RESEARCH ARTICLE

The Phenotypic Spectrum of Progressive Supranuclear Palsy: A Retrospective Multicenter Study of 100 Definite Cases

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ABSTRACT: The phenotypic variability of progressive supranuclear palsy (PSP) may account for its frequent misdiagnosis, in particular in early stages of the disease. However, large multicenter studies to define the frequency and natural history of PSP phenotypes are missing. In a cohort of 100 autopsy-confirmed patients we studied the phenotypic spectrum of PSP by retrospective chart review. Patients were derived from five brain banks with expertise in neurodegenerative disorders with referrals from multiple academic hospitals. The clinical characteristics of the 100 cases showed remarkable heterogeneity. Most strikingly, only 24% of cases presented as Richardson's Syndrome (RS), and more than half of the cases either showed overlapping features of several predescribed phenotypes, or features not fitting proposed classification criteria for PSP phenotypes. Classification of patients according to predominant clinical features in the first 2 years of the disease course allowed a more comprehensive description of the phenotypic spectrum. These predominance types differed significantly with regard to survival time and frequency of cognitive deficits. In summary, the phenotypic spectrum of PSP may be broader and more variable than previously described in single-center studies. Thus, too strict clinical criteria defining distinct pheno-

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types may not reflect this variability. A more pragmatic clinical approach using predominance types could potentially be more helpful in the early recognition of and for making prognostic predictions for these patients. Given the limitations arising from the retrospective nature of this analysis, a systematic validation in a prospective cohort study is imperative.

Key Words: progressive supranuclear palsy; phenotypes; clinical diagnostic criteria; neuropathology

In 1963, J.C. Steele, J.C. Richardson, and J. Olszewski described eight cases of progressive supranuclear palsy (PSP) with a clinical syndrome,[1] now termed Richardson's syndrome (RS).[2] Several atypical phenotypes have been described since then.[2-25] In 2005, a single-center systematic analysis of 103 definite PSP cases highlighted a second distinct phenotype, PSP with parkinsonism (PSP-P).[2] In 2007, this and another group described pathologically verified PSP cases manifesting as pure akinesia with gait freezing (PSP-PAGF).[13,14] Further single-centre clinico-pathological studies with smaller numbers of patients identified additional PSP phenotypes: PSP with corticobasal syndrome (PSP-CBS),[15-17] frontotemporal dementia (PSP-FTD),[18-20] progressive nonfluent aphasia (PSP-PNFA),[21-23] and cerebellar ataxia (PSP-C).[24,25]

The variety of phenotypes may account for the low sensitivity of the current clinical criteria for the diagnosis of PSP.[26,27] To increase sensitivity and facilitate early recognition of non-RS patients, some authors proposed separate criteria for the non-RS PSP phenotypes.[28] However, the incidence and natural history of the non-RS phenotypes are largely unknown, because large multicenter clinicopathological studies are missing, and most series reported to date have been derived from single centers, with unavoidable recruitment bias.

To address this issue, we analyzed a large series of autopsy-confirmed PSP cases from different university medical centers with detailed clinical documentation throughout the disease course.

Materials and Methods

Protocol Approvals and Patient Consents

Before death, all donors gave written informed consent according to the Declaration of Helsinki for the use of their brain tissue and medical records for research purposes. This work was approved by local institutional review boards and ethics committee at each participating center.

Identification of Cases

Patients with a neuropathological diagnosis of PSP[29] were identified from the neuropathology files of the following brain banks:

1. Center for Neuropathology and Prion Research, Ludwig-Maximilians-University, Munich, Germany
2. MRC London Neurodegenerative Diseases Brain Bank, King's College, London, UK
3. Netherlands Brain Bank, Amsterdam, Erasmus Medical Center, Rotterdam, The Netherlands
4. Neurological Tissue Bank of the Biobanc–Hospital Clinic–IDIBAPS, Barcelona, Spain
5. Brain Bank of the Royal University Hospital, University of Saskatchewan, Canada

Cases were randomly selected for our study from the inventories of the participating brain banks. Cases with insufficient clinical data were excluded. They originated from different university centers and were evaluated clinically by movement disorder specialists, behavioral neurologists, or psychiatrists, as documented in the patients' files.

