprotect, Amylyx, Aprineua, Asceneuron, Bayer, Bial, Biogen, Biohaven, Epidarex, Ferrer, Kyowa Kirin, Lundbeck, Novartis, Retrotape, Roche, Sanofi, Servier, Takeda, Teva, and UCB; received honoraria for scientific presentations from AbbVie, Bayer, Bial, Biogen, Bristol Myers Squibb, Kyowa Kirin, Pfizer, Roche, Teva, UCB, and Zambon. G.U.H. was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy ID 390857198), the European Joint Programme on Rare Diseases (Improve-PSP), Niedersächsisches Ministerium für Wissenschaft und Kunst (MWK)/VolkswagenStiftung (Niedersächsisches Vorab), Petermax-Müller Foundation (Etiology and Therapy of Synucleinopathies and Tauopathies), and the German Parkinson Society (DPG): ProAPS. The authors have no conflicts of interest to disclose. None of the authors have received financial support or funding for research covered in this article regardless of date. No funding source is associated with this study.

Funding agency: The sponsors listed here had no role in the design and conduct of the study; analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The other authors declared no conflicts of interest.

Received: 6 September 2024; **Revised:** 3 December 2024; **Accepted:** 23 December 2024

Published online 10 January 2025 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30112

certainty increase rate as potential endpoint measures. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: progressive supranuclear palsy; suggestive of PSP; longitudinal; validation; diagnostic criteria

Progressive supranuclear palsy (PSP) is a neurodegenerative disease defined by intracerebral aggregation of 4-repeat tau within neurofibrillary tangles, oligodendrocytic coiled bodies, and tufted astrocytes, with these neuropathological specifications being necessary for a definite PSP diagnosis.^{1,2} The current diagnostic criteria, established by the Movement Disorder Society (MDS)-endorsed PSP study group, operationalized the diagnosis of seven PSP phenotypes and proposed three distinct diagnostic certainty levels for PSP diagnosis during life.¹ A “probable PSP” diagnosis requires vertical gaze palsy (O1) or slowness of vertical saccades (O2) and at least one other core PSP feature, which is a combination of clinical signs predicting PSP pathology with high specificity.^{1,3} On the contrary, “possible PSP” and especially “suggestive of PSP” (s.o. PSP) categories were conceptualized as lower diagnostic certainty levels, aiming to increase the sensitivity for PSP and reducing diagnostic delay in early disease stages,^{1,4} therefore accepting compromised specificity.^{1,4,5} The MDS-PSP criteria first introduced the diagnostic category of conditions s.o. PSP, aiming to identify patients very early in the clinical course, relying on a few clinical signs preceding the appearance of the full clinical picture of PSP.¹ This new category may thus be of high relevance to identify target populations for clinical trials, with potentially disease-modifying therapies to be administered in the early phase of the neurodegenerative process. A large clinicopathological study⁴ showed that 66% of patients with an “s.o. PSP” diagnosis evolved to probable PSP before death, but the result was limited by the retrospective nature of the study relying on symptoms reported in patients’ charts. Thus far, there is no prospective longitudinal study investigating the increase in diagnostic certainty over time in PSP patients. In the current study, we leveraged the detailed longitudinal prospective data of two German multicenter observational PSP studies⁶ with the main aim of investigating the percentage of patients increasing their diagnostic certainty over time. This approach aimed to (1) validate the MDS criteria for PSP with low diagnostic certainty (s.o. and possible PSP) prospectively against long-term clinical follow-up and (2) to provide reliable reference data on the natural history of early-stage PSP for conceptualizing future clinical trials.

Patients and Methods

Study Participants

Patients with PSP diagnosis from two German multicenter prospective observational studies (DescribePSP and ProPSP)⁶ were included in this cohort study. Patients underwent multiple visits with standardized clinical examination and optional biomaterial sampling, with the same core protocol in both studies.⁶ More details on the study protocols and biomaterial sampling are described in previous publications^{6,7} and in the supplementary materials. For the current study, we selected patients according to the following inclusion criteria: (1) diagnosis of any PSP subtype and diagnostic certainty according to the MDS-PSP criteria,^{1,8} (2) available demographic data (sex, age at baseline visit), and (3) at least two visits with available information on PSP subtype and diagnostic certainty level (probable, possible, or s.o. PSP). For each patient, all visits with the aforementioned information were selected. Ethics approval was obtained at each site from the local ethics committee, and all participants provided written informed consent.

