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PROGRESSIVE SUPRANUCLEAR PALSY IN A SAMPLE OF BRAZILIAN POPULATION

Clinical features of 16 patients

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ABSTRACT - Progressive supranuclear palsy (PSP) is an uncommon disorder characterized by marked postural instability, vertical gaze abnormalities and axial rigidity. The purpose of this study is to report the clinical features of 16 consecutive subjects seen over a 10-year period at a Movement Disorders Clinic. These subjects fulfilled criteria for probable PSP namely those of the National Institute of Neurologic Disorders and Stroke (NINDS) and the Society for PSP (SPSP). This patient-group represented 2.1% of all degenerative parkinsonians observed and the mean age of onset of the disease was 64.7 years (sd = ± 7.2). Postural instability with falls was the most frequent initial feature presented in PSP patients (62.5%). The hallmark of the disease, the supranuclear vertical gaze palsy, appeared after 2.3 years of disease onset, and only 12.5% had such manifestation at the first evaluation. Transient tremor was observed with a relatively high frequency in this group (44%), but only 19% had rest tremor. Chronic dacryocystitis, probably related to a paucity of blinking, was observed in two patients as an inaugural manifestation. In the first evaluation, only 19% of the 16 patients were diagnosed as probable PSP. The mean interval prior to the final diagnosis was 2.4 years.

KEY WORDS: progressive supranuclear palsy, parkinsonism, movement disorders, chronic dacryocystitis.

Paralisia supranuclear progressiva em uma amostra da população brasileira: aspectos clínicos de 16 pacientes

RESUMO - A paralisia supranuclear progressiva (PSP) é entidade incomum, caracterizada por severa instabilidade postural, anormalidades do olhar conjugado vertical e rigidez axial. O propósito desse estudo é apresentar os aspectos clínicos de 16 pacientes consecutivamente atendidos em período de 10 anos em uma unidade especializada no atendimento de movimentos anormais. Tais pacientes preencheram os critérios para diagnóstico de PSP provável, de acordo com aqueles recomendados pelo NINDS (EUA) e pela SPSP. O grupo representou 2,1% de todos os casos de parkinsonismo degenerativo atendidos naquele período. O início das primeiras manifestações se deu, em média, aos 64,7 anos (± 7,2). Instabilidade postural inaugurou o quadro na maioria dos casos (62,5%) e a manifestação mais característica da doença, a paralisia supranuclear vertical do olhar conjugado, esteve presente inicialmente em apenas 12,5%. Ela só foi observada após 2,3 anos, em media, de evolução da moléstia. Tremor transitório foi observado com frequencia relativamente alta (44%), porém apenas 19% apresentavam tremor de repouso. Sintomas iniciais sugestivos de dacriocistite crônica, provavelmente relacionada à pobreza de piscamento, foram observados em 2 casos. Na primeira avaliação, somente 19% dos pacientes foram diagnosticados como PSP provável e o intervalo médio para esse diagnóstico final foi 2,4 anos.

PALAVRAS-CHAVES: paralisia supranuclear progressiva, parkinsonismo, desordens do movimento, dacriocistite crônica.

Thirty-eight years ago, John Steele, Jerzy Olszewski and J. Clifford Richardson described nine patients[1,2] with a different form of clinical parkinsonism. The brains of four of these patients were submitted to a *post-mortem* study that showed a pattern of pathological abnormalities, completely different from that of classical Parkinson's disease. The clinical hallmarks of progressive supranuclear palsy (PSP) are: axial rigidity with postural instability frequently associated with falls and supranuclear vertical gaze palsy[1-12]. Despite the disease being seemingly easy to diagnose, this can sometimes prove difficult. Litvan et al.[9] found an unexpectedly high false positive PSP diagnosis, ranging from 15 to 50% when cases were

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Table 1. Ninds/Spsp criteria.

Mandatory inclusion criteria

Possible PSP

1. Gradually progressive disease onset with initial manifestation after the age of forty.
2. Supranuclear vertical gaze abnormalities with pursuit movements downwards or upwards with a restriction of less than 50% compared to normal, or the two following criteria: slowed vertical saccades and postural instability with falls in the first year of the disease.
3. There are no other entities that can explain the clinical manifestations as indicated by the exclusion clinical criteria.

Probable PSP

4. Obligatory presence of supranuclear vertical gaze palsy (upwards or downwards) and postural instability with falls in the first year of the disease.

Definite PSP

5. Possible or probable PSP with pathologic confirmation.

Auxiliary criteria

6. Symmetrical akinesia or rigidity, more proximal than distal
7. Abnormal neck postures, especially retrocollus
8. Poor L-dopa response
9. Early dysarthria and dysphagia
10. Early cognitive deficits, including at least two of the following: apathy, deficit of abstraction, poor verbal fluency, imitation behavior, frontal release signs.

