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Predictors of survival in a series of clinically diagnosed progressive supranuclear palsy patients

Claudia dell'Aquila, Stefano Zoccolella, Valentina Cardinali, Michele de Mari, Giovanni Iliceto, Bruno Tartaglione, Paolo Lamberti, Giancarlo Logroscino*

Department of Basic Medical Sciences, Neurosciences and Organs of Senses, University of Bari, Piazza Giulio Cesare, 9, 70124 Bari, Italy

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ABSTRACT

Background: Investigations into prognostic factors in progressive supranuclear palsy have shown conflicting results. We performed a retrospective study in order to identify clinical predictors of survival in clinically diagnosed progressive supranuclear palsy patients referred to our centre.
Methods: Data on medical history, survival and five clinical disability milestones (inability to walk unassisted, unintelligible speech, severe dysphagia, dementia and institutionalization) were collected from outpatients' medical records and by a telephone interview to caregivers. Patients were subdivided into Richardson's syndrome and PSP-Parkinsonism according to symptoms during the first 2 years of disease. Survival was analyzed by the Kaplan–Meier method and Cox regression analysis.
Results: Forty-three consecutive patients were enrolled (86% Richardson's syndrome). Motor disturbances were the most frequent symptoms of onset. During the follow-up, 60.5% of patients died after a median survival of 7.1 years (2.2–18). Older age at onset (>63) (HR 2.8; 95% CI: 1.3–5.7; $p = 0.007$), early dysphagia (HR 2.3; 95% CI: 1–5.3; $p = 0.05$) and early cognitive deficits (HR 3.6; 95% CI: 1.6–8.2; $p = 0.002$) were predictors of shorter survival. Compared to PSP-Parkinsonism patients, Richardson's syndrome patients had shorter survival and higher mortality risk although not statistically significant (HR 3 95% CI: 0.9–9.9; $p = 0.07$). Seventy-seven percent of patients developed severe disability during follow-up: shorter time to the first clinical disability milestone predicted shorter survival (HR 7.8; 95% CI: 2.3–26; $p = 0.0008$). Conclusions: early dysphagia, cognitive impairment, older age at onset, and time to disability were predictors of shorter survival; Richardson's syndrome had a less favorable course than PSP-Parkinsonism. Clinical milestones should be considered as possible endpoints in future clinical trials.

1. Introduction

Progressive Supranuclear Palsy (PSP) is the second most common neurodegenerative parkinsonism after Parkinson's disease (PD) and is associated with a higher degree of disability and shorter survival than PD.

PSP prevalence is 6.4 cases per 100,000 and median survival varies from 5 to 10 years from disease onset [1].

The clinical picture of PSP includes parkinsonism, early postural instability, falls, supranuclear gaze palsy, pseudobulbar symptoms, cognitive impairment and personality changes [2]. Recently, two major clinical subtypes of PSP have been described: 1) Richardson's syndrome (RS), characterized by the typical features listed above; 2) PSP-Parkinsonism (PSP-P) characterized by asymmetry of parkinsonian symptoms, tremor and a temporary response to L-dopa [3].

Pure akinesia and gait freezing (PAGF) and a frontotemporal dementia-like picture have also been associated with PSP pathology [4,5]. The natural history of PSP has been described in just a few studies, with different designs and providing contrasting results. Age at onset [6–8,22], early falls [8,9], dementia [7,9], bulbar symptoms [8], degree of disability [10], clinical phenotypes and shorter time to disability [11] have all been indicated as possible predictors of survival.

To date, no effective treatment is available for PSP [12–14].

The accurate identification of prognostic factors and disease course are key for better designing future clinical trials.

This study aims to characterize the natural history of PSP and to find predictors of shorter survival including relevant disability milestones.

* Corresponding author. Tel.: +39 0805592250; fax: +39 0805478532.
E-mail address: giancarlo.logroscino@neurol.uniba.it (G. Logroscino).

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2. Methods

Patients were identified at the Movement Disorders Unit and at the Unit for Diagnosis and Therapy of Dementia at Bari University from 1998 to 2008.

All patients fulfilling the Neurological Diseases and Stroke-Society for PSP (NINDS-SPSP) clinical diagnostic criteria for probable and possible PSP [15] were included in the study.

All patients had been examined at least once by a neurologist with expertise in movement disorders.

2.1. Data collection

Data were obtained from outpatients' medical records; information on age, date and symptoms of onset, neurological exam and symptoms reported at first visit and at follow-up, treatment response and date of death were recorded.

Information on the occurrence and time of onset of 5 disability milestones (inability to walk unassisted, unintelligible speech, severe dysphagia, dementia and institutionalization) were abstracted from medical records. These milestones were selected considering that all were likely to require further medical attention and were associated with loss of patient autonomy.

Data collection was completed through a telephone interview to the principal caregiver, in order to integrate medical records information, especially for patients lost at clinical follow-up.

Clinical condition (dead/alive) at the end of the study period was determined for each patient. Date of death was obtained either from medical records ($n = 10$), caregiver interview ($n = 9$) or from the registry office ($n = 7$).

Clinical features were entered as present or absent at onset, within the first 3 years of disease and at first visit at our centre; unreported symptoms and signs were considered as absent.

