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Short communication

Are PSP patients included in clinical trials representative of the general PSP population?

Louise-Laure Mariani[a], Raquel Guimarães-Costa[a], David Grabli[a], Benjamin Le Toullec[a], Florence Cormier-Dequaire[a], Bertrand Degos[a,b], Bruno Dubois[a], Marie Vidailhet[a], Lucette Lacomblez[a], Jean-Christophe Corvol[a,*]

[a] Sorbonne Université, Assistance Publique Hôpitaux de Paris, Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS UMR 7225, Department of Neurology, Hôpital Pitié-Salpêtrière, F-75013, Paris, France
[b] AP-HP, Neurology Unit, Hôpital Avicenne, Hôpitaux Universitaires de Paris, Seine Saint Denis, Bobigny, France

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ABSTRACT

Background: Progressive supranuclear palsy (PSP) is a rare parkinsonian syndrome with a wide spectrum of clinical presentations. Recently, the MDS published revised diagnosis criteria to provide early and reliable diagnosis of PSP and its variants. Two large randomized clinical trials were initiated in 2017, but the question remains regarding the extrapolation of their results to the general PSP population.
Objective: To determine if PSP patients included in clinical trials are representative of the general PSP population.
Methods: We conducted a single center retrospective study of PSP patients referred to a tertiary department of Neurology (Pitié-Salpêtrière Hospital, Paris) for clinical diagnosis and clinical trial inclusion, over a 12-month period. We collected and analyzed gender, age at examination, age at disease onset, disease duration, and core clinical features regarding oculo-motor dysfunction, postural instability, akinesia and cognitive dysfunction, and inclusion/exclusion criteria of clinical trials to assess eligibility for inclusion. We assessed the relative proportions of different PSP subtypes, as defined by the MDS-PSP criteria, in the whole population compared to patients eligible in trials.
Results: 206 PSP patients were included, among which 175 (85%) were diagnosed with probable PSP-Richardson's syndrome (RS) subtype, with a mean age of 73 and mean disease duration of 5 years. Among those patients, 29 (21%) were eligible (age 71 ± 10.7, disease duration 3.1 ± 1.2 years) and 19 were included in trials, all with a diagnosis of probable PSP-RS. As compared to the whole population, patients included in clinical trials tended to be younger, and showed more PSP-RS subtypes ($p < 0.05$).
Conclusion: The PSP population included in trials is very similar to the general PSP population, but younger, with shorter disease duration. By definition, only probable PSP subtypes are included in clinical trials. The time window for inclusion is short because of diagnosis delay, fast disease progression and old age of the population.

1. Introduction

Progressive supranuclear palsy (PSP) is a rare parkinsonian syndrome characterized by parkinsonism with poor response to levodopa, early postural instability, supranuclear gaze palsy, and frontal cognitive disturbances. Neuropathologically, PSP is defined by the accumulation in the brainstem of neurofibrillary tangles, insoluble deposits composed of 4R tau. Depending on the predominant clinical presentation, PSP has a wide phenotypic spectrum with the classic Richardson's syndrome (PSP-RS) described above, but also patients with progressive gait freezing (PSP-PGF), predominant parkinsonism (PSP–P), frontal syndrome (PSP–F), oculomotor dysfunction (PSP-OM), speech/language disorder (PSP-SL), postural instability (PSP-PI) or cortico-basal syndrome (PSP-CBS) [1–3]. PSP prognosis is poor with a 5–7 years mean survival after onset [1,4–7]. There is no cure for PSP. Two large randomized clinical trials targeting tau pathology have been initiated in 2017. But the inclusion criteria based on the National Institute of Neurological Disorders and Stroke and Society for PSP (NINDS-SPSP) favor disease specificity, so, may not represent the whole PSP spectrum [8]. Recently, the Movement Disorder Society (MDS) published revised

* Corresponding author. CIC Neurosciences, Bâtiment ICM, Hôpital Pitié-Salpêtrière, 47/83 Bd de l'Hôpital, 75013, Paris, France.
E-mail address: jean-christophe.corvol@aphp.fr (J.-C. Corvol).

