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Progression of two Progressive Supranuclear Palsy phenotypes with comparable initial disability

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ABSTRACT

Introduction: To avoid bias and optimize statistical power of disease-modifying therapeutic trials, it is critical to include homogeneous populations with similar rate of progression over time. Patients with Progressive Supranuclear Palsy (PSP)-Parkinsonism phenotype have overall slower disease progression than those with PSP-Richardson syndrome phenotype. However, it is unclear if the progression rate of PSP-Parkinsonism is the same when the PSP-Parkinsonism converts to PSP Richardson syndrome. We aimed to determine and compare disease progression rate of patients with the two most common PSP phenotypes: PSP-Parkinsonism and PSP Richardson syndrome, participating in the TAUROS trial.

Methods: 138 patients, 56 with PSP-Parkinsonism and 82 with PSP-Richardson syndrome, with similar clinical severity at baseline, were followed up to 60 weeks. PSP-Parkinsonism allocation was based on experts' judgement and PSP-Richardson on probable NINDS-PSP criteria. Global disease progression was measured by the PSP Rating Scale as primary outcome measure and several secondary outcome measures.

Results: PSP-Richardson syndrome patients had significantly faster progression based on the primary and three secondary outcome measures: the Dementia Rating Scale-2, Frontal Assessment Battery, and lexical fluency scale. Analyses including only patients with a baseline symptom duration under five years showed similar results. PSP phenotype was the strongest predictor for disease progression.

Conclusion: This research showed that even when disease severity and clinical features at baseline are similar, patients with PSP-Richardson syndrome progressed significantly faster than those with PSP-Parkinsonism. Therefore, unless stratified by phenotype, future therapeutic clinical trials should not lump PSP patients with these phenotypes as a single disorder even if they have similar disease severity at screening.

1. Introduction

Progressive Supranuclear Palsy (PSP) was originally characterized by vertical supranuclear gaze palsy, parkinsonism, retrocollis, and pseudobulbar palsy [1]. Executive dysfunction (subcortical dementia) and early falling were described at a later date [2,3]. This phenotype was later named PSP-Richardson syndrome when other clinical presentations were later described. These include pure akinesia and gait freezing (PSP-PGF), PSP-Parkinsonism (PSP-P), PSP-progressive non-

fluent aphasia, behavioral variant of frontal dementia, and PSP-corticobasal syndrome among others [4]. These phenotypes can be diagnosed in life once they develop PSP-Richardson syndrome features. Recently, the Movement Disorder Society defined clinical diagnostic criteria for these additional phenotypes [5] to include modifications of the National Institute of Neurologic Diseases and Stroke and Society for PSP (NINDS-SPSP) criteria that define the PSP-Richardson syndrome phenotype [3]. These criteria have yet to be validated.

PSP-Richardson syndrome and PSP-P are the most common PSP

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phenotypes (70–85%) of PSP [6,7]. PSP-P patients usually present with an asymmetric progressive parkinsonism that during the first years resembles Parkinson disease (PD) and may benefit from levodopa therapy [6]. This phenotype has a slower disease progression, better prognosis and longer survival than the PSP-Richardson syndrome phenotype [6]. The diagnosis of PSP-P is retrospective, it is made when a patient with parkinsonism who initially benefits from levodopa therapy develop additional PSP features (i.e., frequent falls, slowing of saccades or supranuclear vertical gaze palsy). However, it remains unclear if when diagnosed during life, patients with the PSP-P phenotype have a similar rate of progression to those with the PSP-Richardson syndrome phenotype. This is relevant because if in a disease-modifying therapeutic trial one of the study arms has more patients who progress slowly and survive longer, one may erroneously conclude that an intervention is beneficial. Thus, to avoid bias and optimize the statistical power of upcoming disease-modifying therapeutic trials, it is essential to reduce sources of variability. To decrease between-patient variability during trials, current PSP studies exclude patients with more than five years of symptom duration. However, an unclear and unconsidered factor in current studies is whether the rate of disease progression varies when these two PSP phenotypes are diagnosed and have similar disease severity.