Central Pathological Verification

In addition to the neuropathological evaluation in each brain bank, brain tissues from 50 randomly selected cases were sent to the Center for Neuropathology and Prion Research, Munich, which is the German national reference center for neurodegenerative disorders and the coordinating center of the BrainNet Europe, for a standardized central verification of the pathological diagnosis. Pathological diagnosis was defined by the presence of neuronal loss and gliosis together with abnormally phosphorylated 4R-tau protein in neurofibrillary tangles and tufted astrocytes in a characteristic distribution involving the globus pallidum, subthalamic nucleus, dentate nucleus, substantia nigra, midbrain, pons, and medulla oblongata.

Data Collection

Retrospective chart review of the cases was performed to extract demographic and clinical information gathered between 1973 and 2008. The demographics abstracted from medical records included sex, age at death, disease duration, and age at onset, defined as first occurrence of a specific motor, cognitive, or behavioral sign or symptom that prevailed throughout the course of the PSP syndrome. If applicable, first and last clinical diagnosis and the duration from disease onset to the clinical diagnosis of PSP were

TABLE 1. Demographic data

	All	PSP-RS	PSP-PI	PSP-OM	PSP-P	PSP-CBS	PSP-FTD	Unclassified
N	100	24	18	7	19	7	12	13
M:F (N, [%])	45:55 [45:55]	8:16 [33:67]	13:5 [72:28]	3:4 [43:57]	6:13 [32:68]	5:2 [71:29]	4:8 [33:67]	6:7 [46/54]
Age at onset (yrs., mean ± SEM [range])	65.2 ± 0.9 [41-91]	62.0 ± 1.4 [51-75]	68.1 ± 1.7 [54-79]	61.9 ± 2.7 [51-72]	67.7 ± 2.3 [41-79]	64.9 ± 2.0 [57-71]	64.1 ± 3.0 [52-91]	66.6 ± 1.5 [50 −78]
Age at death (yrs., mean ± SEM [range])	73.3 ± 0.9 [55-93]	68.5 ± 1.5 [55-82]$^{\#\#\#}$	75.6 ± 1.9 [63-90]**	68.4 ± 2.6 [58-79]$^{\#\#\#}$	80.3 ± 2.0 [64-92]***	72.1 ± 1.7 [65-79]$^{\#}$	70.8 ± 2.7 [57-93]$^{\#\#}$	74.3 ± 2.1 [59-85]$^{*,\#}$
Disease duration (yrs., mean ± SEM [range])	8.7 ± 0.4 [2-28]	7.3 ± 0.6 [4-17]$^{\#\#\#}$	8.2 ± 0.7 [4-16]$^{\#\#\#}$	7.4 ± 0.4 [6-9]$^{\#\#}$	12.8 ± 1.5 [4-28]***	8.3 ± 2.0 [3-19]$^{\#}$	7.6 ± 1.0 [2-13]$^{\#\#\#}$	8.2 ± 1.0 [3-17]$^{\#\#}$
5-year mortality (%)	20.0	29.2	16.7	0.0	5.3	28.6	33.3	23.1

Demographic data of all analyzed definitive PSP patients and of the patients subgrouped according to clinical predominance types: RS, Richardson's syndrome; PI, postural instability; OM, oculomotor; P, Parkinsonism; CBS, corticobasal syndrome; FTD, frontotemporal dysfunction; Unclassified, patients not fitting any of these predominance types.
ANOVA followed by post hoc LSD test: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, vs. RS; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, vs. PSP-P.

noted. Standardized clinical features were recorded as given in the Supplemental Data (Table S1). These features were considered present if specifically mentioned in the clinical notes. They were considered absent if they were specifically mentioned as absent, or if they were not mentioned ("not available"). The onset of features relative to disease onset was recorded. If the onset of a symptom or sign could not be abstracted from the files, the year of onset was excluded from the analysis of their temporal evolution.

Statistical Analysis

For descriptive analyses, data are presented with the mean ± standard error of the mean (SEM). Normal parametric values were compared by analysis of variance (ANOVA), followed by post hoc least significant difference (LSD) test. Differences in frequencies of symptoms and diagnosis were compared between PSP predominance types using the chi-squared test and Bonferroni correction. A p-value < 0.05 was considered statistically significant.

Principal Component Analysis

A complete set of clinical variables each coded as 1 = present or 0 = absent was available from all (n = 100) cases. To identify similar groups of variables, these data were entered into a principal components analysis. Statistical analysis was performed using SPSS for Windows version 20. From the principal component analysis, the first two components were selected, and a "Varimax" rotation on these components was performed. This kind of rotation maximizes the number of variables with high loadings on each factor. The loadings of each variable on both of these components were plotted against each other as a scatter plot. The plot was examined, and three groups of variables in different areas were selected. A between-groups, hierarchical cluster analysis using squared Euclidean distance measures was performed to verify that these sets of clinical features grouped together. Cases that exhibited a greater number of characteristics from group 1 than from group 2 or 3 were deemed to fall within set 1, and similarly for the other two groups.