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diagnosis criteria to provide early and reliable diagnosis of PSP and its clinical variants [2]. In this study, we investigated the generalizability of the results of clinical trials by assessing if the PSP patients eligible and included in clinical trials are representative of the general PSP population seen in a reference center for PSP. Generalizability of trial results is of importance to both clinicians and medicine agencies, to know if positive trial results are applicable to a broader level. Our results support that the population included in current PSP trials is representative of the general PSP population.

2. Methods

We conducted a single center retrospective study of PSP patients referred to the Department of Neurology at the Pitié-Salpêtrière Hospital (Paris) for clinical diagnosis and pre-screening for clinical trials, the year preceding trials initiation. Study objective was to assess if the PSP patients eligible and included in clinical trials were representative of the general PSP population. Outcome was the relative proportions of different PSP subtypes in the whole population as compared to eligible patients.

2.1. Participants

For all patients, hospital database, hospital charts and letters from referring neurologists were reviewed to collect gender, age at examination, age at disease onset, disease duration, and core clinical features regarding oculo-motor dysfunction, postural instability, akinesia and cognitive dysfunction. For the 141 patients pre-screened for eligibility in the ARISE and PASSPORT clinical trials (inclusion and exclusion criteria specified in esupp Table 1), complementary information for specific inclusion/exclusion criteria was gathered by telephone interview if needed.

Diagnosis and classification (MDS-PSP criteria) were independently reviewed by three movement disorders specialists (LLM, RGC, JCC) by prioritizing diagnostic certainty (e.g. probable > possible), and then the order of clinical subtype as described in the MDS-criteria [2]. When diagnosis was discordant, cases were reviewed by the three specialists until a consensus was reached. Only the patients presenting with PSP-RS subtype and less than 5 years duration could be eligible for inclusion in the ARISE and PASSPORT clinical trials they were screened for.

2.2. Statistical analysis

We performed a descriptive analysis for each variable using Graphpad Prism 6 software (GraphPad Software Inc., CA, US). Categorical variables are expressed as the number of patients presenting the symptom and as percentages [n(%)]; and continuous variables as mean ± SD. Kruskal-Wallis test was used to compare quantitative variables. Categorical variables were compared using chi-square or Fisher exact tests when appropriate.

2.3. Data availability

Data presented in this report will be made available to bona fide investigators upon request to the corresponding author.

3. Results

3.1. Patient characteristics

Fig. 1 describes the flow chart of patients and Table 1 shows the patients demographics and characteristics. Between September 2016 and October 2017, 239 patients were identified as “PSP” either because they were coded as such, or because they were referred for a suspected diagnosis of PSP. After discarding patients with missing data or with other diagnosis (n = 33), 206 PSP patients were analyzed, with a mean age at examination of 73.1 ± 9.8 years-old and a disease duration (DD) of 5.2 ± 3.0 years, among which 175 (85%) were diagnosed with probable PSP-RS (Table 1a). The most frequent core symptoms were falls, spontaneous or at pull test, in 193 (94%), oculomotor dysfunction with either vertical gaze palsy or slow saccades in 181 (88%), frontal presentation in 159 (77%) and axial levodopa resistant parkinsonism in 143 (69%) (Table 1a). Among them, a total of 141 patients were formally pre-screened for inclusion in clinical trials.

In October 2017, at the end of the pre-screening period, 74 (52%) patients had a disease duration > 5 years and were thus not eligible

Table 1a
PSP patients characteristics.

	All patients	Pre-screened	Eligible	p value
n =	206	141	29	
Patients demographics				
Sex ratio M/F	1.6	1.3	1.5	ns
Age at onset	67.4 ± 9.3	67.7 ± 9.7	66 ± 5.8	ns
Age at screening	73.1 ± 9.8	73.2 ± 10.4	71 ± 10.7	ns
Disease duration	5.2 ± 3.0 ****	5 ± 2.4	3.0 ± 1.2 ****	**** < .0001
PSP subtype classification				
Probable				
PSP-RS	175 (85)	129 (91)	29 (100)	ns
PSP-PGF	1 (0.5)	1 (1)	0	
PSP-P	8 (4)	5 (4)	0	
Possible				ns
PSP-CBS	2 (1)	2 (1)	0	
PSP-PGF	6 (3)	0	0	
PSP-SL	2 (1)	1 (1)	0	
Suggestive of				ns
PSP-PI	1 (0.5)	1 (1)	0	
PSP-RS	2 (1)	0	0	
PSP-P	9 (4)	2 (1)	0	

