Original Article

Subtypes of PSP and Prognosis: A Retrospective Analysis

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Abstract

Background: Progressive supranuclear palsy (PSP) is a clinically heterogeneous disease characterized by supranuclear gaze palsy and varying combinations of Parkinsonism, gait disturbances, postural instability, and fronto-limbic cognitive dysfunction. A major challenge in clinical diagnosis is the existence of subtypes whose clinical features overlap with those of other Parkinsonian disorders. **Objectives:** To categorize patients of PSP into its using the recently proposed movement disorder society criteria (2017) and to determine the prognosis of the PSP subtypes. **Methods:** Demographic and clinical data of patients diagnosed with PSP over a 21 year period were collected by review of medical records and categorized into its subtypes. Subtype prognosis was assessed from the interval between disease onset and attainment of the first of 5 clinical disability milestones namely wheelchair dependency, unintelligible speech, severe dysphagia, severe cognitive impairment, and urinary catheterization. **Results:** When categorized into subtypes, out of the 334 patients with PSP, PSP-RS predominated (72%), followed by PSP-parkinsonism (PSP-P) (13.5%), PSP-corticobasal syndrome (PSP-CBS) (5.1%), PSP-frontal (PSP-F) (4.2%), PSP-progressive gait freezing (PSP-PGF) (4.2%), PSP-postural instability (PSP-PI) (0.6%), and PSP-speech/language (PSP-SL) (0.3%). PSP-P reaches the milestones of wheelchair dependency, unintelligible speech, and dysphagia later than other subtypes. **Conclusion:** PSP-RS was the commonest and PSP-OM the rarest PSP subtype in our retrospective PSP cohort analysis. PSP-P had a better prognosis than all other subtypes of PSP. A large proportion of these cases would remain unclassified using NINDS-SPSP (1996) criteria.

Keywords: Diagnostic criteria, movement disorders criteria, prognosis, progressive supranuclear palsy, subtypes

Introduction

Progressive supranuclear palsy (PSP) is characterized by supranuclear gaze palsy and Parkinsonism which is often symmetrical, axial rigidity, gait disturbances, postural instability with early falls, and fronto-limbic cognitive dysfunction. The estimated prevalence of PSP is 6.4 per 100,000.[1] Pathologically it is characterized by hyperphosphorylated tau protein forming fibrillary aggregates (globose neurofibrillary tangles) in neurons and glia in areas such as cerebral neocortex, pallidum, subthalamic nucleus, substantia nigra, periaqueductal grey matter, superior colliculi, and dentate nucleus.[2] The gold standard for the diagnosis of "definite PSP" is the post-mortem neuropathology. However, in the clinical setting, the diagnosis of PSP is made using clinical diagnostic criteria. The major challenge in clinical diagnosis is the existence of subtypes of PSP whose clinical features overlap with those of other Parkinsonian disorders and neurodegenerative diseases which show neuropathological features of PSP. Recently, several PSP subtypes have been reported and they include PSP-RS,[3-5] PSP-P,[6,7] PSP-CBS,[8-10] PSP-F,[11-13] PSP-PGF,[14-16] PSP-SL,[17-19] PSP-PI,[20] PSP-C, and PSP-OM.[21-24] There is no reliable pathological or radiological biomarker to aid the diagnosis of these subtypes. The National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) criteria (1996) is commonly used but it doesn't consider the recent PSP subtypes.[25] The recent movement disorder society (MDS) criteria, 2017, enable the diagnosis of various PSP subtypes.[26] The prognosis is also likely to vary depending on the clinical subtype. Ante-mortem diagnosis and prognosis of PSP could become important when disease- and protein-specific neuroprotective therapies become available in future. The purpose of the present study was to categorize patients of PSP into its subtypes using the recently proposed MDS criteria and to study the frequency, clinical characteristics and prognosis of the PSP subtypes.

Methods

Study design

This retrospective study reviewed the case records of patients with a clinical diagnosis of PSP attending the movement disorders clinic of a University Hospital. The study was approved by the Institutional Ethics Committee.