Statistical Analysis

Comparisons between groups were performed using Fisher’s test, two-sample *t* test, Wilcoxon rank-sum test, and analysis of variance (ANOVA) or analysis of covariance (ANCOVA) with age as covariate, as appropriate, and are provided in Supplementary Materials. *P*-values were Bonferroni corrected for multiple comparisons. Patients underwent multiple follow-up assessments over a time span of up to 2.5 years. For each follow-up visit, the time from baseline assessment was calculated, and the visits were grouped into five time points: 0.5 years $\pm$ 3 months, 1 year $\pm$ 3 months, 1.5 years $\pm$ 3 months, 2 years $\pm$ 3 months, and 2.5 years $\pm$ 3 months from baseline. Longitudinal clinical progression between baseline and the last follow-up visit was calculated as the annualized percentage and raw change rates in the PSP rating scale (PSPRS) total score. The cumulative percentage of patients increasing their diagnostic certainty for PSP within each of the five considered time intervals was calculated after imputing missing data using bootstrapping procedure ($n = 1000$ repetitions). The mean value and 95% percentile intervals (2.5th–97.5th percentiles) of the diagnostic

certainty increase rate were calculated. Full details on data organization and missing data handling strategies are provided in Supplementary Materials. After the longitudinal diagnostic certainty increase rates were calculated, we estimated the sample size per group required in a two-arm (drug vs. placebo) trial to observe a 20%, 30%, or 50% reduction of this rate over 1, 1.5, or 2 years based on a two-sample comparison of proportions with 5% significance level and 80% power (*pwR* R package). The sample size was also estimated to detect similar changes in clinical progression rate in the intervention arm using the annualized PSP rating scale⁹ percentage or raw changes, as previously described.^{10–12}

Results

This study included data from two large prospective observational studies in PSP patients, for 254 patients with available follow-up information (665 visits). Full data are presented in Table S1. After patients with a diagnosis of probable PSP at baseline visit ($n = 193$) were excluded, we identified 61 patients (33 from DescribePSP, 28 from ProPSP) with possible or s.o. PSP diagnosis at baseline and available longitudinal clinical assessment, and data from 164 visits were included in the analyses (Fig. 1). The final cohort of 61 patients included 48 s.o. PSP and 13 possible PSP patients at baseline, showing milder clinical severity than probable PSP patients (Table S1). No significant differences were observed between s.o. and possible PSP patients in demographic and clinical variables (Table 1). Plasma neurofilament light chain levels were also similar between the two patient groups. Fourteen of the 21 patients with a CBS phenotype had available cerebrospinal fluid (CSF) amyloid and p-tau₁₈₁ data; among these, 5 patients (3 s.o. PSP-CBS and 2 possible PSP-CBS) showed a CSF Alzheimer's disease (AD) profile, with decreased A β 42/40 ratio and increased p-tau₁₈₁ concentrations. All patients enrolled based on their clinical diagnosis were included in the main analyses; in addition, we performed a subanalysis excluding PSP-CBS patients with Alzheimer's CSF profile (low amyloid, high p-tau) because these patients most likely have Alzheimer's rather than PSP pathology (see later).

Longitudinal Clinical Progression Rate

All the 61 patients underwent multiple follow-up assessments (median: 3 visits, range: 2–4 visits) over a time span of up to 2.5 years (last follow-up, mean: 16.7 months, range: 5.7–31.5 months), as presented in Table 1 and Figure S1. Patients exhibited significant worsening of clinical symptoms over time (PSPRS score at baseline vs. PSPRS score at the last follow-up: $P < 0.0001$), with a mean annualized percentage PSPRS

score increase of 39.4% (corresponding to 7.8 points), with a trend toward faster progression in possible PSP than in s.o. PSP patients (Table 1). Individual patient data are shown in Figure S2.

Longitudinal Assessment of PSP Subtypes

Most patients fulfilled criteria for PSP-CBS, PSP with predominant parkinsonism (PSP-P), and PSP Richardson's syndrome (PSP-RS) subtypes, with only a few cases of PSP with predominant ocular motor dysfunction (PSP-OM), PSP with progressive gait freezing (PSP-PGF), PSP with predominant postural instability (PSP-PI), and PSP with predominant frontal presentation (PSP-F) (Fig. 2). Nearly half of patients with PSP-P diagnosis at baseline retained the same diagnosis at follow-up, whereas the others developed a PSP-RS phenotype. A similar trend was observed in PSP-CBS cases. Overall, the prevalence of the PSP-RS subtype increased over time, from 10 of 61 (16.4%) patients at baseline to 26 of 61 (42.6%) patients at the last-available follow-up visit (Fig. 2).

Longitudinal Diagnostic Certainty Increase

Among the 61 included patients, 39 patients (63.9%) evolved into higher diagnostic certainty categories within the 2.5-year follow-up period; in 2 s.o. PSP patients the diagnostic certainty level remained unchanged after this time interval (28.4 and 31.2 months, respectively); the remaining 20 had only been followed up for shorter time periods, with no diagnostic certainty increase at the last-available visit. Full details considering possible PSP and s.o. PSP patients separately are presented in Table S2, S5. The percentage of patients increasing PSP diagnostic certainty within each of the five considered time points (bins of 6-month intervals between 0.5 and 2.5 years) was calculated. As shown in Figure 3 and Table S3, the cumulative percentage of patients increasing their diagnostic certainty ranged from 30.4% of patients within a 6-month follow-up to 80.4% of patients within 2.5 years of follow-up. Of note, Table S3 indicates that 51.7% (95% percentile interval: 45.9%–57.4%) of patients showed diagnostic certainty increase within 1 year, which is the time interval typically considered in clinical trials. These patients with diagnostic certainty increase within 1 year exhibited higher ocular motor dysfunction scores at baseline and slightly longer disease duration than the other patient group, as shown in Table S6. Almost identical results in terms of diagnostic certainty increase rates were obtained by focusing on s.o. PSP patients only (Tables S3–S5; Fig. S3). Consistent results were obtained excluding PSP-CBS patients with CSF profile indicative of AD, showing a slight but significant increase in diagnostic certainty change rates at all follow-up time points (Tables S4 and S5; Fig. S3).