Ages and disease duration are expressed in years. These continuous variables are expressed as mean ± standard deviation (SD).
Categorical variables are expressed as the number of patients presenting the symptom and as percentages (n (%)).
Abbreviations: F: female, LDA: Levodopa, M: male, ns: not significant (p > 0.05); PSP: Progressive Supranuclear Palsy; PSP-P: PSP with predominant Parkinsonism; PSP-PGF: PSP with progressive gait freezing, PSP-CBS: PSP with predominant Cortico-basal syndrome; PSP-SL: PSP with predominant speech/language disorder; PSP-PI: PSP with predominant postural instability; PSP-RS: PSP with Richardson's syndrome.
Kruskal-Wallis with Dunn's multiple comparisons test and Chi-square or Fisher exact tests when appropriate. ****p < 0.0001.

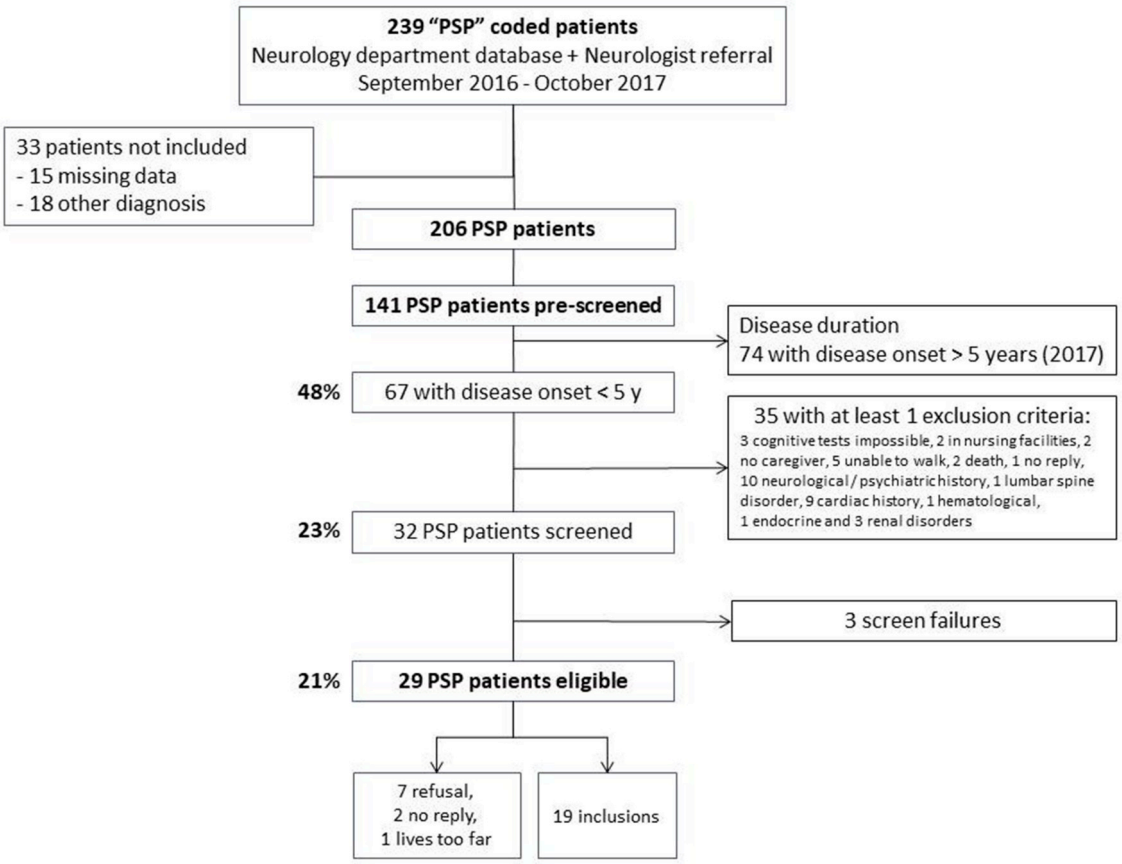

Fig. 1. Flow chart of patients with progressive supranuclear palsy.
Abbreviations: DD: disease duration; PSP: progressive supranuclear palsy.
Listing of exclusion criteria may exceed the number of patients because patients could present with more than one contraindication at a time.