Case selection

Hospital case records of patients with a diagnosis of "PSP", "evolving PSP", either at initial consultation or during

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follow-up from 1996 to 2017, were identified using a text word and diagnostic code search and screened for eligibility for the study. Only case records which had at least 2 years of follow-up data after initial diagnosis of PSP by experienced movement disorders specialists were included for analysis. Case records with clinical and/or radiological features suggestive of other atypical or secondary Parkinsonism were excluded.

Data collection

Demographic and clinical data of eligible patients with a diagnosis of PSP were collected PSP subtype diagnosis applied based on the MDS criteria for PSP (2017). A clinical data proforma was designed to record the presence or absence of clinical features when specifically mentioned, and if not, as not available, in the initial or any follow-up visits. Age of onset was defined as age at the time of the first reported symptom attributable to PSP and duration of disease as the interval between the ages of onset and diagnosis in the clinic. The clinical data collected included bradykinesia, rigidity, tremors and whether symmetric; falls and their time of onset, freezing of gait, memory dysfunction, apathy, change in personality, executive dysfunction, reduced verbal fluency, expressive speech difficulty, apraxia of speech, visuo-spatial dysfunction, apraxia (oro-buccal or limb), dystonia (axial/limb), dysarthria, dysphagia, autonomic dysfunction (urinary urgency with or without incontinence and orthostatic hypotension), pyramidal tract signs, vertical gaze palsy, slow vertical saccades, square-wave jerks, apraxia of eyelid opening, family history, and levodopa response (an improvement of >30%). Prognosis was assessed based on attainment of and, time to attain from disease onset the five clinical disability milestones chosen for the study. These included wheelchair dependency, unintelligible speech, dysphagia requiring percutaneous endoscopic gastrostomy (PEG), severe cognitive impairment, and urinary catheterization. The above information was collected from case records.

Statistical analysis

Demographic and clinical data were expressed as mean ± SD for continuous variables and Categorical variables were expressed as percentages. The continuous and categorical variables were compared among the groups using Chi-square test and Student's t-test. The interval from the first symptom to each clinical milestone was graphically assessed using Kaplan-Meier curves, and the curves from each subgroup were compared using log-rank test. Comparison of the number of patients and time to reach clinical milestones of disability among the PSP subtypes was performed using Chi-square test and Analysis of variance (ANOVA). *P* value of <0.05 was considered as statistically significant. Statistical analysis was performed using SPSS Statistical Software Package (release 22.0, SPSS Inc.; Chicago, Ill).

Results

334 patients were diagnosed as PSP-subtypes.

Demographic and clinical characteristics

The mean age at presentation was 63.9 ± 7.7 years (range: 41 − 86). Among the patients, 209 (62.2%) were male (male:female ratio = 1.6:1). The mean age of male patients at initial diagnosis was 65.2 ± 7.2 years (range: 48 − 86) and female patients, 61.9 ± 8.3 years (range: 41 − 80). The mean age at disease onset was 61.5 ± 7.8 (range: 40 − 85) years; it was 62.5 ± 7.3 years (range: 43 − 85) for male patients and 59.8 ± 8.3 (range: 40 − 79) years for females. The mean duration of illness was 2.5 ± 1.7 years (range: 1 − 13) and the mean duration of follow-up was 2.9 ± 1.5 years (range: 2-12).

PSP-subtypes: PSP-RS constituted the majority (*n* = 241; 71.7%) followed by PSP-P (n = 45; 13.4%), PSP-CBS (*n* = 17; 5.1%), PSP-F (*n* = 14; 4.2%), PSP-PGF (*n* = 14; 4.2%), PSP-PI (*n* = 2; 0.6%) and PSP-SL (*n* = 1; 0.3%). No case could be categorized as PSP-OM. The diagnosis at the initial visit in the majority of cases was PSP (*n* = 265; 79.3%) followed by Parkinson's disease (*n* = 36; 10.8%), frontotemporal dementia with parkinsonism (*n* = 14 cases; 2%), cortico-basal degeneration (*n* = 12; 3.6%), normal pressure hydrocephalous and vascular parkinsonism (*n* = 4; 1.2%), multiple system atrophy (*n* = 2; 0.6%) and primary gait freezing (*n* = 1; 0.3%). The common motor symptoms of PSP were bradykinesia (*n* = 329; 97.9%), postural instability (*n* = 315; 93.8%), falls (*n* = 281; 83.6%) and rigidity (*n* = 270, 80.4%). Tremor was the least common motor symptom (*n* = 108; 32.1%). Majority of patients had falls within 1 year of onset of symptoms (*n* = 190; 56.5%), 94 patients (28%) had falls within 3 years of onset, 31 patients (9.2%) had falls after 3 years of onset and 19 patients (5.7%) had no falls till their last follow-up.