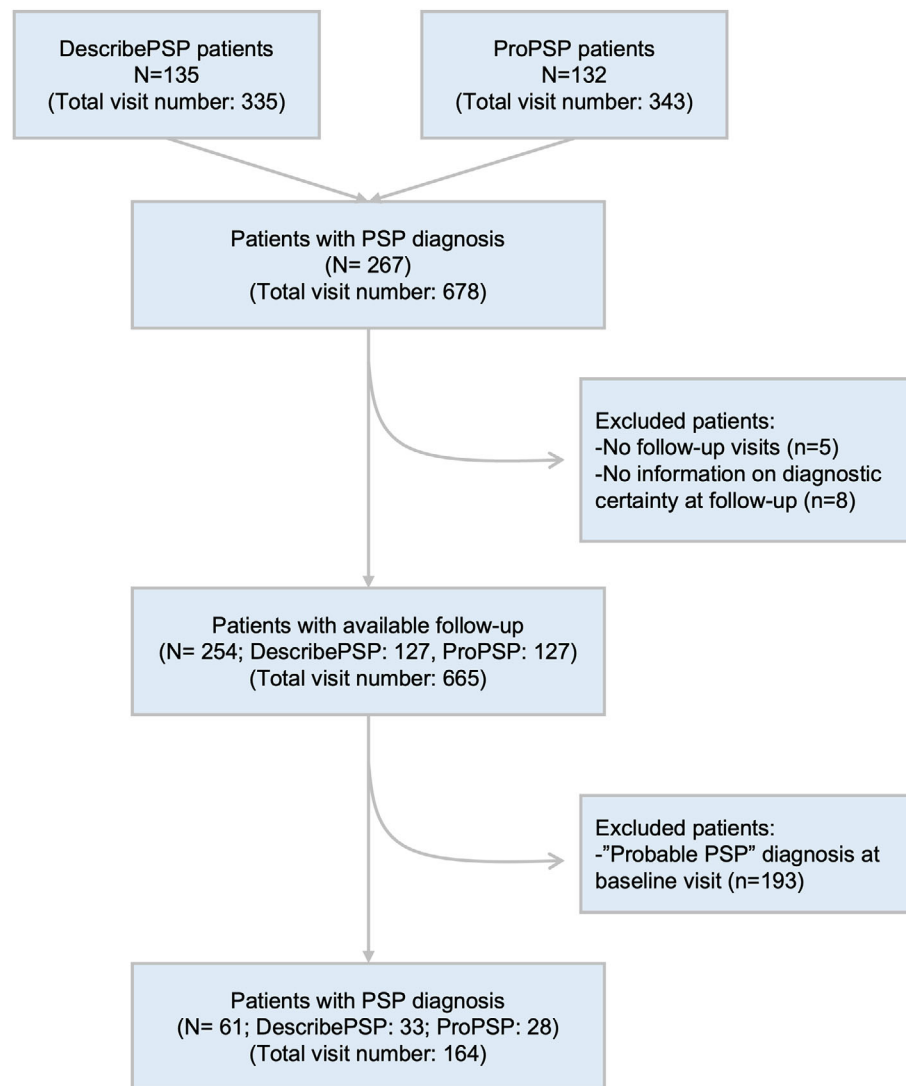


FIG. 1. The figure shows a flowchart of the study inclusion/exclusion procedures. Patients fulfilling the Movement Disorders Society (MDS)-progressive supranuclear palsy (PSP) diagnostic criteria with at least two visits with available clinical information on diagnostic certainty and subtype were included in the current analysis from the DescribePSP and the ProPSP cohort studies; the final cohort included patients with a diagnosis of “possible PSP” or “suggestive of PSP” at baseline. All available visits for each patient were considered in the analyses. [Color figure can be viewed at wileyonlinelibrary.com]

These PSP-CBS patients may have AD rather than PSP pathology, and it is plausible to expect they have lower rates of diagnostic certainty increase into probable PSP; this finding confirms that it is worth checking these biomarkers and exclude patients with AD profile, as suggested by the MDS-PSP criteria.