Table 1b
PSP patients core clinical features.

Core clinical features	n = 206	141	29	p value
Ocular Motor Dysfunction				
O1: Vertical gaze palsy	96 (47)	75 (53)	16 (55)	ns
O2: Slow saccades	85 (41)	57 (40)	10 (34)	
O3: SWJ or eyelid apraxia	7 (3)	4 (3)	0	
Postural Instability				
P1: Falls	175 (85)	121 (86)	24 (83)	ns
P2: Pull test falls	18 (9)	12 (9)	3 (10)	
P3: Pull test steps	5 (2)	4 (3)	0	
Akinesia				
A1: Freezing	30 (15)	18 (13)	0	ns
A2: Axial parkinsonism, LDA resistant	143 (69)	96 (68)	24 (83)	
A3: Parkinsonian tremor, LDA responsive	22 (11)	19 (13)	1 (3)	
Cognitive Dysfunction				
C1: Speech disorder	4 (2)	3 (2)	0	ns
C2: Frontal presentation	159 (77)	104 (74)	20 (69)	
C3: Cortico-basal syndrome	4 (2)	2 (1)	0	

Abbreviations: LDA: Levodopa; ns: not significant ($p > 0.05$); SWJ: Square Wave Jerks.
Categorical variables were compared using Fisher exact test.

(esupp Table). Thirty-five of the 67 remaining patients presented at least one exclusion criteria related to the severity of the disease in terms of cognitive (n = 3) or motor (n = 5) deficits, institutionalization (n = 2), death (n = 2), absence of caregiver (n = 2) or comorbidities (n = 25) (Fig. 1).

Finally, 32 (23%) patients were screened, and 29 (21%) were eligible (age 71, disease duration 3 years) all of which with probable PSP-RS subtype (Fig. 1, Table 1a). The three screen failures were related to impossibility to comply properly with neuropsychological evaluation in two patients and a medical history of clinically significant hematologic disorder and stroke in one patient. Seven patients refused to participate. The main reasons for refusal were impossibility/refusal to comply to multiple visits, refusal of caregiver to participate, fatigue and no specific interest in participating in clinical research protocol. Finally 19 patients could be included.

When comparing the global population of PSP patients (n = 206) to the eligible ones (n = 29), eligible patients showed a significant shorter disease duration ($p < 0.0001$), a trend to younger age at screening, more PSP-RS subtypes and less freezing of gait (Tables 1a and 1b). They did not show significant differences in gender, age at onset, other PSP subtypes than PSP-RS, or other core clinical symptoms than freezing of gait.

The pre-screening period lasted one year before the trials were finally initiated. During this period, 16 patients initially eligible were no longer when trials were initiated, corresponding to a 33% drop out within 12 months because of disease duration (n = 7), age limit (n = 4), disease progression (wheelchair bound after 12 months) (n = 3), or death (n = 2).

4. Discussion

Evidence-based practices are generally based on controlled clinical trials performed in a specific population selected to yield accurate estimates of the effect of the investigational drug during the trial. The intervention population is however not always relevant to the final target general population leading to some issue for clinicians and health policymakers to extrapolate the results of trials to real life practice. This

issue of generalizability is particularly important for PSP considering the wide spectrum of its clinical presentation, and the urge to provide a cure for this rare but debilitating and severe disease. Our study shows that the population included in PSP clinical trials is very similar to the general PSP population. Despite such strict inclusion criteria as used in the present trials (PSP-RS subtype, disease duration below 5 years), the population of these randomized controlled trials represents the overall PSP population. Most of our referred population fulfilled the criteria for PSP-RS subtype corresponding to the target population of these clinical trials. Probable PSP-P and PSP-PGF patients, and patients with possible PSP or suggestive of PSP, not eligible in clinical trials represented 15% of the pre-screened population. Almost all of these patients, not fulfilling probable PSP-RS criteria but classified as PSP variant by the MDS criteria, would not have been classified as PSP patients if the previous NINDS-SPSP criteria were applied. These results further emphasize how the new MDS criteria appraise a broader spectrum of PSP and its clinical variants.