Classification Into Predescribed Phenotypes

Based on previous descriptions of definite PSP cases with clinical presentations other than RS, several distinct PSP phenotypes have been identified.[2,13,15,16,20,23,24,30] Patients were classified into these predefined phenotypes according to the criteria shown in Supplemental Data Table S2, left column. This classification was done independently by three movement disorders neurologists (G.R., M.S., G.U.H.), and a subsequent consensus was reached for this classification.

Classification According to the Predominant Clinical Features During the First 2 Years

Because an early identification of the patients is crucial, we aimed to develop a disease model based on early presentations. We identified what features predominated the early clinical presentation (first 2 years from disease onset) that would allow classification into subgroups relevant for early diagnosis and prognosis. We termed these *PSP-predominance types*. Definitions of these are given in Supplemental Data Table S2, right column.

Diagnostic Accuracy of NINDS-SPSP and NNIPPS Criteria for the Predominance Types

Fulfillment of the National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) criteria[26]

TABLE 2. Diagnosis of PSP: Frequency

	All	PSP-RS	PSP-PI	PSP-OM	PSP-P	PSP-CBS	PSP-FTD	Unclassified
Diagnosis of PSP in first clinical record	26.2	66.7$^{\#\#}$	16.7	66.7$^{\#}$	5.3**	0.0*	10.0*	38.5
Diagnosis of PSP in last clinical record	70.0	100.0$^{\#\#\#}$	77.8$^{\#}$	100.0$^{\#}$	31.6***	57.1	33.3	84.6$^{\#}$
NNIPPS	28.0	62.5$^{\#\#\#}$	50.0$^{\#\#}$	14.3	0.0***	0.0*	0.0**	23.1
NINDS-SPSP possible	25.5	25.0	5.6	71.4	26.3	0.0	33.3	46.2
NINDS-SPSP probable	35.0	75.0$^{\#\#\#}$	77.8$^{\#\#\#}$	0.0	0.0***	0.0	0.0	7.7
NINDS-SPSP total	60.0	95.8$^{\#\#\#}$	77.8$^{\#}$	71.4	26.3***	0.0***	33.3***	53.3*

Frequency (%) of correct clinical diagnosis of all analyzed definitive PSP patients and of the patients subgrouped according to clinical predominance types: RS, Richardson's syndrome; PI, postural instability; OM, oculomotor; P, parkinsonism; CBS, corticobasal syndrome; FTD, frontotemporal dysfunction; Unclassified, patients not fitting any of these predominance types. Fulfillment of the NNIPPS, NINDS-SPSP possible, NINDS-SPSP probable, or NINDS-SPSP total (= possible or probable) criteria was verified by retrospective chart review.
Chi-squared test and Bonferroni adjustment: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, vs. RS; $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, vs. PSP-P.

and the NNIPPS criteria[31] for the clinical diagnosis of PSP was verified retrospectively for each of the first 10 years after disease onset and for the final ante mortem record. The NINDS-SPSP criteria for "possible" and "probable" PSP[26] as well as a combination of both, referred to as NINDS-SPSP "total," were separately analyzed.

Results

Characteristics of All Cases

For 101 of 178 originally identified cases, detailed documentation of the demographic and clinical features throughout the entire course of the disease was available. In one case, the diagnosis was changed to corticobasal degeneration on central neuropathological verification, because of the presence of astrocytic plaques. In all other cases, the diagnosis of PSP was confirmed, leaving 100 PSP cases for our final analysis. The demographic data of these 100 patients is given in Table 1.

On average, 18 of the 35 predefined symptoms were stated as being either present or absent in the patient files. The year of onset was available for 83% of all symptoms being reported as present. A report on presence or specifically stated absence of supranuclear gaze palsy and falls was available in 90% of cases. Of those cases having a positive report of supranuclear gaze palsy or falls, the year of onset was available in 94% and 96% of cases, respectively.