Using NINDS-SPSP criteria, out of the 334 patient records, 120 (36%) were classified as probable PSP, 87 (26%) as possible PSP, and the remaining 127 (38%) were unclassifiable. Using the MDS Criteria (2017), 241 patients were categorized as Probable PSP-RS, 42 as Probable PSP-P, 14 as Probable PSP-F, 13 as probable PSP-PGF,17 as Possible PSP-CBS, 1 as possible PSP- PGF and 1 as possible PSP-SL (0.3%). 2 were suggestive of (s.o) PSP-P (0.6%) and 2 s.o PSP PI (0.6%). None was diagnosed as PSP-OM.

Attainment of clinical milestones of disability

Wheelchair dependency due to repeated falls was the most common and earliest milestone reached in all PSP patients (n = 292; 87.4%). The mean interval to its attainment was 4.4 ± 2.2 years (range: 1-23). A single patient had unintelligible speech, two needed urinary catheterization, one had severe dysphagia needing PEG, and another had severe cognitive impairment requiring assistance as the first milestone reached. The frequency of each disability milestones and duration of attainment from disease onset, at last, follow-up are shown in Table 1. 188 patients (56%) had one, 64 patients (19%) had two, 30 patients (9%) had three, six patients (2%) had four, and another six patients (2%) had reached all disability milestones at last follow-up. Forty patients (12%) had not reached any disability milestone.

Demographic and clinical characteristics of subtypes

This is depicted in Table 2. The ages at first visit ($P = 0.99$) and at disease onset ($P = 0.87$) did not differ significantly among the subtypes. PSP-P had a longer duration of illness compared to PSP-RS ($P = 0.001$), PSP-CBS ($P = 0.03$), PSP-F ($P = 0.005$) and PSP-PGF ($P = 0.03$). There was no significant difference noted among the other subtypes. PSP-P and PSP-F had significantly longer duration of follow-up compared to PSP-RS and PSP-PGF, and PSP-P cases were also significantly longer compared to PSP-CBS. There was no significant difference among other subtypes. The presence of tremor was highest in PSP-P (84.4%; $P < 0.001$) compared to other subtypes and least in PSP-RS (24.9%) and PSP-F (14.3%). The presence of rigidity was highest in PSP-RS (94.6%), PSP-P (97.8%) and PSP-CBS (94.1%) and less predominant in PSP-F (21.4%) and PSP-PGF (14.3%) cases ($P < 0.001$). Bradykinesia and postural instability were present to similar proportions in all groups. Falls within the first year of disease- onset was highest in PSP-RS (71.4%) and PSP-CBS (64.7%). It was less comparatively less common in PSP-P, PSP-F, and PSP-PGF ($P < 0.0001$). Falls within 3 years were common in PSP-F (64.3%) and PSP-PGF (57.1%) ($P = 0.003$). Falls after 3 years of onset of illness was seen in PSP-P (48.3%) ($P < 0.001$). Slow vertical saccades were more common in PSP-P and PSP-PGF ($P < 0.001$). Vertical gaze palsy was more common in PSP-RS and PSP-F cases ($P < 0.001$). Pyramidal signs were more common in PSP-RS and PSP-CBS cases ($P < 0.001$).