Sample Size Calculation for Clinical Trials in Patients with Low PSP Diagnostic Certainty

We observed a 51% mean rate of diagnostic certainty increase within 1 year in s.o. PSP patients (Table S3). It is possible to hypothesize that disease-modifying drugs slowing down the progression of the disease may reduce the increase in diagnostic

certainty; thus, we calculated the sample size per arm required to observe a 20%, 30%, or 50% reduction in the diagnostic certainty increase rate in clinical trials. Sample sizes of 372, 163, and 55 patients, respectively, were estimated to detect a 20%, 30%, or 50% treatment effect in 1-year studies in s.o. PSP patients; expectedly, the numbers were smaller with longer observation periods of 1.5 or 2 years of follow-up (Table 2). Of note, the rate of s.o. PSP patients increasing their diagnostic certainty as a possible novel outcome parameter for clinical trials required smaller sample sizes compared to a similar percentage reduction in the PSPRS score change over 1 year (Table 2). Data on the whole PSP cohort were consistent, with similar results (Table 2).

TABLE 1 Demographic and clinical data of patients with PSP diagnosis

Data	All patients (n = 61)	s.o. PSP patients (n = 48)	Possible PSP patients (n = 13)	P-value possible vs. s.o. PSP
Sex (M/F)	34/27	28/20	6/7	0.534 ^a
Age (y)	69.4 ± 6.5	68.8 ± 6.9	71.5 ± 4.5	0.102 ^b
Disease duration (y) at baseline	2.7 ± 2.6	2.8 ± 2.77	2.0 ± 1.73	0.628 ^b
PSPRS total score	22.4 ± 10.2	22.4 ± 10.5	22.4 ± 9.2	0.975 ^b
PSPRS history score	4.8 ± 2.7	5.0 ± 2.7	4.0 ± 2.7	0.245 ^b
PSPRS mentation score	2.9 ± 2.8	3.0 ± 2.9	2.5 ± 2.5	0.581 ^b
PSPRS bulbar score	1.9 ± 1.7	2.0 ± 1.8	1.4 ± 1.3	0.350 ^b
PSPRS ocular score	2.8 ± 1.9	2.6 ± 1.9	3.4 ± 2.1	0.286 ^b
PSPRS limb score	5.3 ± 2.7	4.9 ± 2.4	7.4 ± 3.4	0.020^b
PSPRS gait and midline	4.6 ± 3.5	4.8 ± 3.2	3.7 ± 4.5	0.096 ^b
SEADL	60.7 ± 24.5	60.2 ± 23.4	61.0 ± 30.7	0.755 ^b
MoCA score	23.1 ± 5.6	23.2 ± 5.1	22.6 ± 7.8	0.841 ^c
Subtype (PSP-RS/PSP variant)	10/51	8/40	2/11	0.999 ^a
Subtype (PSP-RS/cortical/subcortical) ^d	10/21/26	8/15/25	2/8/3	0.112 ^a
Plasma NF-L (pg/mL)	24.4 ± 9.0	23.3 ± 9.6	27.1 ± 7.3	0.368 ^c
Longitudinal data				
Patients (N) with two/three/four visits, respectively	28/24/9	20/20/8	8/4/1	0.481 ^a
Maximum follow-up length (mo)	16.7 ± 7.3	16.8 ± 7.7	16.4 ± 5.6	0.958 ^b
Age at the last follow-up (y)	70.8 ± 6.5	70.2 ± 6.9	72.9 ± 4.6	0.113 ^b
PSPRS score at the last follow-up ^e	32.6 ± 13.7	31.0 ± 12.9	38.6 ± 15.7	0.163 ^b
Annualized PSPRS change	7.8 ± 7.6	7.0 ± 7.3	11.4 ± 8.4	0.066 ^b
Annualized PSPRS percentage change	39.4 ± 44.0	36.0 ± 44.6	55.3 ± 38.7	0.083 ^b

Data are shown as mean ± standard deviation. Disease duration was since the symptom onset. Plasma NF-L was available in 27 patients (8 possible PSP and 19 s.o. PSP). The cortical PSP group included PSP with predominant cortico-basal syndrome (PSP-CBS) and PSP with predominant frontal presentation (PSP-F); the subcortical PSP group included PSP with predominant parkinsonism (PSP-P), PSP with predominant postural instability (PSP-PI), PSP with predominant ocular motor dysfunction (PSP-OM), and PSP with progressive gait freezing (PSP-PGF). Significant *P*-values are highlighted in bold font; no *P*-values survived Bonferroni correction for the number of tests ($P < 0.05/21 = P < 0.0024$).

Abbreviations: PSP, progressive supranuclear palsy; s.o. PSP, suggestive of PSP; PSPRS, PSP rating scale; SEADL, Schwab and England Activities of Daily Living scale; MoCA, Montreal Cognitive Assessment; PSP-RS, PSP Richardson's syndrome; NF-L, neurofilament light chain.

^aFisher's exact test.

^bTwo-sample *t* test or Wilcoxon rank-sum test.

^cANCOVA (analysis of covariance) with age as covariate.