Clinical Diagnosis

The percentage of patients correctly diagnosed during their lifetime or fulfilling formal diagnostic criteria is shown in Table 2; the latency from disease onset to diagnosis is shown in Table 3. Diagnostic accuracy for PSP-Richardson's syndrome (PSP-RS) and PSP-Oculomotor (PSP-OM) subtypes was good both early in disease course (2 years) and ever (by final clinical record), whereas PSP-P and PSP-FTD had a significantly lower percentage of cases correctly diagnosed both early in disease and ever. Additionally, PSP-P had the longest time to correct diagnosis, and PSP-RS had the shortest time. The most common misdiagnosis was Parkinson's disease in 12% of the cases. Other clinical diagnoses included corticobasal syndrome (6%), multiple system atrophy (4%), Alzheimer's dementia (4%), frontotemporal dementia (3%), Pick's

TABLE 3. Diagnosis of PSP: Latency

	All	PSP-RS	PSP-PI	PSP-OM	PSP-P	PSP-CBS	PSP-FTD	Unclassified
Clinical diagnosis	4.9 ± 0.6 [1-10]	2.3 ± 0.7 [1-3]$^{\#\#\#}$	4.3 ± 0.5 [3-5] $^{*,\#\#\#}$	6.0 ± 0.0 [6-6]$^{\#\#\#}$	10.0 ± 0.0 [10-10]***	7.0 ± 0.0 [7-7]$^{\#\#\#}$	4.0 ± 0.0 [4-4]$^{\#\#\#}$	5.0 ± 1.3 [1-8]$^{\#\#\#}$
NNIPPS	2.7 ± 0.2 [1-6]	1.8 ± 0.2 [1-3]	3.4 ± 0.2 [3-5]***	4.0 ± 0.0 [4-4]*	-	-	-	4.0 ± 1.0 [3-6]***
NINDS-SPSP possible	5.0 ± 0.8 [1-19]	1.0 ± 0.0 [1-1]$^{\#\#\#}$	4.0 ± 0.0 [4-4]$^{\#}$	2.6 ± 0.6 [1-4]$^{\#\#\#}$	11.0 ± 2.2 [7-19]***	-	5.5 ± 1.3 [3-9] $^{*,\#\#}$	4.7 ± 0.6 [3-6] $^{*,\#\#\#}$
NINDS-SPSP probable	3.2 ± 0.4 [1-14]	1.8 ± 0.2 [1-3]	4.9 ± 0.8 [3-14]***	-	-	-	-	3.0 ± 0.0 [3-3]
NINDS-SPSP total	4.0 ± 0.5 [1-19]	1.6 ± 0.1 [1-3]$^{\#\#\#}$	4.9 ± 0.8 [3-14] $^{***,\#\#\#}$	2.6 ± 0.6 [1-4]$^{\#\#\#}$	11.0 ± 2.0 [7-19]***	-	5.5 ± 1.3 [3-9]$^{\#\#\#,**}$	4.4 ± 0.5 [3-6]$^{\#\#\#,**}$

Latency (years, mean ± SEM [range]) from disease onset to correct clinical diagnosis of all analyzed definitive PSP patients and of the patients subgrouped according to clinical predominance types: RS, Richardson's syndrome; PI, postural instability; OM, oculomotor; P, parkinsonism; CBS, corticobasal syndrome; FTD, frontotemporal dysfunction; Unclassified, patients not fitting any of these predominance types.
Fulfillment of the NNIPPS, NINDS-SPSP possible, NINDS-SPSP probable, or NINDS-SPSP total (=possible or probable) criteria was verified by retrospective chart review.
ANOVA followed by post hoc LSD test: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, vs. RS; $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, vs. PSP-P.

disease (3%), depression (3%), essential tremor (3%), and vascular encephalopathy (2%).

Clinical Characteristics Throughout the Disease

The signs and symptoms predominant during the first 2 years of disease are reported in Supplemental Data Table S3. The symptoms occurring during the entire clinical course are reported in Supplemental Data Table S4. The latency from disease onset to first record of the symptoms is reported in Supplemental Data Table S5.

Principal Component Analysis

Three approximate groups were generated by principal component analysis, as shown in Figure 1A. The variables grouped together in each characteristic set were: set 1 = falls, supranuclear gaze palsy, bradykinesia; set 2 = tremor, resting tremor, asymmetry at onset; set 3 = frontotemporal dysfunction, cognitive dysfunction. A cluster analysis of clinical variables confirmed this grouping of variables as reasonable (Fig. 1B). This suggests that sufficient information was incorporated into the first two components of the principal components analysis to determine groupings of characteristics between patients. This mathematical approach confirmed the existence of the three major previously described phenotypical subgroups of definite PSP, namely PSP-RS, PSP-P, and PSP-FTD, in our cohort. However, this explained only 37.4% of the variance seen in all cases.