The interval of 3 years was established as the shortest interval from disease onset for which each patient had a reportable follow-up clinical evaluation.

Where medical records and caregiver interview were in conflict, the information obtained from medical records was used.

Definitions were as follows: 1) age at onset: age when the first clinical symptoms attributable to PSP appeared, as referred by patients or caregivers at first visit; 2) date of diagnosis: date of the first visit when PSP was suspected; where patients had already been diagnosed with PSP before their first visit to our centre, the date of first diagnosis was used.

3) Disease duration from time of onset: interval from disease onset to death or to the end of follow-up (30 June 2008); 4) Disease duration from time of diagnosis: interval from diagnosis to death or to the end of follow-up (30 June 2008); 5) follow-up duration: interval from the first visit to our centre until death or until the end of the study period.

Dementia was diagnosed when a cognitive impairment in more than one area of cognition with consequent permanent disability in performing activities of daily living (DSM IV REV) was present [16].

According to clinical features at onset and during the first 2 years of disease, patients were subdivided into PSP-P like and RS-like phenotype as described by Williams et al. [3].

2.2. Statistical analysis

Univariate comparison of demographic and clinical variables used *t*-test and chi-square when appropriate. Survival time was calculated for all deceased patients.

Patients were stratified according to median age at onset, presence or absence of each clinical feature at onset or within the first 3 years of disease and according to clinical phenotype.

For each milestone of disability, the latency of appearance from disease onset was calculated: patients were then stratified according to median latency of appearance of the first milestone and presence or absence of each clinical milestone.

Survival curves for each patient subgroup were estimated by the Kaplan–Meier method and differences in survival were measured by the log rank test, using death at 10 years as the censored variable. Survival time was measured from disease onset.

The risk of death for subgroups was calculated using the Cox proportional hazard model in univariate analysis; variables associated with a change in risk of death were entered in the multiple regression model. Significance was tested at the 5% level. There were no missing values for the variables included in the analysis.

The study was approved by the local ethics committee.

3. Results

During the study period, we identified 43 patients (53.5% males) fulfilling the NINDS-SPSP clinical diagnostic criteria for probable (33) and possible (10) PSP. Clinical and demographic characteristics of patients are summarized in Table 1.

Six (14%) patients were classified as PSP-P, while 37 (86%) were classified as RS. No differences were found in sex distribution, degree of diagnosis certainty (possible or probable) and age at onset between the RS and PSP-P groups; however, RS patients had shorter disease duration and follow-up and underwent a significantly lower number of visits during follow-up compared to PSP-P patients (Table 1).

3.1. Symptoms at onset

Motor symptoms, especially walking problems and unsteadiness, were the most frequently reported symptoms at onset (79.1%) and were described as asymmetric only in 11.6% of patients. Neurobehavioral problems were referred by 44.2% of patients and included mood or behavioral symptoms (30%), such as depression and apathy, and memory impairment (30%). Bulbar symptoms occurred in 25% of patients, while only 2 patients complained of oculomotor impairment. Tremor was the presenting symptom in 16% of patients. Urinary disturbances, extra-axial dystonia and sleep disturbances were rarely reported.

3.2. Clinical features at first visit

Bradykinesia, gait disorders and postural instability were referred by more than 90% of patients at their first visit, while falls by more than 80%. Postural instability was recorded as "severe" in 53.8% of patients and falls were reported to be frequent in 60% of cases; two patients were wheelchair-bound at first visit. Oculomotor deficits were observed in 88% of patients and consisted in slow or hypometric vertical saccades (37.8%), vertical supranuclear gaze palsy (29.8%) and complete gaze palsy (13.5%).

Table 1
Demographic and clinical characteristics of patients with PSP.

	PSP ($n = 43$)	RS ($n = 37$)	PSP-P ($n = 6$)	
M/F	23/20	19/18	4/2	n.s.
Age at onset[a]	62.8 ± 6.7	63.2 ± 6.7	60.4 ± 7.8	n.s.
Interval between onset/diagnosis (years)[b]	3.1 (0.4–8)	3.0 (0.4–6)	5.0 (2.9–8)	$p = 0.01$
Interval between onset/first visit (years)[b]	3.2 (0.4–13)	3.2 (0.4–12.9)	3.4 (0.8–8)	n.s.
N. of visits[a]	5.2 ± 6	4.3 ± 4	10.2 ± 10	$p = 0.03$
Disease duration from onset (years)[b]	7 (1.2–18)	6.7 (1.2–14.9)	10.2 (4.9–18)	$p = 0.02$
Disease duration from diagnosis (years)[b]	4 (0.06–10.3)	3.7 (0.06–10.3)	6.1 (0.4–9.9)	n.s.
Follow-up duration (years)[b]	3.7 (0.1–11.3)	3.4 (0.1–7.7)	7.3 (0.6–11.3)	$p = 0.002$
Deceased (%)	60.5%	62.2% (23)	50% (3)	n.s.
Age at death[a] ($n = 26$)	69.6 ± 6.2	69.8 ± 6.0	68 ± 10	n.s.
Median survival (years)[b]	7.1 (2.2–18)	6.8 (2.2–15)	10.5 (7.8–18)	$p = 0.02$

Comparison is made between RS and PSP-P patients.
[a] Mean ± standard deviation.
[b] Median (range).