Mandatory exclusion criteria

- Presence of recent encephalitis,
- Presence of alien hand syndrome, sensorial cortical deficits, frontal or temporo-parietal focal atrophy,
- Presence of hallucinations or delusions unrelated to L-dopa,
- Presence of Alzheimer's cortical dementia type,
- Presence of unexplained early and prominent cerebellar signs or dysautonomia,
- Presence of severe asymmetric parkinsonian signs,
- Presence of relevant structural neuroimaging abnormalities,
- Presence of Whipple disease confirmed by PCR.

presented blindly to six neurologists, whereas Rajput et al.[13] had no misdiagnosis of PSP in their prospective study.

With the aim of increasing the sensitivity and specificity of PSP clinical diagnosis, with no biological marker having been established, an international workshop was jointly sponsored by the National Institute of Neurologic Disorders and Stroke of the United States (NINDS) and the Society for PSP (SPSP). After this meeting, the resulting clinical consensual criteria were drawn up and divided into three groups: mandatory inclusion criteria, mandatory exclusion criteria and auxiliary criteria[14], wich are listed in Table 1.

According to Litvan[15], the clinical criteria for probable PSP have a high predictive value, high specificity but lower sensitivity. They are ideal for use in scientific studies, mainly in genetics, drug trials, and epidemiological analytical studies on PSP. The possible PSP criteria have a lower specificity but maintain high sensitivity, making early diagnosis easier. They are more useful for current clinical practice and descriptive epidemiological studies.

In Brazil, there had never been a study of a large number of PSP patients. Therefore, a survey based on probable PSP criteria was performed at the Movement Disorder Unit of the Department of Neurology of São Paulo University Medical School from 1987 to 1997. The objective of this study is to describe the main clinical manifestations, atypical features and possible different patterns of PSP in this group of Brazilian patients.

Table 2. Data on patients with PSP.

Patient	Age	Age at onset	Sex	Race
1	79	79	M	Afro -Brazilian
2	62	59	F	White
3	68	61	F	Afro -Brazilian
4	57	57	F	White
5	72	69	M	White
6	65	55	M	White
7	71	69	M	White
8	65	64	M	White
9	66	62	M	White
10	67	66	M	Afro -Brazilian
11	64	64	F	White
12	77	72	M	White
13	60	57	F	White
14	60	56	M	White
15	81	76	F	White
16	70	70	M	White

F, female; M, male.

METHOD

Sixteen patients who fulfilled the NINDS -SPSP criteria for probable PSP were studied. The following data was analyzed: sex, race, age at first evaluation, age at disease onset, first clinical manifestation, time-interval before detection of vertical gaze palsy, presence of tremors, presence of axial rigidity, pseudobulbar manifestations, staring facial expression, first diagnosis given, and time-interval before diagnosis of PSP. The assessment of this information was carried out retrospectively in seven cases and prospectively in the remaining nine. The presence of dementia was diagnosed according to DSM-IV criteria. Statistical analysis of relevant data was performed by the MINITAB software program and Anderson-Darling normality test.

The analysis of L-dopa response was performed in an open and uncontrolled study. The initial drug dosage regimen was 125 mg of L-dopa three times a day, being increased to the maximum level tolerated by the patient. The analysis of the L-dopa benefit was obtained by objective examination performed by a fully qualified movement disorder neurologist and, subjectively, by the patient's own impression. The drug's effectiveness was classified according to three different types of response: a) absence of response - no objective or subjective benefit; b) modest response - objective benefit without subjective benefit or *vice versa*; c) good response - objective and subjective benefits.

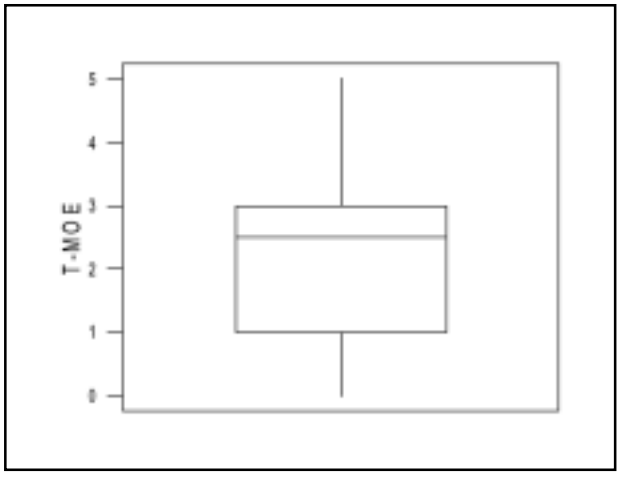

Fig 1. Box-plot of mean interval before vertical supranuclear gaze palsy appearance. T-MOE, interval (years) before appearance of supranuclear palsy.