Classification According to Predescribed Phenotypes

Based on previous descriptions of definite PSP cases with clinical presentations other than RS, definitions of subgroups have been proposed and termed PSP-phenotypes.[32] A graphical representation of these phenotypes is shown in Figure 1C and their definitions in Supplemental Data Table S2, left column. Most of these phenotypes were rare in their pure form. Importantly, 17% of all cases showed overlapping features between these predescribed phenotypes (Fig. 1D). Furthermore, 37% of patients remained unclassified because they did not fit in any phenotype, either because of the absence of particular cardinal features (80%), or because of the presence of exclusion criteria (20%).

Classification According to the Clinical Features Predominating During the First 2 Years

We classified patients according to the predominant clinical features during the first 2 years of the disease and termed these groups "PSP-predominance types." Early predominant features observed in our and previous reports of definite PSP[1-28,32] were oculomotor (OM) dysfunction, postural instability (PI), the combination of which defines RS, parkinsonism (P), frontotemporal dysfunction (FTD), progressive non-fluent aphasia (PNFA), corticobasal syndrome (CBS), pure akinesia and gait freezing (PAGF), and cerebellar (C) dysfunction. A graphical representation of the concept is shown in Figure 1E, and their definitions in Supplemental Data Table S2, right column. The concept of predominance types does not preclude an overlap of various clinical features at later disease stages, as opposed to the predescribed PSP phenotypes. For clear distinction, PSP-predominance types are written in italic; PSP-phenotypes, in roman.

Distribution of the Patients in the Predominance Types

The distribution of these predominance types is shown in Figure 1F. *PSP-RS* was represented by only 24% of all cases. *PSP-PAGF, PSP-PNFA,* and *PSP-C* predominant cases were not present in our series. Freezing of gait was reported in 4% of our cases during the first 2 years, but at the same time, these cases showed other prominent features and thus were included in the *PSP-RS, PSP-PI,* and *PSP-P* groups. PNFA was present in 16% of all patients throughout the clinical course and in 5% during the first 2 years of disease. In the latter, FTD or early CBS signs were prominent; therefore, these were included in the *PSP-FTD* or the *PSP-CBS* groups. A clinically heterogeneous group, showing various combinations of cerebellar, subcortical, or cortical symptoms during the first 2 years, remained unclassified (13%). Interestingly, the most common symptom of the unclassified cases was dysarthria, which was present in 36% during the first 2 years of disease and in all cases at final record. Most unclassified cases developed supranuclear gaze palsy (90%) and falls (85%) later in the course, and 11 of these 13 patients were diagnosed clinically as PSP at final record.

Demographic Data of the Predominance Types

The demographic data for each predominance type is given in Table 1. A significantly longer survival time was seen in *PSP-P* patients compared with all other groups ($P < 0.001$ compared with *PSP-RS, PSP-PI,* and *PSP-FTD*). PSP-P were significantly older at death than all other subtypes ($P < 0.001$ compared with *PSP-RS* and *PSP-OM*).

Evolution of Clinical Features and Survival of the Predominance Types

The temporal evolution of key clinical features and cumulative mortality are shown in Figure 2A–H.

Clinical Diagnosis and Fulfillment of Clinical Criteria in the Predominance Types

Frequency of and latency to clinical diagnosis for the predominance types are shown in Tables 2 and 3.