To address these issues, we studied 138 PSP patients who participated in the TAUROS study [8] who were followed prospectively for up to 60-weeks. We included patients from both active and placebo arms of this clinical trial because the study drug, Tideglusib, failed to show slowing of disease progression or other relevant clinical effects [8]. Although a subset of patients from this study was reported to have better MRI volumetric outcome than those in placebo, this was only a subset of patients (37 patients) and the measures that progressed less did not affect the usual areas of the brain which are involved by PSP pathology. The differences between volumetric MRI values in active and placebo groups were more prominent in whole brain, cerebrum, parietal lobe, and occipital lobe) [9] rather than mesencephalum.

In the TAUROS study, at the onset of the trial the investigators characterized the phenotype of the PSP patients as PSP-Richardson syndrome, PSP-P and PGF based on the knowledge at the time of the study [6,10].

The main aims of the present study were to: (1) describe the characteristics at baseline of patients with the PSP-Richardson syndrome and PSP-P phenotypes; (2) compare their progression over 60 weeks; and (3) compare the progression of those with PSP-Richardson syndrome and PSP-P with less than five years of symptom duration.

2. Methods

2.1. Sample

The TAUROS trial [8] enrolled 144 PSP patients meeting the NINDS-SPSP criteria for possible or probable PSP [3] between December 2009 and November 2011. The patients were allocated to three treatment arms (31 on placebo, 59 on 600 mg Tideglusib and 54 on 800 mg Tideglusib) and were followed up for up to 60 weeks.

Site investigators (neurologists with movement disorder expertise) defined at the onset of the trial the PSP phenotype based on the retrospective assessment of patients' symptom presentation and progression. The NINDS-SPSP probable criteria is highly sensitive for diagnosis of the classic PSP-Richardson syndrome phenotype [11]. However, its sensitivity for diagnosis of other phenotype of disease is lower [12,13]. Site investigators classified 82 patients who met the probable NINDS-SPSP criteria as having the PSP-Richardson syndrome phenotype. Of the remaining 62 patients who met the possible NINDS-SPSP criteria which is less specific for PSP-Richardson syndrome phenotype [11], 56 were originally classified with PSP-P considering the definition at the time for PSP-P [6] and one was diagnosed with PSP-PGF. We excluded five PSP patients because of incomplete data.

All patients were 40–85 years old, had > 12 months history of progressive disease, were not in nursing care facilities, and were able to swallow 150 mL of water suspension without aspiration and able to walk at least 10 steps (for more details see [8]).

Since current therapeutic trials usually include only patients with less than 5 years of symptom duration, re-analyses of 111 patients meeting this criterion (47 PSP-P and 64 PSP-Richardson syndrome patients) was also conducted. 24 patients (17.39%) had more than 5 years of symptom duration. Three participants (2.17%) were excluded from these re-analyses due to lack of symptom duration data.

2.2. Clinical and MRI evaluations

Disease progression was assessed with the PSP rating scale (PSPRS) that has good reliability and validity in evaluating PSP progression [14]. It includes 28 subitems (total score range: 0–100) which evaluate daily living activities, cognition and behavior, bulbar function, ocular motor function, limb motor, and gait/midline motor features. Cognition was assessed with the Dementia Rating Scale-2 (DRS-2, total score range: 0–144) [15]; Frontal Assessment Battery (FAB, total score range: 0–18) [16]; and Verbal Fluency test. Apathy was evaluated with the Starkstein Apathy Scale (total score range: 0–42) [17] and quality of life with the European Quality-of-Life Questionnaire (EQL, score range, 0–100) [18]. The functional state of patients was assessed by Modified Schwab and England Scale (score range, 0–100) [19] and Unified Parkinson's Disease Rating Scale part II (UPDRS, total score range: 0–52) [20]. The "Time up and go" scale [21] assessed patients' functional mobility.