Table 1: Frequency of milestones reached and time to reach from onset by PSP patients ($n = 334$)

Milestones	Number of patients (%)	Duration from disease onset (years)* (range)
Wheelchair dependency due to repeated falls	294 (87.5%)	4.4 ± 2.2 (1- 23)
Unintelligible speech	40 (11.9%)	6.1 ± 2.7 (2- 15)
Severe dysphagia needing PEG	34 (10.1%)	5.6 ± 1.6 (2- 9)
Urinary catheterisation	85 (25.3%)	5.8 ± 3.1 (3- 25)
Severe cognitive impairment	11 (3.3%)	5.9 ± 2.3 (4- 11)

Abbreviation: PEG- Percutaneous endoscopic gastrostomy.* Mean ± SD (standard deviation)

Likely diagnosis of PSP subtypes based on NINDS-SPSP criteria (1996)

A total of 112 cases (46.5%) of PSP-RS would be diagnosed as Probable PSP and 74 (30.7%) would be diagnosed as possible PSP. The remaining 55 patients (22.8%) would be unclassified. 5 cases (29.4%) of PSP-CBS would be diagnosed as probable PSP and 6 (35.3%) would be diagnosed as possible PSP. The remaining 6 cases (35.3%) would remain unclassified. Large proportion of cases of PSP-P, PSP-F, and PSP-PGF would be unclassified using NINDS-SPSPS criteria.

Occurrence of disability milestones in PSP subtypes

Wheelchair dependency due to repeated falls was the most common first milestone reached in all subtypes. 224 (92%) PSP-RS (92.9%), 29 (64.4%) PSP-P, 15 (88.2%) PSP CBS, 10 (71.4%) PSP-F and 10 (71.4%) of PSP-PAGF patients reached this milestone first. PSP-RS and PSP-PGF had higher percentage of patients attaining wheelchair dependency ($P < 0.001$) at the last follow up. PSP-P attained wheelchair dependency later than other subtypes ($P < 0.001$).

Table 2: Clinical characteristics of PSP subtypes

	PSP-RS ($n = 241$)	PSP-P ($n = 45$)	PSP-CBS ($n = 17$)	PSP-F ($n = 14$)	PSP-PGF ($n = 14$)
Male:Female (*N*), [%]	148:93 (61:39)	35:10 (78:22)	7:10 (41:59)	6:8 (43:57)	11:3 (79:21)
Age (years) [a]	63.9 ± 7.6 (41- 86)	63.4 ± 8.8 (47- 80)	64.2 ± 7.0 (51- 78)	63.8 ± 8.4 (52- 77)	64.0 ± 7.5 (51- 75)
Age at onset [a] (years)	61.6 ± 7.6 (40- 85)	60.3 ± 8.3 (43- 77)	61.7 ± 7.2 (48- 76)	61.8 ± 8.2 (50- 75)	61.6 ± 7.3 (50- 72)
Disease duration (years) [a]	2.3 ± 1.4 (1-7)	3.5 ± 3.1 (1- 13)	2.4 ± 1.7 (1- 7)	2.0 ± 1.0 (1- 5)	2.4 ± 1.3 (1- 6)
Duration of Follow-up (years) [a]	2.7 ± 1.1 (1- 8)	4.4 ± 2.7 (1- 12)	2.6 ± 0.8 (2- 4)	3.6 ± 1.7 (2- 8)	2.4 ± 1.1 (1- 5)
Tremor [b]	60/24.9	38/84.4	7/41.2	2/14.3	1/7.1
Rigidity [b]	209/86.7	40/88.9	16/94.1	2/14.3	2/14.3
Bradykinesia [b]	239/99.2	45/100	17/100	13/92.9	13/92.9
Postural instability [b]	241/100	35/77.8	15/88.2	11/78.6	10/71.4
Falls within first year [b]	172/71.4	2/4.4	11/64.7	1/7.1	3/21.4
Falls within 3 years [b]	62/25.7	10/22.2	4/23.5	9/64.3	8/57.1
Falls after 3 years [b]	5/2.1	22/48.9	0/0	3/21.4	1/7.1
Slow vertical saccades [b]	111/46.1	41/91.1	11/64.7	7/50	13/92.9
Vertical gaze palsy [b]	135/56	7/15.6	6/35.3	7/50	0/0
Apraxia of eyelid opening [b]	42/17.4	10/22.2	4/23.5	0/0	1/7.1
Square-wave jerks [b]	18/7.5	3/6.7	1/5.9	0/0	0/0
Pyramidal signs [b]	127/52.7	5/11.1	11/64.7	3/21.4	4/28.6