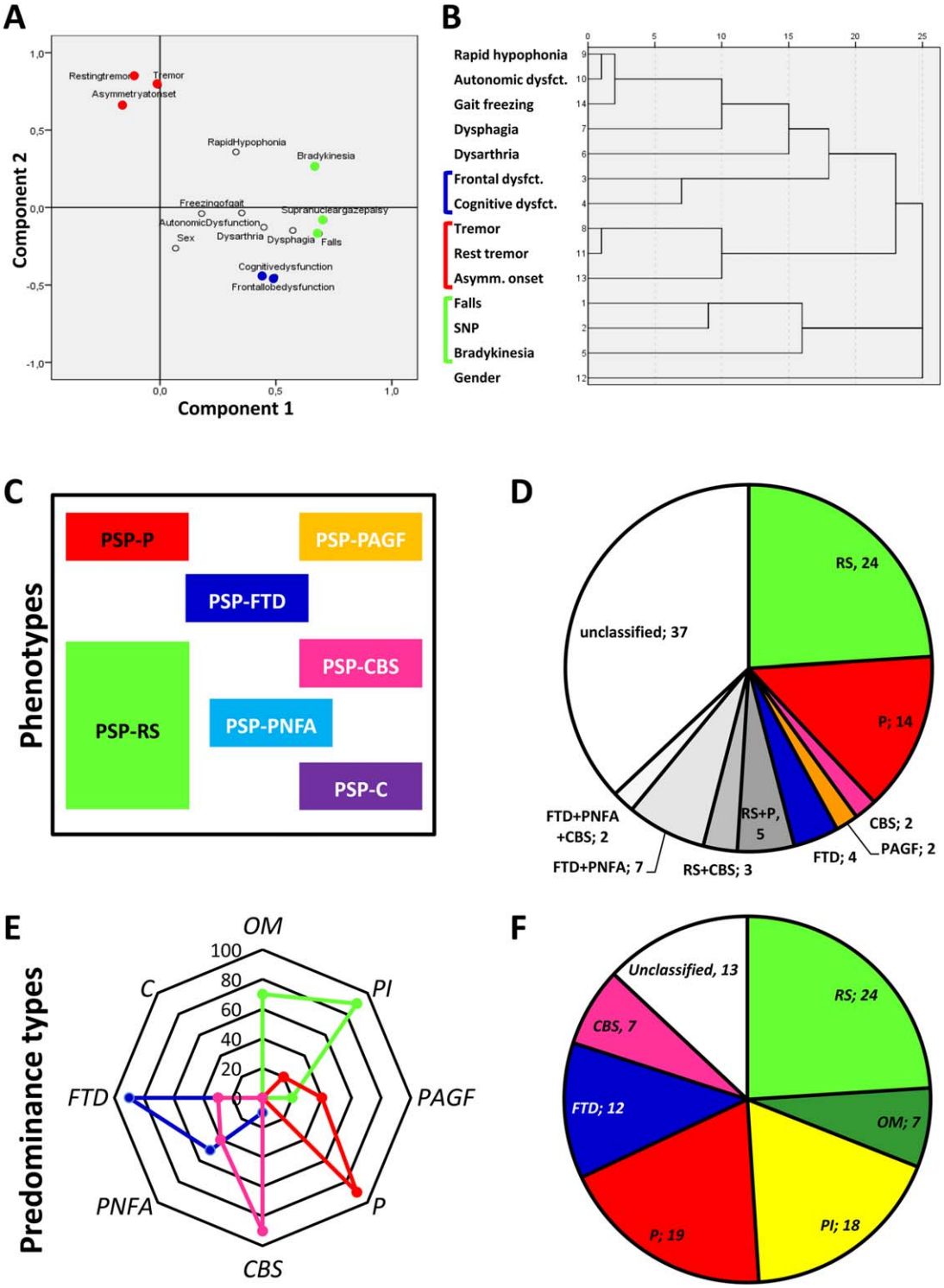

FIG. 1. (**A**) Plot of factors for components 1 and 2 derived from factor analysis. (**B**) Hierarchical cluster analysis of clinical variables: dendrogram using average linkage between groups: Both factor and cluster-analysis identify three sets of variables: Set 1: Falls, supranuclear gaze palsy, bradykinesia (green); Set 2: Tremor, resting tremor, asymmetry at onset (red); Set 3: Frontal lobe dysfunction, cognitive dysfunction (blue). (**C**) Disease concept dissecting the neuropathological disease entity PSP into different clinical "phenotypes" (modified from Josephs and Duffy[23]). (**D**) Classification of the N = 100 definitive PSP cases from our series according to the "phenotypes" model. Most phenotypes are rare in their pure form; many cases show a mixed picture with features of more than one phenotype; many cases remain unclassified. (**E**) Alternative disease concept, viewing PSP as entity with a broad clinical spectrum, defined by a set of cardinal features, which can predominate in the early clinical course ("predominance types"). C, cerebellar; CBS, corticobasal syndrome; FTD, frontotemporal dysfunction; OM, oculomotor; P, parkinsonism; PAGF, pure akinesia with gait freezing; PI, postural instability; PNFA, progressive nonfluent aphasia. Numbers from 0 to 100 indicate increasing symptom severity. Colored lines are examples for typical patients: green = PSP-RS (Richardson's syndrome), red = PSP-P, pink = PSP-CBS, blue = PSP-FTD. (**F**) Classification of the *N* = 100 definitive PSP cases from our series according to the "predominance types" model.