Evaluation of midbrain MRI atrophy at baseline was done qualitatively in 136 out of 138 patients (55 PSP-P and 81 PSP-Richardson syndrome patients) using a four-score visual scale that included examples of normal, mild, moderate, and severe midbrain MRI atrophy on axial plane. Before study initiation, all the investigators were trained on the assessment of the clinical scales and visual evaluation of MRI. Only a subset of patients (37 patients) had repeated MRI evaluations [9].

2.3. Follow up

Ten visits were planned during 60 weeks of trial duration: one screening visit, a second baseline visit, seven follow up visits at weeks 2, 4, 8, 12, 26, 40 and 52, and a wash out visit at week 60. See [Supplementary Table 1](#) for further details. Eighty-seven patients completed the 60-week planned follow up. The mean follow-up time for the total sample of 138 patients was 49.7 ± 18.7 weeks.

2.4. Statistical analysis

Subscales of PSPRS, UPDRS, and EQL were analyzed as continuous variables to measure severity, and then dichotomized to measure the presence of the symptom or sign. We used Fisher's exact test and the Mann-Whitney *U* test for the categorical and the continuous analysis, respectively, to compare baseline measurements between PSP subtypes. The Mann-Whitney *U* test was also used to compare changes in various clinical scales between PSP subtypes at 60 weeks. Delta score for each scale or measurement was defined as the score of a scale or measurement in the 60th-week visit minus baseline visit scores.

In analyzing longitudinal PSPRS data, we used linear mixed effects models and used patient characteristics (age, gender, race, alcohol consumption level, domiciliary status, profession, and smoking status) and clinical test scores (UPDRS, up & go, DRS, FAB, verbal fluency, Starkstein apathy scale, modified Schwab and England scale, EQL, and MRI midbrain atrophy) as independent variable to predict PSPRS. In addition, we included an interaction term between time and each independent variable in the PSP-P, PSP-Richardson syndrome, and total cohort to investigate whether progression was moderated by any of these variables of interest.

We used the logistic regression analysis proposed by Ridout to investigate any patterns in drop-outs, and concluded that it was feasible for the missing data to be missing completely at random (MCAR).

All statistical tests were two-sided and we considered p-values less than 0.05 as statistically significant results. All the analyses were done using the latest version of R (3.3.2). FDR adjustment of p-values for multiple testing was performed and adjusted p-values are shown in the tables based on maintaining a false discovery rate of 5%

2.5. Ethics

Participants signed an informed consent prior to study participation. The study protocol was approved by each local ethics committee at each of the 24 clinical trial site centers in United Kingdom, Spain, Germany, and the United States.

3. Results

3.1. Baseline characteristics

There were no between-phenotype (PSP-P and PSP-Richardson Syndrome) differences in age, gender (Supplementary Table 2) or disease severity evidenced by clinical scales scores at the baseline visit (Supplementary Table 3) both in the total sample and in the subgroup with symptom duration under five years. Table 1 shows that in both samples (total and under 5 years) there were no between-phenotype differences in the frequency of clinical features except that patients with the PSP-P phenotype had more freezing of gait, and less bradyphrenia than those with PSP-Richardson syndrome. In addition, in both samples, the PSP-P patient group had a higher percentage of normal midbrain MRI. In other words, in the total sample, 34.5% of PSP-P and

9.9% of PSP-Richardson Syndrome patients had normal midbrain MRI. In the sample with less than five years of disease duration, the midbrain MRI was normal in 37% of PSP-P patients and 12.5% of PSP-RS patients of ($p = 0.006$ and $p = 0.20$) respectively). MRI findings are detailed in the Supplementary Table 3.