Abbreviation: PSP- Progressive Supranuclear palsy. [a] expressed as Mean ± Standard deviation (Range); [b] (Number/percentage)

The frequency of patients attaining unintelligible speech was similar in PSP-RS, PSP-P, and PSP-F subtypes. PSP-P attained unintelligible speech later compared to PSP-RS and PSP-F ($P < 0.001$). PSP-F had higher percentage of cases attaining urinary catheterization ($P = 0.05$). The interval to attaining urinary catheterization requirement did not differ among the subtypes ($P = 0.85$). The frequency of patients attaining severe dysphagia requiring PEG was similar among the subtypes. PSP-P attained this milestone later than other subtypes. PSP-F had a higher percentage of cases attaining severe cognitive impairment ($P = 0.007$) and reached this milestone earlier than PSP-RS ($P = 0.04$). The frequency and time to attainment of each milestone is illustrated in Table 3.

Kaplan-Meier survival curve analysis of time to attainment of each milestone from disease onset among the subtypes

PSP-P cases reached wheelchair dependency [Log Rank (Mantel-Cox), df = 6, $P < 0.0001$], unintelligible speech [Log Rank (Mantel-Cox), df = 2, $P = 0.001$] and severe dysphagia needing PEG [Log Rank (Mantel-Cox), df = 4, $P = 0.002$] later than all other subtypes. There was no significant difference in the interval to attainment of urinary catheterisation and severe cognitive impairment among the subtypes [Log Rank (Mantel-Cox), df = 3, $P = 0.28$], [Log Rank (Mantel-Cox), df = 2, $P = 0.28$] respectively [Figure 1].

Discussion

PSP is an atypical Parkinsonian syndrome in which variants or subtypes have been recently identified. The NINDS-SPSP criterion (1996) is widely used criteria for the diagnosis of PSP-RS cases. However, it is insufficient to diagnose the subtypes of PSP. A clear diagnosis of PSP-RS can be made only 3 to 4 years after the onset of the first symptom as supranuclear gaze palsy may not be apparent at the onset. The Movement Disorders Society Criteria for PSP (2017) has been designed for research and clinical practice to diagnose early and variant/subtypes of PSP subtypes which include PSP-RS, PSP-P, PSP-CBS, PSP-F, PSP-PGF, PSP-SL, PSP-PI, and PSP-OM. Ali F *et al*., (2019) showed that the MDS criteria has higher sensitivity of 87.9%, compared with 45.5% for the NINDS-SPSP criteria, and specificity of 85.7%, compared with 90.5%.[27]

The natural history of the non-RS phenotypes of PSP is largely unknown and the study by Respondek *et al*., (2014) is the only one that throws light on the prognosis of different PSP subtypes.[24] The present study was aimed at retrospective re-categorization of patients with a clinical diagnosis of PSP into its subtypes using the Movement Disorders Society Criteria for PSP (2017) in order to understand the clinical characteristics and the prognosis of each subtype from the time taken to reach any of the five clinical disability milestones. The earlier the attainment of the milestone, the poorer was the prognosis of the subtype. 334 patients of PSP when categorized into the subtypes, we found that PSP-RS was the most common subtype and PSP-P had a longer disease duration, more frequent tremor and levodopa responsiveness, fewer milestones reached, and more delayed attainment of disability milestones indicative of a more favorable prognosis.

Most of the patients of our cohort were diagnosed using NINDS-SPSP criteria (1996). Probable PSP constituted 36% and Possible PSP 25% and 38% of cases were unclassifiable. The MDS 2017 PSP criteria were used retrospectively to re-categorize these patients. All 334 cases could be categorized into the various subtypes. PSP-RS was the predominant subtype (72%), followed by PSP-P (13.5%), PSP-CBS (5.1%), PSP-F (4.2%), PSP-PGF (4.2%), PSP-PI (0.6%), and PSP-SL (0.3%). When NINDS-SPSP criteria were applied to PSP-RS diagnosed using MDS PSP criteria (2017), 46.5% of PSP-RS cases would be classified as probable PSP, 31% as possible PSP and the remaining 23% would be unclassifiable. This difference could be explained on the bases of the differences in the timing of falls. While the MDS-PSP criteria (2017) includes repeated unprovoked falls within 3 years or tendency to fall on the pull-test within 3 years or