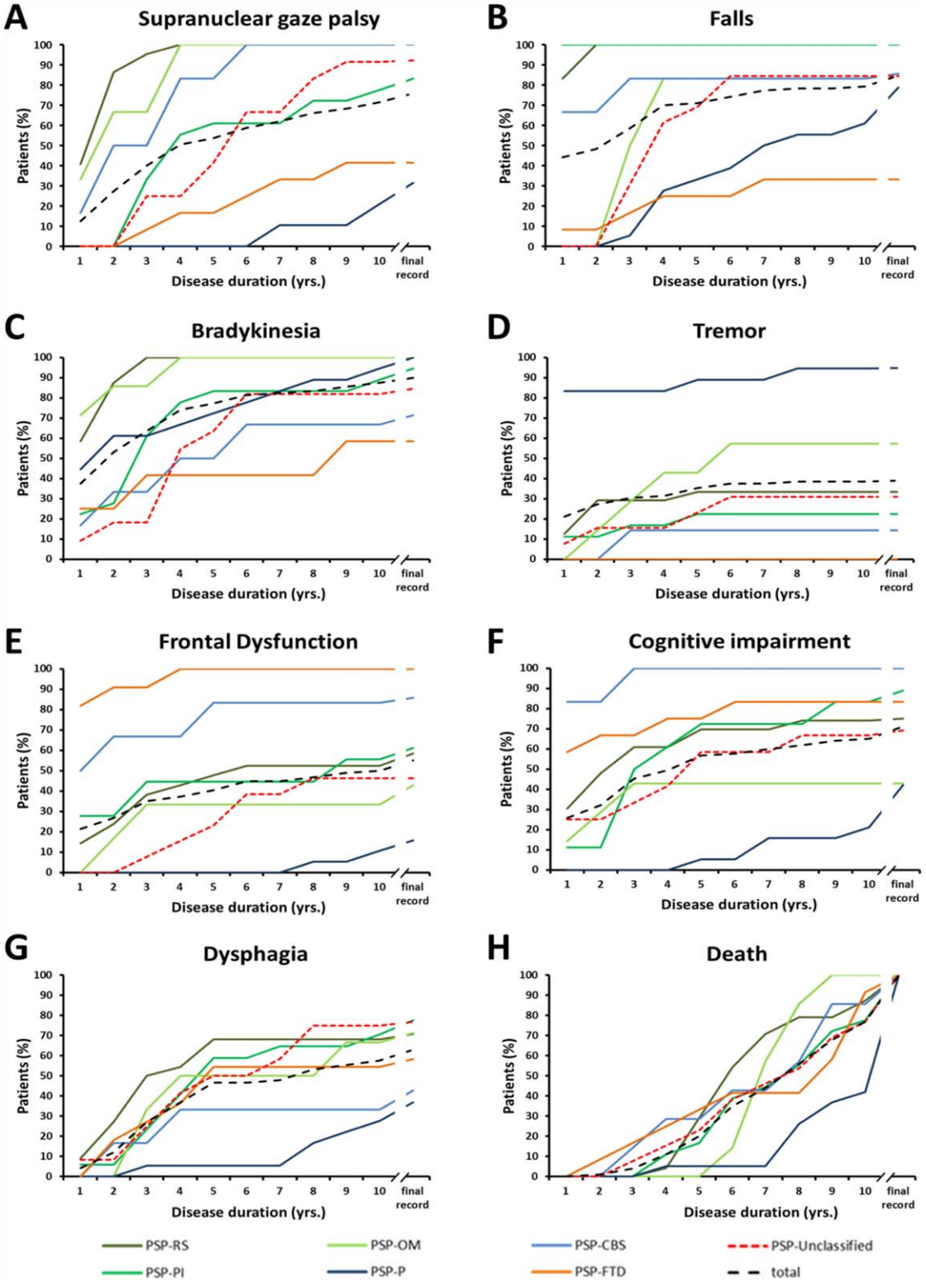

FIG. 2. Frequency of important clinical features as a function of time after disease onset in the different PSP-predominance types in the N = 100 definitive PSP cases from the present series.