3.2. Disease progression per phenotype

There were no statistical differences in the percent of trial completers between the two PSP phenotypes both in the total sample (PSP Richardson syndrome 50.5 ± 17.7 , PSP-P 48.7 ± 20.2) and in the less than five-year sample (PSP Richardson syndrome 51.6 ± 16.6 , PSP-P 47.9 ± 20.6). Analysis of the whole TAUIOS study sample showed a balanced distribution of the two PSP phenotypes between study arms ($p = 0.69$, Pearson's Chi-square test). In both samples total delta scores of PSPRS and Starkstein apathy scale-Caregiver were significantly smaller in the PSP-P patients than in the PSP Richardson syndrome patients (Table 2). The delta scores for the executive function (FAB) were smaller in the PSP-P group than in the PSP-Richardson syndrome patients in the sample under five years.

Using the linear mixed effects model, the between-group trend of changes for the PSPRS was significantly different in the under five-year sample but not in the total sample. With the same PSPRS score at baseline, the PSPRS score at the last visit of a patient with the PSP-Richardson syndrome phenotype was estimated to be 3.76 units larger than that of a patient with PSP-P ($P = 0.039$). Similarly, in the total sample, patients with the PSP-Richardson syndrome phenotype had 3.075 points higher PSPRS score than the PSP-P patients, although this difference was not significant ($P = 0.059$). Longitudinal analysis of disease progression using linear mixed effects models showed that in both samples the curvatures of changes of the cognitive measures

Table 1

Baseline clinical features per phenotype (Numbers and percentages refer to all patients for which data were available).

Clinical features	Total sample of patients				Sample with < 5 years symptom duration			
	PSP phenotype		P value	Adjusted P value*	PSP phenotype		P value	Adjusted P value*
	PSP-P	PSP-RS			PSP-P	PSP-RS		
	N (%)	N (%)			N (%)	N (%)		
Cognitive features								
Bradyphrenia	37 (66.1)	67 (82.7)	0.041	0.385	32 (68.1)	55 (85.9)	0.035	0.333
Disorientation	18 (32.1)	35 (43.2)	0.215	0.520	15 (31.9)	30 (46.9)	0.123	0.393
Grasping/imitative behavior	25 (44.6)	31 (38.3)	0.484	0.613	20 (42.6)	26 (40.6)	0.848	0.948
Psychiatric features								
Emotional incontinence	22 (39.3)	33 (40.7)	1.000	1.000	20 (42.6)	28 (43.8)	1.000	1.000
Anxiety/depression	27 (48.2)	39 (48.1)	1.000	1.000	22 (46.8)	33 (51.6)	0.702	0.929
Withdrawal	41 (73.2)	70 (86.4)	0.075	0.385	35 (74.5)	57 (89.1)	0.072	0.342
Motor features								
Limb rigidity	45 (80.4)	72 (88.9)	0.219	0.520	38 (80.9)	56 (87.5)	0.426	0.929
Abnormal finger tapping	48 (85.7)	75 (92.6)	0.253	0.525	41 (87.2)	58 (90.6)	0.758	0.929
Neck rigidity or dystonia	45 (80.4)	73 (90.1)	0.133	0.421	40 (85.1)	56 (87.5)	0.782	0.929
Difficulties in arising from chair	47 (83.9)	73 (90.1)	0.302	0.525	39 (83.0)	56 (87.5)	0.588	0.929
Bulbar features								
Dysarthria	51 (91.1)	79 (97.5)	0.122	0.421	44 (93.6)	62 (96.9)	0.649	0.929
Drooling	30 (53.6)	46 (56.1)	0.862	1.000	23 (48.9)	41 (64.1)	0.124	0.393
Dysphagia	37 (66.1)	59 (72.8)	0.450	0.611	30 (63.8)	48 (75.0)	0.215	0.584
Gait and postural stability								
Falls	56 (100.0)	75 (92.6)	0.081	0.385	47 (100.0)	59 (92.2)	0.071	0.342
Postural instability	52 (92.9)	76 (93.8)	1.000	1.000	43 (91.5)	59 (92.2)	1.000	1.000
Freezing of gait	44 (78.6)	47 (57.3)	0.011	0.209	36 (76.6)	34 (53.1)	0.017	0.323
Eye movements abnormalities								
Voluntary downward saccades	53 (94.6)	79 (97.5)	0.399	0.583	45 (95.7)	63 (98.4)	0.573	0.929
Voluntary upward saccades	53 (94.6)	80 (98.8)	0.304	0.525	45 (95.7)	63 (98.4)	0.573	0.929
Sphincter problems								
Urinary incontinence	34 (60.7)	43 (53.1%)	0.388	0.583	27 (57.4)	34 (53.1)	0.702	0.929