Table 3: Frequency and duration from disease onset of each milestone

	PSP-RS ($n = 241$)	PSP-P ($n = 45$)	PSP-CBS ($n = 17$)	PSP-F ($n = 14$)	PSP-PGF ($n = 14$)	*P*-value
Wheelchair dependency (N/%); Duration (years)	226/93.8[a]; 4.1 ± 1.5	29/64.4; 7.6 ± 4.1[b]	15/88.2[a]; 3.8 ± 1.3	11/78.6; 4.3 ± 1.7	10/71.4; 4.7 ± 1.4	[a] $P < 0.001$ [b] $P < 0.001$
Unintelligible speech (N/%); Duration (years)	31/12.9; 5.3 ± 1.8	7/15.6; 9.7 ± 3.4 [c]	0/0	2/14.3; 4.5 ± 0.7	0/0	[c] $P < 0.001$
Urinary catheterisation requirement (N/%); Duration (years)	24/10; 5.5 ± 1.5	3/6.7; 6.3 ± 3.8	2/11.8; 5.0 ± 1.4	5/35.7 [d]; 5.6 ± 1.5	0/0	[d] $P = 0.05$
Severe dysphagia requiring PEG (N/%); Duration (years)	70/29; 5.2 ± 2.0	9/20; 10.8 ± 6.2[e]	3/17.6; 4.3 ± 1.1	2/14.3 6.5 ± 2.1	0/0	[e] $P < 0.001$
Severe cognitive impairment (N/%); Duration (years)	6/2.5; 5.6 ± 1.9	1/ 2.2	0/0	3/ 21.4 f 4.8 ± 0.6	0/0	[f] $P = 0.007$

Abbreviation: PSP- Progressive Supranuclear palsy; PEG- Percutaneous endoscopic gastrostomy. [a, b, c, d, e, f] *P*-value <0.05