Cranial computerized tomography or magnetic resonance imaging was performed in all cases to exclude frontal or temporo-parietal focal atrophy, one of the NINDS-SPSP mandatory exclusion criteria.

RESULTS

In this Movement Disorder Unit, PSP represented only 2.1 % of all cases of degenerative parkinsonism seen throughout the ten-year survey.

Table 2 depicts the following data: sex, age, race, age at first evaluation and age at onset. According to the analysis of there data, a slight predominance of male (1.6/1) and white (81%) individuals were observed in this group. The mean age at onset of this group was 64.75 years (sd = ± 7.28). The age was 66.28 years for men (sd = ± 7.30) and 62.33 years for women (sd = ± 7.20). Concerning race, the mean age of the Afro-Brazilian patients in this group was 68.67 years (sd = ± 9.29) while for whites was 63.85 years (sd = ± 6.87). The mean period of time before the detection or appearance of vertical gaze palsy (upwards and downwards) was 2.34 years (min:0/max:5) as depicted in Figure 1. We did not subject Case 3 to statistical analysis, because the patient had only sought neurological assistance after 7 years of the disease and so precise information pertaining to the manifestation of vertical gaze palsy could not be obtained.

The most common first clinical manifestation was postural instability with falls (n = 10;62.5%). Inaugural supranuclear vertical gaze palsy occurred in only two patients (12.5%). Curiously, two patients (12.5%) had ocular complaints, as probable inaugural manifestations, resembling chronic dacryocystitis. These patients were first seen by ophthalmologists but dacryocystography did not confirm the diagnosis of chronic dacryocystitis.

Table 3. Main clinical manifestations.

Patient	Initial manifestation	Interval before appearance of vertical gaze palsy	Presence of tremor	Presence of DSM-IV dementia	Presence of signs of pseudobulbar palsy and/ or disarthria
1	Postural instability + possible dacryocystitis	1 year	No	Yes	1 year
2	Depression	3 years	No	No	1 year
3	Postural instability + Bradykinesia	No data	No	No	1 year
4	Postural instability + tremor + dacryocystitis	2 years	Present in the beginning –rest and intentional tremor with 8 Hz	No	1 year
5	Depression + bradykinesia	3 years	No	No	1 year
6	Postural instability + pseudobulbar palsy + hand tremor	3 years	Presence of exacerbated physiological tremor at the beginning	No	1 year
7	Postural instability + vertical gaze palsy + slight hand tremor	Since the beginning	Presence of exacerbated physiological tremor at the beginning	No	1 year
8	Bradykinesia + vertical gaze palsy	Since the beginning	Rest tremor in lower limbs	No	1 year
9	Postural instability + pseudobulbar palsy	5 years	No	Yes	1 year
10	Postural instability	1 year	No	Yes	1 year
11	Postural instability + rigidity + hands tremor	2 years	Presence of exacerbated physiological tremor at the beginning	No	2 years
12	Bradykinesia + hands essential tremor	3 years	Present only at the beginning	No	3 years
13	Right leg rest tremor	2.5 years	Rest 4 Hz tremor only at the beginning	Yes	No
14	Postural instability	3 years	No	Yes	1 year
15	Dementia	4 years	No	Yes	2 years
16	Postural instability	2 years	No	No	2 years

Tremor was observed transiently in 44% (n=7) of the cases, whereas the typical rest tremor of Parkinson's disease was observed in only 19% (n=3). Axial rigidity was present in all patients, albeit not observed or reported as the first manifestation and progressive pseudobulbar palsy was observed in 94% of the patients being one of the initial manifestations in five (31%) cases. Only 37.5 % (n=6) of patients had dementia according to DSM-IV criteria, although only 33% (n=2) of this subgroup performed badly in recent memory tasks of the Mini-Mental State Examination[16]. The main clinical data are listed in Table 3.

Parkinson's disease was the most commonly given first diagnosis (n=6;31%) where PSP was considered as the first diagnosis in only 19% (n=3) of the cases. Excluding Case 3, the mean period of time before a suspected PSP diagnosis in this group was 2.13 years (sd= ±1.50).

All patients received L-dopa according to the method described above. No L-dopa related dyskinesia was observed and possibly only 13% of the patients experienced any temporary benefit with this drug. Thirty-one percent of the cases had a modest benefit whilst the majority (56%) had no benefit. Table 4 shows the data of first diagnosis, the time–interval before the diagnosis of PSP and the benefit with L-dopa.