*for adjusted p-values please see the text.

Significant p values are bolded.

PSP: Progressive supranuclear palsy, PSP-P: Progressive supranuclear palsy - Parkinsonism, PSP-RS: Progressive supranuclear palsy- Richardson syndrome.

Table 2

Delta clinical scale scores (mean changes during study period) (Numbers and percentages refer to all patients for which data were available).

Scale	Total sample				Sample with less than 5 years of symptom duration			
	PSP phenotype		P value	Adjusted P value*	PSP phenotype		P value	Adjusted P value*
	PSP-P [mean (SD)]	PSP-RS [mean (SD)]			PSP-P [mean (SD)]	PSP-RS [mean (SD)]		
PSPRS total	9.83 (7.33)	14.62 (9.88)	0.035	0.191	9.76 (6.96)	15.69 (9.95)	0.015	0.150
UPDRS-II	6.64 (5.52)	6.56 (5.49)	0.996	0.996	6.79 (5.88)	6.80 (5.78)	0.924	0.924
Up & Go Time	8.69 (16.43)	13.68 (17.79)	0.206	0.453	9.95 (14.39)	14.70 (19.31)	0.341	0.536
DRS2	0.36 (11.64)	−5.92 (15.78)	0.052	0.191	0.59 (10.99)	−6.31 (16.75)	0.058	0.160
FAB	0.50 (3.02)	−0.89 (3.31)	0.077	0.212	0.78 (3.11)	−1.11 (3.42)	0.041	0.150
Verbal fluency/Lexical fluency	1.65 (5.50)	0.05 (4.33)	0.294	0.462	1.52 (5.58)	0.00 (4.48)	0.418	0.575
Verbal fluency/Category fluency	−1.23 (7.20)	−3.22 (5.90)	0.277	0.462	−1.00 (7.36)	−4.11 (5.42)	0.088	0.194
Starkstein Apathy scale-Patient	0.45 (4.92)	0.87 (4.56)	0.921	0.996	0.56 (4.78)	0.77 (4.91)	0.869	0.924
Starkstein Apathy scale-Caregiver	0.30 (3.65)	2.02 (4.41)	0.041	0.191	0.56 (3.98)	2.69 (4.19)	0.032	0.150
Modified Schwab and England	−22.22 (19.44)	−18.60 (16.66)	0.480	0.660	−24.14 (19.18)	−20.98 (16.40)	0.595	0.727
EQL	−7.70 (19.39)	−7.57 (27.33)	0.968	0.996	−8.15 (20.33)	−12.63 (26.55)	0.330	0.536

*for adjusted p-values please see the text.

Significant p values are bolded.

DRS: Dementia rating scale, EQL: European Quality-of-Life, FAB: Frontal assessment battery, PSP: Progressive supranuclear palsy, PSP-P: Progressive supranuclear palsy - Parkinsonism, PSP-RS: Progressive supranuclear palsy- Richardson syndrome, PSPRS: Progressive supranuclear palsy rating scale, UPDRS-II: the Unified Parkinson's Disease Rating Scale part II.