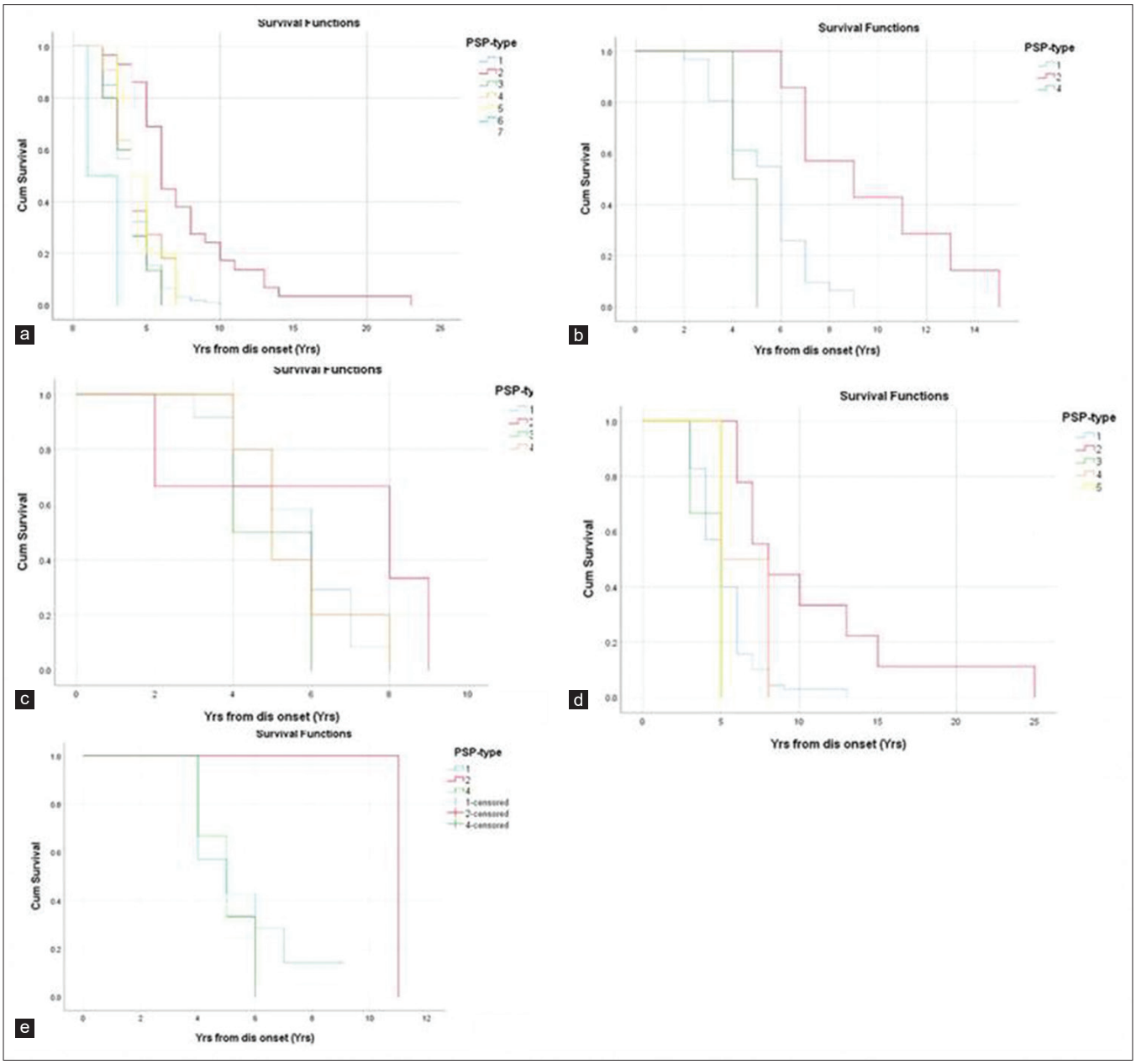

Figure 1: (a) Kaplan–Meier survival curve depicting interval in years from disease onset to wheelchair dependency due to frequent falls. 1-PSP-RS; 2-PSP-P; 3-PSP-CBS; 4-PSP-F; and 5-PSP-PGF; (b) unintelligible speech. 1-PSP-RS; 2-PSP-P; and 4-PSP-F; (c) urinary catheterization requirement. 1-PSP-RS; 2-PSP-P; 3-PSP-CBS; and 4-PSP-F; (d) severe dysphagia needing PEG. 1-PSP-RS; 2-PSP-P; 3-PSP-CBS; 4-PSP-F and 5-PSP-PGF; (e) severe cognitive impairment. 1-PSP-RS; 2-PSP-P; and 4- PSP-F

more than two steps backward on the pull-test within 3 years in the diagnosis of PSP-RS whereas NINDS-SPSP criteria (1996) includes prominent postural instability with falls within one year of disease onset as a diagnostic criterion for PSP.

We found that PSP-RS and PSP-PGF had higher frequencies of cases attaining wheelchair dependency and PSP-RS reaches this milestone the earliest than other subtypes. The frequency of milestones of disability reached was lower in PSP-P, PSP-CBS, and PSP-PGF subtypes even though the mean duration of follow-up was significantly longer in PSP-P than other subtypes. Among these, PSP-P cases had more frequent wheelchair dependency, unintelligible speech, and severe dysphagia requiring PEG later than the other subtypes. As expected, PSP-F developed severe cognitive impairment earlier than others. Kaplan − Meier survival analysis had shown that PSP-P took longer from disease onset to reach wheelchair dependency, unintelligible speech, and severe dysphagia requiring PEG feeding.

The existence, clinical characteristics, and prognosis of the PSP-RS and PSP-P were described by Williams D *et al*., (2005).[5] The phenotype characterized by early falls, early cognitive dysfunction, abnormalities of gaze, and

postural instability, which is similar to those first described in PSP by Richardson *et al*., (1963)[2] was named PSP-RS and the other phenotype characterized by asymmetric onset, tremor, early bradykinesia, non-axial dystonia and a response to levodopa medications resembling Parkinson's disease as PSP-parkinsonism (PSP-P). RS had a shorter duration of disease and the female to male ratio was 1: 1.8, whereas the sex distribution was equal in PSP-P and ran a longer disease course. PSP-P had asymmetric and symmetrical tremors, asymmetric rigidity, levodopa responsiveness, longer disease course delayed development of severe disability which was also seen in our cohort.