Sixty-six percent of the cases of this cohort had been included in our previous analysis of the accuracy of the NINDS-SPSP and NNIPPS diagnostic criteria.[27]

Discussion

We assessed the phenotypic spectrum in a multicenter cohort of 100 autopsy-confirmed PSP patients. Our

results depend on an elaborate retrospective chart review of comprehensive medical files. Evidently, the data quality is limited by the lack of standardized prospective clinical assessment and recording. Because of the brain bank bias for diagnostically difficult or atypical cases and the exclusion of cases with inadequate clinical notes, this series is useful to demonstrate the phenotypic range of PSP, but the relative frequencies of the various phenotypes in this series may not be a valid reflection of those in the real world. Although the contributing centers of this series are mainly known for their expertise in movement disorders, we found an unexpectedly low frequency of cases presenting with PSP-RS and PSP-P. An unbiased sampling approach might therefore even further stress the importance of nonmotor PSP presentations. Despite all given limitations, we provide here the first quantitative description of the relative distribution and comparative natural history of clinical phenotypes of definite PSP in a large multicentric cohort. The most striking observation was that RS, considered to be the classical presentation of PSP, accounted for only 24%, whereas 76% had a clinical presentation considered to be "atypical."

Consistent with previous reports,[2-28,30,32] many of our cases had no or late onset of supranuclear gaze palsy or falls. During the first 2 years of disease, fewer than one third exhibited supranuclear gaze palsy and only approximately half had falls. Many cases presented with atypical signs, some of which are considered exclusion criteria for the clinical diagnosis of PSP,[26,31] such as rest tremor or cerebellar signs.

Principal component analysis confirmed three clinical constellations, namely 1) oculomotor dysfunction and falls (ie, RS), 2) parkinsonism, and 3) frontal and cognitive dysfunction, as the three more common clinical presentations of PSP (Fig. 1A, 1B).[2,20] However, they explained only 37% of the clinical variance in our cohort. The less common phenotypes of CBS, PAGF, and PNFA were also present in our cohort.

The phenotypic spectrum of PSP may be even broader than previously reported. This variability extends beyond the existing strictly defined phenotypes that were present only in 46% of our study population. This implies that the attempt to split the disease into distinct phenotypes with strict inclusion and exclusion criteria only captures the extremes of the phenotypic spectrum of PSP, but not its wide variability. As such, this may not be the ideal approach to increase sensitivity in diagnosing PSP.

We therefore studied the predominant clinical features in the first 2 years of the disease, abandoning rigorous exclusion criteria with regard to the further course. The most common PSP-predominance types were *PSP-RS, -PI, -OM, -P, -FTD,* and *-CBS*, capturing almost the entire population (87%), whereas many of these patients developed other features later in the disease course. Thirteen cases remained unclassified; most of those presented mainly with early postural instability (30% during the first 2 years) and bulbar dysfunction (45% during the first 2 years). Further studies will be needed to determine whether there is indeed a "*bulbar*" predominance type of PSP.

Acknowledging the high frequency of the non-RS presentations in our series and the low sensitivity of the available diagnostic criteria for these cases, we suggest that this broad phenotypic spectrum be taken into account in the clinical diagnostic criteria for possible PSP, similar to the recent proposal for the diagnostic criteria of corticobasal degeneration.[33] However, the clinical criteria for probable PSP may in our opinion remain largely unchanged, because of their high specificity.[26,27,34] Additionally, no prospective, comparative studies between cohorts with different pathologies (CBD, FTD, and so forth) are currently available.

In terms of prognosis, the mildest clinical course was observed in *PSP-P*, as suggested previously.[2,32] After 10 years, *PSP-P* patients had the lowest frequency of supranuclear gaze palsy, frontal dysfunction, cognitive decline, and dysphagia, and they survived significantly longer than patients of any other predominance type. Dysphagia, predisposing for aspiration pneumonia, developed simultaneously among the groups, with the exception of the *PSP-CBS* and *PSP-P* groups, who became dysphagic only late in the disease course. Cumulative mortality after 5 years was approximately 30% in *PSP-RS, PSP-CBS,* and *PSP-FTD*, but only in 5.3% *PSP-P* and 0% in *PSP-OM*. These data suggest that a stratification of PSP cases according to the symptoms present in the first 2 years may allow clinically relevant predictions about individual prognosis.

In summary, based on the presented clinical observations in 100 cases recruited in a multicentric, multidisciplinal setting, we demonstrated an extensive clinical diversity of definite PSP. This investigation is the first to estimate the distribution and natural history of different phenotypes of PSP. On the basis of the reported observations, we propose a clinical disease model, which comprehensively captures the clinical diversity and allows important prognostic predictions. Given the limitations of the retrospective nature of this study, a prospective multicentric cohort study to validate this disease concept and a revision of the clinical criteria for the diagnosis of PSP to incorporate the "atypical," or *non-RS* predominance types, are underway. ■

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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.