(DRS2, FAB, and lexical fluency scales) were significantly faster in patients with PSP Richardson syndrome than in those with PSP-P (Fig. 1A and B).

To conduct a sensitivity analysis, we repeated our analyses of delta scores and the trend of changes as well as baseline comparisons separately in the active and placebo arms of the original TAUROS study. PSP-Richardson patients consistently had larger delta scores of the clinical rating scales, PSPRS, Starkstein apathy-Caregiver, and FAB, than the PSP-P patients in both subgroups. The trend of changes (analyzing the interaction term between time and PSP phenotype) also showed a consistent more rapid worsening of PSPRS, DRS, FAB, and lexical fluency in the PSP-Richardson phenotype in both active and placebo arms. Considering the smaller sample size of the placebo arm ($n = 30$), these results were statistically significant in the active but not in the placebo arms.

A multiple linear regression model considering the effects of the various clinical scales and disease phenotype, showed that the PSP phenotype as a variable was the best predictor of PSPRS changes during the study period ($P = 0.030$).

4. Discussion

This is the first large prospective clinical study comparing the clinical characteristics and disease progression of patients with two of the main PSP phenotypes, PSP-Richardson syndrome and PSP-P. Despite similar disease severity at baseline, patients with PSP-Richardson syndrome phenotype progressed significantly faster than those with PSP-P. This was evident in a sample that included all the PSP patients as well as in the sample that included only those with less than five years of symptom duration. These findings have clear implications for the design of clinical therapeutic trials.

Even if the yearly changes of the PSPRS for the total sample of PSP patients was almost the same as previously reported [22], the yearly changes for each of the phenotypes were significantly different in both samples (all patients and the group with less than five year of symptom duration). This is of particular importance because the PSPRS is the scale currently used as a primary outcome measure in all the PSP therapeutic clinical trials. Similar results were found when analyzing tests frequently used as secondary outcome measures in clinical trials such as the DRS2, FAB, lexical fluency and the Starkstein apathy scale-

Caregiver. Furthermore, because the slopes of disease progression in the patients with PSP-Richardson syndrome and PSP-P phenotypes diverge in both samples (Figure-1), it is expected that these differences will likely increase with time.

Previous studies suggested that it takes on average six years since symptom onset for patients with PSP-P to develop similar features than PSP-Richardson syndrome patients [7,23]. However, in our study even in the sample with less than five-year symptom duration at trial onset the two phenotypes overlapped clinically at baseline and had similar disease severity.

Of note, current PSP disease modifying therapeutic trials exclude patients with more than five years of symptom duration to avoid including patients with a slower disease progression (ClinicalTrials.gov NCT02985879). This is based on prior studies that show that patients with a longer disease duration meeting the inclusion criteria would progress more slowly. However, this study shows that current therapeutic trials may allow the inclusion of patients with the PSP-P phenotype who have a slower disease progression even when they have less than five-year since symptom onset. Then, by not considering patients' phenotype, current therapeutic trials increase the between-patient variability which may increase between-group bias and decrease the study statistical power. In view of these findings, future PSP clinical therapeutic trials would benefit from not lumping PSP patients with these two phenotypes as a single disorder even if at screening, they seem clinically homogeneous. These findings also stress the relevance of obtaining in the history a detailed timeline of when each clinical feature was developed in order to adequately characterize the phenotype of patients.

Finally, we found that patients with PSP-P had a higher percentage of MRIs with qualitative normal midbrain size than those with PSP-Richardson syndrome at the baseline. This finding is supported by pathological studies which have shown PSP-P patients have less severe tau pathology and less prominent cell depletion in the extranigral midbrain structures than PSP-Richardson syndrome patients [23]. Moreover, because the mean annual MRI midbrain volume changes are associated with the annual variations in the PSPRS [24], and the PSPRS score changes are more severe in patients with PSP-Richardson syndrome, it is fitting that the percentage of subjects with normal MRI midbrain sizes would be higher in PSP-P patients.