Nath *et al*., (2003) showed that PSP subgroup with early falls and bulbar dysfunction had a shorter survival, and those with a diagnosis of probable PSP according to the NINDS-SPSP criteria had a worse prognosis.[28] O'Sullivan *et al*., (2008) showed that RS and PSP-P groups had similar mean ages of disease onset; however, patients with RS had shorter disease duration than those with PSP-P. Patients with RS reached their first clinical milestone earlier, had frequent falls, significant cognitive impairment, and severe dysphagia than patients with PSP-P. Time to wheelchair dependence and residential care were shorter in RS.[29] Our study also found that cases with PSP-RS reached wheelchair dependency, unintelligible speech, urinary catheterization, and severe dysphagia requiring PEG earlier than by PSP-P cases. However, there was no difference between PSP-RS and PSP subtypes other than PSP-P, in terms of time interval from disease onset to the attainment of these milestones. Respondek G *et al*., (2014) on the cohort of 100 autopsies besides confirming the existence of variants of PSP reported longer disease duration or survival time in patients with PSP-P when compared to PSP-RS, PSP-OM, PSP-PI, PSP-FTD, and PSP-CBS. The PSP-P cases were older at death than all other subtypes. In their study, dysphagia predisposing to 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.[24] In our clinically diagnosed subtypes we found similar longer disease duration in PSP-P and a delayed occurrence of dysphagia requiring PEG in them.

Donker Kaat L *et al*., (2007) in their study on 152 patients with PSP reported the existence of a subgroup of PSP patients with a predominant frontal presentation. This group was of younger age at onset than the total cohort. Their presenting symptoms were behavioral changes (96%), cognitive dysfunction (71%), or both and accompanied by falls (68%). The survival of the frontal presentation PSP was not different from the non-frontal presentation of PSP. Our cases with PSP-F had apathy, executive dysfunction, change in personality, and reduced verbal fluency along with memory dysfunction as their predominant symptoms at the first visit. There was no difference of age at onset between PSP-F and other subtypes as reported earlier.[10]

Tsuboi *et al*., (2005) in their study on the clinic-pathological characteristics of 5 cases of PSP-CBS in comparison with PSP-RS showed that there was no significant difference in the age of onset between the groups but PSP-CBS had significantly longer disease duration and later age at death. There was similar frequency of pyramidal tract signs in both groups.[7] Our observations also indicate a longer interval to severe disability in PSP-CBS.

The strength of our study was the inclusion of large sample of patients with a clinical diagnosis of PSP made by experienced movement disorder specialists and the availability of follow up data from the case records of patients seen in the movement disorders clinic in order to apply the MDS PSP criteria for subtype diagnosis. We used the attainment of five clinical milestones as an indicator of prognosis of the disease and were able to prognosticate each subtype with a sufficient sample size. The limitations of the study were the retrospective analysis of clinical data from the case records. Second, the prognosis of a neurodegenerative disease like PSP is determined from the interval from disease onset to death. We did not have mortality data of our patients. However, we used the attainment of five clinical milestones of severe disability as indicators of the prognosis of the disease in subgroups had a mean duration of follow up which was similar. Third, the diagnosis of PSP though made by the movement disorder specialists was clinical and none of the patients had autopsy for neuropathological confirmation.

The present study showed that MDS PSP criteria can be applied in the clinical setting to diagnose the different subtypes of PSP. PSP-RS comprised majority around 70% of total cases while PSP-P, PSP-CBS, PSP-F, PSP-PGF, PSP-PI, and PSP-SL constituted the remaining 30%. PSP-RS was similar to PSP-CBS, PSP-F, and PSP-PGF in the age at onset, age at first evaluation, duration of disease, number of disability milestones reached, and time to attainment of the milestones. However, PSP-P patients had longer disease duration and follow-up, more frequent occurrence of tremor, levodopa response, fewer disability milestones reached, and longer interval to disability milestones. These differences are likely to be due to the differences in the distribution and load of the tau pathology in the subtypes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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