^dThe possible PSP group included 2 PSP-RS, 8 PSP-CBS, 2 PSP-PGF, and 1 PSP-OM patients; the "suggestive of PSP" group included 8 PSP-RS, 13 PSP-CBS, 2 PSP-F, 22 PSP-P, 1 PSP-OM, and 2 PSP-PI patients.

^eBaseline PSPRS total score versus PSPRS total score at the last follow-up: $P < 0.0001$ (paired Wilcoxon rank-sum test).

Discussion

The current study demonstrated that most patients with s.o. or possible PSP diagnosis increased their diagnostic certainty over time, validating the operational MDS-PSP criteria for these diagnostic categories in a prospective multicenter setting against the long-term clinical follow-up. Notably, about 50% of patients converted to higher diagnostic certainty categories within 1 year, rendering the increase in diagnostic

certainty a potential experimental endpoint for clinical trials to demonstrate the efficacy of new disease-modifying therapies.

Several interventional trials have been conducted in PSP over the past decades, but all failed in demonstrating drug efficacy so far.¹³⁻¹⁶ One of the main reasons may be the inclusion of patients with well-established clinical presentation and advanced neuropathological disease stage¹⁷; although this approach may reduce clinical misdiagnosis, it limits the possibility of testing

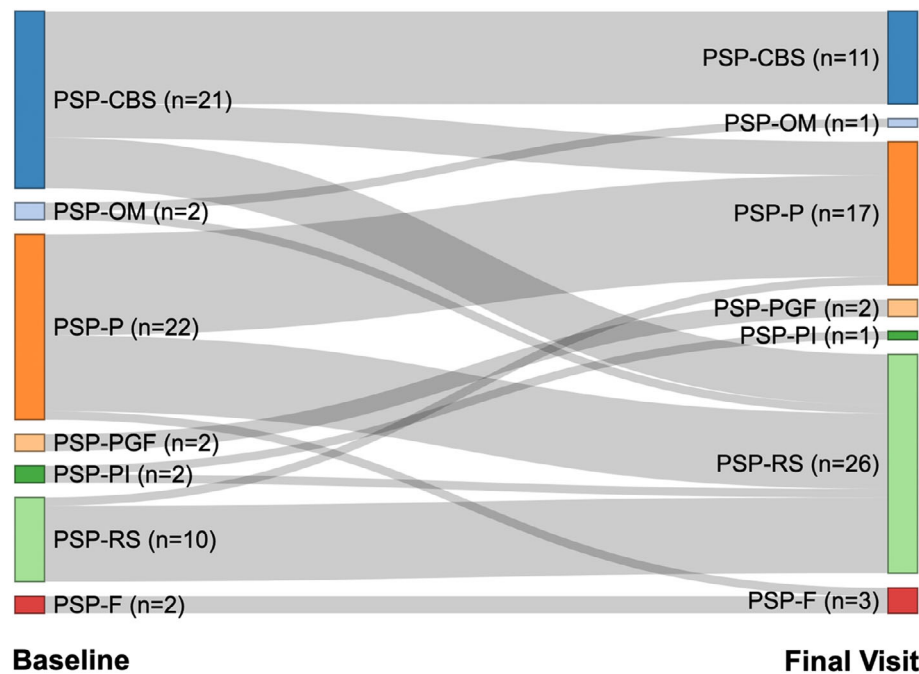


FIG. 2. PSP subtypes at baseline visit and at the last follow-up visit (mean time interval: 16.7 ± 7.3 months) in the whole cohort ($n = 61$). Abbreviations: PSP, progressive supranuclear palsy; PSP-CBS, PSP with predominant cortico-basal syndrome; PSP-F, PSP with predominant frontal presentation; PSP-OM, PSP with predominant ocular motor dysfunction; PSP-P, PSP with predominant parkinsonism; PSP-PGF, PSP with progressive gait freezing; PSP-PI, PSP with predominant postural instability; PSP-RS, PSP Richardson's syndrome. [Color figure can be viewed at wileyonlinelibrary.com]

potential disease-modifying drugs in the earliest stages of the PSP pathophysiological process, when treatments may be more effective in attenuating downstream