It should be emphasized that the provided FDR adjusted p-values

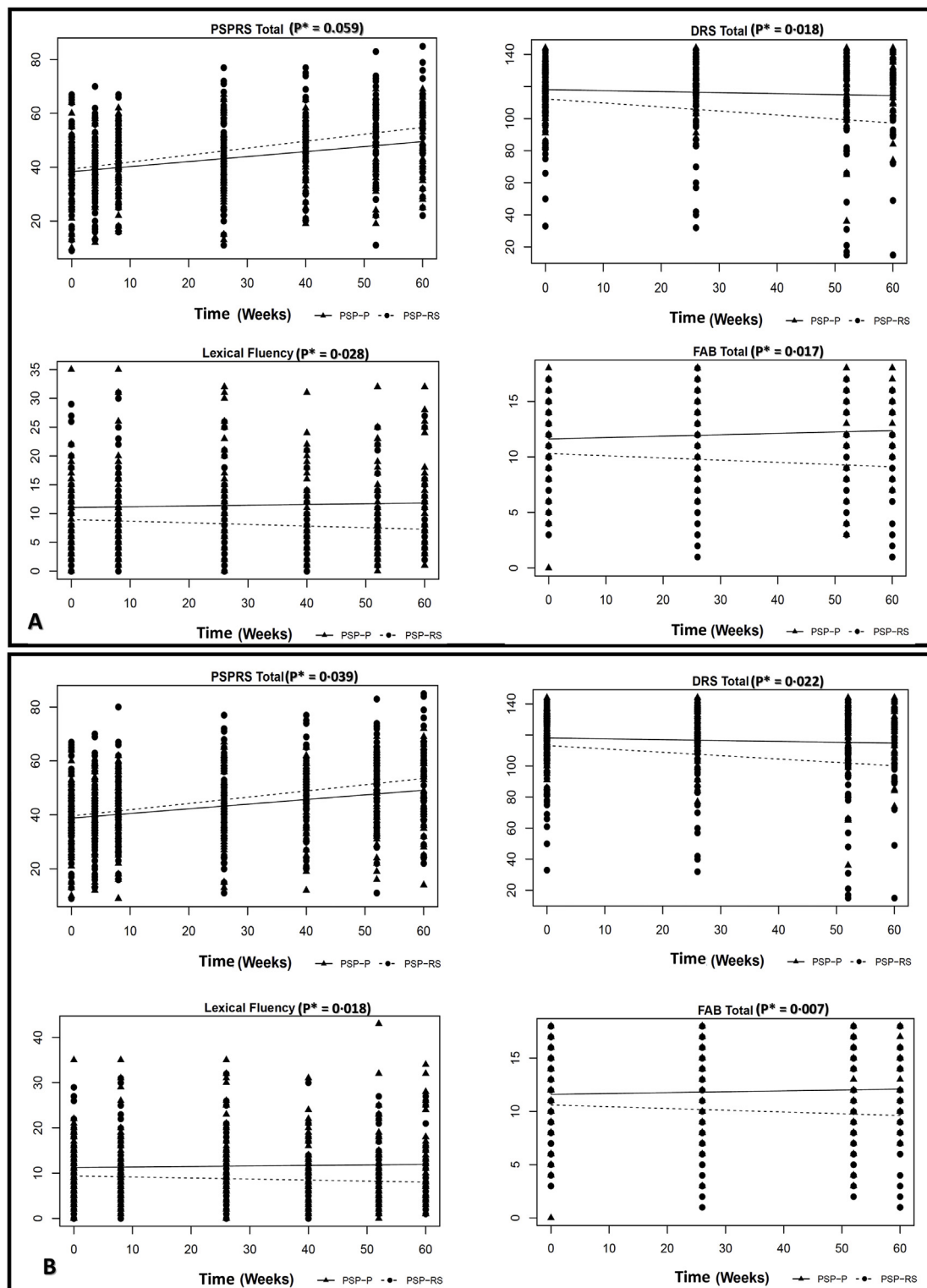


Fig. 1. Changes in the total PSPRS, DRS2, FAB, and lexical fluency scores at the various study visits based on PSP phenotype. A) Total patients; B) Patients with less than five years of symptom duration (DRS: Dementia rating scale 2, FAB: Frontal assessment battery, PSP: Progressive supranuclear palsy, PSP-P: Progressive supranuclear palsy - Parkinsonism, PSP-RS: Progressive supranuclear palsy- Richardson syndrome)* The mentioned P-values in each graph are from the interaction term between the time and the predictor.

indicate above-mentioned results might be in part explained based on a multiple comparisons effect.

This study has some limitations. We used clinical trial data of the TAUROS study because it did not show any clinical benefit of Tideglusib [8], the tested drug. However, it was reported that

Tideglusib reduced the progression of atrophy in the MRI in the whole brain in a substudy that included only 37 out of the 144 patients [9]. Because these patients were not randomized, and their phenotypes are unknown, it is not free of bias. More importantly, the significant findings were in the parietal and occipital lobes which are not areas affected

in PSP. In fact, the lack of Tideglusib benefit led to the discontinuation of trials in PSP patients.

Despite that in the TAUROS study patients were not stratified according to their phenotype, the groups were by chance well balanced among the three treatment arms. Another limitation is that there was no operationalized definition of PSP-P or PSP-PGF at the time of the TAUROS study and allocation of patients to various clinical subgroups was based on clinicians' judgement. In addition, the quantification of the midbrain MRI atrophy was based on comparing MRI midbrain films to MRI figures with various degrees of atrophy severity. However, the investigators were experts in the field of movement disorders and they were able to classify patients using the Williams' definitions, the only one available at that time. Moreover, the study used the NINDS-SPSP criteria, therefore, the patients classified as having PSP-Richardson met the NINDS-SPSP criteria which are