Table 4. First Diagnosis And Time-interval Before Diagnosis of PSP.

Patient	First Diagnosis	Time-interval before probable PSP diagnosis according to Ninds (Years)	Benefit With L-dopa
1	Pharmacological parkinsonism secondary to flunarizine	0	Modest
2	PD	3	Absent
3	?	7	Absent
4	PD	2	Modest
5	PSP	0	Modest
6	?	3	Good
7	?	3	Modest
8	PSP	0	Absent
9	PD	1	Good
10	PD	1	Absent
11	?	2	Mild
12	PD	5	Absent
13	PD	3	Absent
14	?	3	Absent
15	PSP	4	Absent
16	NPH or CVD	2	Absent

PD, Parkinson's disease; PSP, progressive supranuclear palsy; NPH, normal pressure hydrocephalus; CVD, cerebrovascular disease.

DISCUSSION

The correct diagnosis of PSP is not a difficult task when the clinical profile of the disease is completely developed. However, at the early stage of the disease, it can be quite difficult to make a precise diagnosis. In this group, only 19% of the patients received the right diagnosis. In 54% of our patients, diagnoses other than PSP were given, and 85% of such cases were misdiagnosed as Parkinson's disease. These difficulties in diagnosis had already been reported by Litvan et al.[9].

Though it seems easy to identify PSP, the mean period of time before correct diagnosis was 2.4 years in the present study. Kristensen[7] reported that this period was 3.9 years in his series and Litvan et al.[8] found that the mean latency for diagnosis was 3.5 years. They estimated that only 50% of patients receive the correct PSP diagnosis at first evaluation.

The presence of a 4 Hz rest tremor is a typical sign, generally associated with Parkinson's disease, and some researchers considered that the presence of such tremors almost excludes the diagnosis of PSP[6]. However, the NINDS-SPSP criteria brought new concepts to diagnosis. The presence of rest tremor was not included as a major exclusion criteria. Despite such manifestations in PSP being quite rare, their very presence does not exclude the diagnosis of probable PSP. In our study, 3 patients (19%) had rest tremors, which were subsequently classified as typical parkinsonian tremors. This finding is similar to that of other series[3,4,8,11,17], except lower when compared with the Fénelon et al. study[5]. The presence of tremor might have significant impact on the difficulty in making the correct diagnosis. We observed that 50% of the cases initially diagnosed as Parkinson's disease, had tremors (Cases 4, 12 and 13). Moreover, 5 patients had tremors as one of the inaugural manifestations.

Good response to L-dopa is commonly related as an auxiliary criterion for the diagnosis of Parkinson's disease, but other diseases may also respond to this drug. Only 13% of our patients had a temporary good response to L-dopa, which was similar to another studies study[18].

Recently, Litvan et al.[10] observed a slight predominance of males in a group of patients with autopsy confirmation. This fact was also noted in this study, although for statistical confirmation, it would be necessary to compare that data with the sex distribution of the patients seen in our Movement Disorders Unit. The same problem occurred concerning race data: apparently, there is a predominance of white patients, but this has yet to be confirmed by statistical analysis. The mean age at onset of the disease is similar to that found in other studies, suggesting that PSP in Brazil follows the same pattern described worldwide. The same conclusion can be drawn concerning the most common first clinical manifestation where postural instability was also the main inaugural finding described in our survey.

In the present study, it is important to point out an uncommon finding: two of our patients looked first for opthalmological care with ocular clinical complaints resembling chronic dacryocystitis, even though this diagnosis was not confirmed by dacryocystography. We speculate that such complaints were probably related to the paucity of blinking commonly observed in PSP patients.

The classic study of Albert et al.[19], PSP was considered a paradigm of "subcortical dementia" since the lesions were concentrated at basal ganglia. Recent

evidence of damage at slices 2 and 3 of frontal lobe association cortex, along with presence of neurofibrillary PSP tangles (NFT) and deposits of tau protein in patients with clinical PSP[20-22] has shown that a "cortical" lesion is also present in many cases of PSP. DeBruin and Lees reported in a meta-analysis[5] that almost 40% of *post-mortem* confirmed cases of PSP had NFT in the cortex, but they did not find a clear link between the presence of cortical NFT and poor cognitive performance. In contrast, Forster et al.[23] found a correlation between the severity of dementia and cortical damage with cortical neuronal loss and gliosis, in PSP patients. In the present study, we also observed that dementia was not a prominent finding in PSP patients, whereas others[5] had observed 71% dementia, in their series of PSP patients. So that, we considered the term "subcortical dementia" inappropriate in many PSP patients with cognitive dysfunction.

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