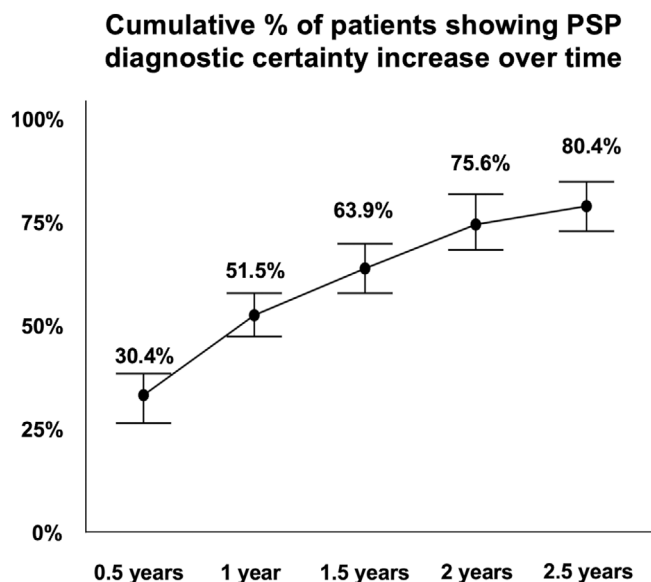


FIG. 3. Percentage of patients increasing their PSP (progressive supranuclear palsy) diagnostic certainty within each of the five considered time intervals (every 6 months between 0.5 and 2.5 years), calculated after imputing missing data using bootstrapping procedure ($n = 1000$ repetitions). The black dots represent the mean value of the 1000 bootstrapped populations; the whiskers are 2.5th and 97.5th percentiles of bootstrapping distribution (95% percentile intervals), meaning that the percentage of patients increasing their PSP diagnostic certainty was within this interval in 95% of the bootstrapped populations.

neurodegeneration and symptom progression. The identification of patients with milder symptoms, more preserved functions, and potentially less-advanced pathophysiology to include in clinical trials may indeed change the trial results, as we learned from the Alzheimer's field, where the anti-amyloid antibody donanemab recently showed better results in patients with low tau pathology levels than in those with more advanced disease.¹⁸ The MDS-PSP diagnostic criteria¹ included a new certainty level for PSP clinical diagnosis, termed "suggestive of PSP," which may represent a useful tool for selecting patients at the very early disease stage to include in future trials. The current study represents an important step forward in this direction. The first new insight coming from this study was that in a prospective multicenter cohort of 254 clinically diagnosed PSP patients, about 25% of patients had a diagnosis of s.o. PSP (19%) or possible PSP (5%) at the first visit, not fulfilling "probable PSP" criteria. This percentage of s.o. PSP patients, although slightly lower than in retrospective pathological studies,^{4,5} confirms the sensitivity increase for PSP obtained by including low diagnostic certainty categories in the criteria.^{4,5,19} It is tempting to hypothesize that all PSP patients might have a clinical presentation consistent with an "s.o. PSP" diagnosis at some early time in the disease process; thus, the prevalence of s.o. PSP patients may vary across clinical settings depending on how "early" patients are being referred to a specialist neurologist. The 19% of s.o. PSP diagnoses within our total PSP

TABLE 2 Sample sizes required for a two-arm, therapeutic trial to detect 20%, 30%, or 50% reduction in diagnostic certainty increase rate in PSP patients

Data	Sample size 20% change	Sample size 30% change	Sample size 50% change
Patients with s.o. PSP diagnosis			
1-year time diagnostic certainty increase rate	372	163	55
1.5-year time diagnostic certainty increase rate	246	110	39
2-year time diagnostic certainty increase rate	151	70	26
Annualized % PSPRS total score change	605	269	97
Annualized raw PSPRS total score change	435	194	70
Whole PSP group (s.o. or possible PSP)			
1-year time diagnostic certainty increase rate	366	160	55
1.5-year time diagnostic certainty increase rate	233	105	37
2-year time diagnostic certainty increase rate	148	69	26
1-year time % PSPRS total score change	490	218	79
1-year time raw PSPRS total score change	382	170	62

Note: The sample size was the minimum number of patients per group to detect a 20%, 30%, or 50% change in the diagnostic certainty increase rate, based on a power calculation for two proportions with equal sample size with a significance level of 0.05 and a power of 80%. The sample size needs to be adjusted for the estimated dropout rate (ie, for an estimated 20% dropout, the numbers in the table need to be increased as follows: recruitment goal = sample size)/(1–0.2). Abbreviations: PSP, progressive supranuclear palsy; s.o., suggestive of PSP; PSPRS, PSP rating scale.

cohort represents the prevalence of the “s.o. PSP” diagnostic category as obtained by prospective consecutive application of the MDS-PSP criteria in Germany tertiary care, academic hospital settings. However, this rate is likely to be increased by employing active recruitment strategies to raise awareness of subtle PSP signs among general practitioners to improve referrals of patients in the early disease stages.

In line with the conception behind the “s.o. PSP” diagnostic category, our cohort of s.o. PSP patients had milder disease severity (mean PSPRS score of 22) compared to patients included in previous clinical trials (mean PSPRS of 35–40),^{13–16} and our longitudinal prospective design demonstrated that patients fulfilled the “s.o. PSP” criteria before reaching a probable PSP diagnosis. These s.o. PSP patients also exhibited a slightly slower 1-year progression rate (mean PSPRS score increase of 7.8 points) compared to patients with possible or probable PSP (typically showing a mean PSPRS score increase of 9–11 points/year),^{13–16} possibly reflecting milder progression in the early disease stages while patients remain in the s.o. PSP category, followed by more rapid progression in later stages.