quite accurate in defining PSP-Richardson but not sensitive by design to identify other phenotypes. A potential limitation is that, because all the included PSP-P patients fulfilled the NINDS-SPSP possible criteria for PSP [3], there is a possibility of selection bias because we may have included PSP-P patients who had a more rapid progression and fulfilled the inclusion criteria in the first years of their disease. However, this could also be considered as a strength of our study because this study shows that PSP-Richardson syndrome patients progress more rapidly than rapidly progressive PSP-P patients in middle stages of their disease.

The other study limitation was that the date of symptom onset was reported only as a year in several patients and symptom duration was calculated since June which may lead to a six-month potential error. In addition, there was missing data of two PSP-P patients (3.57%) and one PSP-Richardson syndrome patient (1.21%). Because 27 PSP-P patients had less than 2 years of symptom duration, we reanalyzed the data excluding this group, but obtained similar results (data not shown). To minimize bias, we used symptom duration as a nominal variable, under or above five years which is the data used to include patients in therapeutic trials.

Despite these limitations, this large multicenter prospective cohort study allowed us to compare the disease progression in the two main clinical phenotypes of PSP. Before PSP patients with other phenotypes can be included in novel disease-modifying therapeutic trials we need to have validated MDS diagnostic criteria⁵ and prospectively evaluate the rate of progression of the various phenotypes. It is hoped that this study's findings will lead to improvement in the design and selection of a homogeneous study population for future PSP therapeutic trials.

Author roles

1. Research Project: A. Conception, B. Organization, C. Execution;
 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.
- A.S.: 1B, 1C, 2A, 2B, 3A
 I.L.: 1A, 1B, 1C, 2A, 2B, 2C, 3B
 E.T.: 1A, 2C, 3B
 T.d.S.: 1A, 2C, 3B
 E.L.: 1C, 2A, 2B, 2C, 3B

Disclosures

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Appendix A. Supplementary data

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