Disease duration was the most discriminant criteria resulting in a younger population with a shorter disease duration. The high percentage of patients with disease durations above the five-year threshold at screening highlights the long delay to diagnose probable PSP. Although when encompassing wider subtypes, an improvement in the latency to PSP diagnosis was recently reported in the US, from ~3.6 years in the 1990s to ~2.4 years in the 2010s [9]. The population that failed the pre-screening was otherwise more advanced, presenting severe cognitive or gait deficits, were institutionalized, or had other comorbidities. Considering this diagnosis delay, and the malignancy of PSP, potential inclusion in clinical trials, when available, should be discussed early, as highlighted by the 33% loss of eligibility occurring within the 12 months of our study [5,10].

One major limitation is the monocentric nature of our study and patients referred to our center may differ from the general PSP population. Patients with more advanced diseases, difficult to manage out of hospitals, are more prone to be followed in tertiary public centers in France, with open access and referral for any PSP patients without specific patient selection. During the period of our study, private neurologists, informed of the upcoming trials, were inclined towards referring PSP patients to our center. The general characteristics of our referred population were very similar to previous case-series in terms of gender ratio (1:1), age at onset (ranged from 61 to 69.6 years old), falls (87–97.9%), and oculomotor impairment (77–99.9%) [1,5–15]. PSP subtype repartition was in favor of PSP-RS subtypes as previously reported in clinical and post-mortem studies.

As compared to pathological-proven studies [1], our cohort showed a higher rate of PSP-RS subtype. This is probably partly due to recruitment bias since several PSP patients were directly referred to our center for inclusion into clinical trials with PSP-RS as one of the inclusion criteria. On the other hand, neuropathological series are more likely to over-represent non-RS atypical cases that were sent for diagnosis confirmation through neuropathology, since a definite diagnosis of PSP currently requires neuropathological examination [2]. A meta-analysis of 11 studies on 1911 patients with PSP of whom 415 had a pathologically confirmed diagnosis, also reports a higher percentage of 67% patients with PSP-RS subtype in clinical studies compared to 44% in post-mortem studies [5]. In addition, because applying MDS criteria can lead to classification of a patient into several subtypes, when assessing diagnosis criteria at a specific time point independently of the initial clinical presentation, we applied rules of prioritization that favor the PSP-RS subtype. Most PSP subtypes will finally fulfill probable PSP-RS criteria whatever the initial clinical presentation, although supranuclear gaze palsy may occur later during disease course in some patients [16,17].

Other limitations of our study are related to its observational and retrospective nature. We did not have access to anatomopathological proven cases in this study. However, MDS criteria are reported to be reliable for the diagnosis of PSP [2,17].

If clinical trials are positive, all the PSP population, regardless of the subtype and disease duration, will probably claim to have access to the treatment. Generalizability of results from clinical trials focusing on a particular sub-population (external validation) is not an easy task and needs, as a first step, to compare the population of the trial with the targeted population in real life [18]. Our study provides information about the potential differences between the clinical trial population and the targeted global PSP population. Although to be confirmed in independent studies, our results support that the population included in current PSP trials is representative of the general PSP population and, if positive, drugs tested in these trials may thus benefit to the wide majority of PSP patients.

Author contributions

Dr. Mariani: concept, acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript. Dr. Guimarães-Costa: acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. D. Grabli: acquisition and interpretation of data, critical revision of the manuscript. B. Le Toullec: acquisition of data, critical revision of the manuscript. F. Cormier-Dequaire: acquisition of data, critical revision of the manuscript. B. Degos: acquisition of data, critical revision of the manuscript. B. Dubois: acquisition of data, critical revision of the manuscript. M. Vidailhet: acquisition of data, critical revision of the manuscript. L. Lacomblez: concept and interpretation of data, critical revision of the manuscript. JC. Corvol: concept, acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript.

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Declaration of interest

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Appendix A. Supplementary data

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