This study provided evidence that about 65% of patients with s.o. PSP or possible PSP diagnosis at the first visit evolved into probable PSP over time, increasing the diagnostic certainty for PSP and confirming the initial diagnosis. This finding is congruent with a recent retrospective pathological study in definite PSP patients⁴ and provides the first prospective validation

of MDS-PSP criteria for these diagnostic categories in a multicenter setting, suggesting that s.o. PSP patients are suitable for being included in clinical trials. Moreover, s.o. PSP patients may represent a key population for testing novel diagnostic biomarkers in patients with yet subtle, equivocal signs, who represent the real clinical challenge; in fact, such patients convert within a reasonable time frame to higher diagnostic certainty, allowing studies in early-stage patients with longitudinal diagnostic confirmation.

The current study first investigated the rates of patients increasing their PSP diagnostic certainty within specified time intervals, providing reliable reference data on the disease natural course. As expected, longer follow-up led to higher rates of diagnostic certainty increase, ranging from 30% within 6 months to about 50% of patients within 1 year and 80% of patients within a 2.5-year follow-up. These rates, including a conversion rate of 50% within a single year, seem very rapid and relevant for an event-based trial design, especially if compared to those of other early-stage neurodegenerative diseases.^{20–22} By taking as an example mild cognitive impairment (MCI) for AD or rapid eye movement sleep behavior disorder (RBD) for Parkinson’s disease (PD), we typically observe a conversion rate of 5%–10% per year in MCI patients to develop overt dementia²⁰ and about 6.5%–10% per year in RBD patients to develop PD symptoms,^{21,22} making long follow-up periods necessary to observe conversion in a significant percentage of the study population.

Conversely, an annual conversion rate of about 50% from s.o. PSP to higher diagnostic certainty categories makes these patients highly suitable for enrollment in clinical trials, which usually consider a relatively short 1-year time interval. It is possible to hypothesize that disease-modifying drugs slowing down disease progression might attenuate the diagnostic certainty increase rate in these patients, and a high conversion rate within a limited time interval is highly valuable to detect drug efficacy. That is, in a two-arm drug versus placebo trial, we might observe a 50% diagnostic certainty increase rate in the placebo arm (consistent with the natural history data presented here) and a lower (ie, 30%–35%) diagnostic certainty increase rate in the drug arm. Our results demonstrated that the diagnostic certainty increase rate may be a useful endpoint in clinical trials specifically designed for early-stage patients with an “s.o. PSP” diagnosis, and the sample size required to observe a reduction in this rate in 1-year trials was even lower than that estimated to observe comparable reduction in the clinical progression rate measured by the PSP rating scale.⁹ Thus, the diagnostic certainty increase rate, if approved by regulatory agencies, may be used as an exploratory outcome measure in addition to clinical measures directly reflecting disability (PSPRS,⁹ modified PSPRS,²³ PSP clinical deficit scale²⁴) in trials on s.o. PSP patients. This outcome measure falls in the field of an event-based trial design (where the event represents the increase in patient’s diagnostic certainty), which is not uncommon in clinical trials focused on the early stages of neuroinflammatory, vascular, or neurodegenerative diseases.^{25–29} In the cerebrovascular field, the incidence of “events” (ie, the occurrence of a stroke in the population at risk) is often compared between the two arms of a trial.²⁶ In the neuroinflammatory field, some trials evaluated the conversion rate from clinically isolate syndrome to multiple sclerosis.²⁵ In Alzheimer’s research, two notable recent trials in early or preclinical Alzheimer’s patients have assessed the time to progression of the global Clinical Dementia Rating score, measuring the time required to observe an increase in this score.^{27,28} In addition, a very similar approach has been studied in RBD patients with good results (using the rates of conversion to dementia/parkinsonism as endpoint measure) and will likely be incorporated in future trials.²⁹ Notably, this is a clinically relevant endpoint because the increase in diagnostic certainty reflects by definition the appearance of new and relevant PSP symptoms, and patients with higher diagnostic certainty show more severe clinical presentation, as demonstrated by the higher PSPRS scores observed in probable PSP than in s.o. PSP patients.

Overall, this study first provides robust prospective evidence that s.o. PSP patients have high rates of conversion to possible/probable PSP, demonstrating that these patients may represent a key population for

upcoming clinical trials to test the real potential of new disease-modifying drugs in a very early disease phase. The addition of magnetic resonance imaging (MRI) or fluid biomarkers to clinical criteria may also be relevant. We found a slight but significant increase in conversion rates after patients with PSP-CBS subtype and cerebrospinal biomarker profile suggestive of Alzheimer’s (AD) pathophysiology were excluded, as suggested by PSP exclusion criteria based on laboratory findings,¹ confirming the validity of this approach. Future studies investigating whether the enrichment of low diagnostic certainty PSP cohorts with neuroimaging or fluid biomarkers supportive of PSP pathology may lead to even higher conversion rates are warranted. The addition of such biomarkers may also improve the predictive value for underlying PSP pathology, which is crucial in trials investigating drugs with molecular targets, and is usually lower in patients with s.o. PSP diagnosis than in those with a probable PSP diagnosis (55%–65% and 85%, respectively).^{4,5} Overall, based on our and previous results, future clinical trials may be conceptualized in patients with s.o. PSP diagnosis possibly enriched by fluid or MRI biomarkers, identifying an optimal population fulfilling three major requisites: early disease stage, rapid evolution through more severe disease stages, and high predictive value for PSP pathology.

Most s.o. and possible PSP patients in our study had a diagnosis of PSP variant, as expected by considering the typically milder disease course of these variants in contrast with the earlier appearance of PSP clinical signs in PSP-RS subtype.^{19,30–32} The prevalence of the PSP-RS subtype, however, increased over time, suggesting that patients converge clinically toward PSP-RS throughout the PSP natural course.^{4,33}

This study has large novelty, consisting of the first prospective observational study in s.o. PSP patients, provides prospective validation of “suggestive of PSP” diagnostic criteria, and has several strengths. First, this is the largest prospective multicenter study in s.o. PSP patients. Second, this is a longitudinal study, and all patients underwent careful diagnostic reassessment at multiple time points, with application of PSP operational criteria for diagnostic degree and PSP subtype.¹ Third, we included patients from the full PSP spectrum, allowing to generate data applicable to the whole s.o. PSP category rather than restricting the study implications to a single PSP subtype. This may be of high relevance for conceptualizing future clinical trials tailored for early-stage s.o. PSP patients rather than limited to quite advanced PSP-RS patients. Fourth, this study proposed a new potential exploratory endpoint measure (the diagnostic certainty increase rate) for clinical trials, which was even more powerful in terms of sample size than the currently employed clinical progression measures and may be added to clinical scales currently

employed to measure symptom and disability progression in PSP. Finally, the analyses were repeated after PSP-CBS patients with CSF profile suggestive of AD were excluded, providing data based not only on the pure clinical diagnosis but also on laboratory findings. There are, however, some limitations. First, postmortem pathological assessment was lacking; clinical diagnosis was confirmed at follow-up in most cases by evolution to probable PSP diagnosis; however, it is possible that some patients may not have PSP pathology. The possible presence of some misdiagnoses in s.o. PSP cohorts should also be considered in the design of future trials in these early-stage patients, as this can affect the required sample size, making biomarkers supporting clinical diagnosis especially valuable for patient selection in this context. Second, our study showed that about 65% of patients evolved into higher certainty diagnostic categories over time; however, some patients who did not convert until the last-available visit had quite short follow-up observation periods. Thus, it is possible that some of them may convert over longer time and that the overall percentage of patients with diagnostic certainty increase is higher than reported. The percentage of patients lost at follow-up may seem quite high (33%) if compared to clinical trials (typical dropout rate: 20%–25%),^{12–15} but it is consistent with the nature of DescribePSP and ProPSP cohort studies, which are longitudinal observational cohort studies providing information on the natural history of the disease, and with the relatively long observational period. To overcome this limitation, we imputed missing information using bootstrapping procedure and calculated the mean and 95% percentile intervals of 1000 populations to provide reliable data and rates at different time points. Some caution, however, should be exercised when interpreting data obtained using imputation strategies, and replication of our data in the independent international cohort is warranted to ensure generalizability. Third, the accurate classification of PSP patients across the various subtypes may be challenging,^{8,34} especially between s.o. PSP-P and other variants; thus, it is possible that some misallocations might have occurred. Fourth, biomarker data, including DaT-SPECT, amyloid or tau PET, and plasma exosome tau dosages,³⁵ were not available; future studies, including such biomarkers, are warranted. Finally, it should be considered that our findings are not directly applicable to the current or past trials in PSP. The inclusion criteria of most trials conducted so far required overt ocular motor dysfunction and falls, thus focusing on PSP-RS phenotype, excluding other PSP variants and early-stage patients as s.o. PSP patients. The current work is the first prospective longitudinal study to demonstrate that the conditions conceptualized as s.o. PSP are suitable to be included in clinical trials, and our results may be

relevant for the design of future trials rather than for comparison with previous or past trial data.

In conclusion, this study provides strong evidence from a prospective multicenter cohort that most patients with an “s.o. PSP” diagnosis convert to possible or probable PSP over time, with about 50% of patients converting within 1 year of follow-up. These data provide a prospective validation of the PSP diagnostic criteria for s.o. PSP and suggest that these patients, especially if enriched by fluid or MRI biomarkers suggestive of PSP pathology, may represent a valid target population for upcoming clinical trials to test the effect of new potential disease-modifying therapies in an early disease stage. ■

Author Roles: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

A.Q.: 1A, 1C, 2A, 2B, 3A

N.F.: 1A, 1B, 1C, 2C, 3B

J.L.: 1B, 3B

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F.B.: 1B, 3B

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Acknowledgments: DescribePSP is supported by the German Center for Neurodegenerative Diseases (DZNE). ProPSP is supported by the German Parkinson's Association (DPG) and the German PSP Association (PSP-Gesellschaft). Open Access funding enabled and organized by Projekt DEAL.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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.