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An evaluation of the progressive supranuclear palsy speech/language variant

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ABSTRACT

Background: The Movement Disorder Society clinical criteria for progressive supranuclear palsy (PSP) provide a framework for assessing the presence/severity of clinical symptoms, and define a speech/language variant of PSP.

Objectives: To evaluate the clinical criteria in a cohort of speech/language patients with longitudinal follow-up.

Methods: Fifty-two patients presenting with progressive apraxia of speech and/or agrammatic aphasia were followed longitudinally for up to six visits with clinical assessments and MRI. We assessed oculomotor, postural instability and akinesia diagnostic levels, and determined whether patients met criteria for possible PSP-speech/language or probable PSP, at each visit. Kaplan-Meier curves assessed time-to-event probabilities according to age. Statistical parametric mapping and midbrain volume were assessed according to disease progression.

Results: Few PSP symptoms were observed early in the disease, with oculomotor abnormalities and falls first observed two years after onset. Falls were more common than vertical supranuclear gaze palsy. Bradykinesia and rigidity commonly developed but axial was rarely greater than appendicular rigidity. During follow-up, 54% met criteria for possible PSP-speech/language, 38% for probable PSP-Richardson's syndrome, and 38% for probable PSP-parkinsonism, most commonly 6-6.9 years after onset. The probability of developing PSP was greater when onset was over age 70yrs. Patients that progressed to probable PSP had more parkinsonism and

oculomotor impairment at baseline, and greater midbrain atrophy, compared to those who did not develop probable PSP.

Conclusions: Symptoms typical of PSP commonly develop in patients presenting with a progressive speech/language disorder. Older age appears to be an important prognostic factor in these patients.

INTRODUCTION

Progressive supranuclear palsy (PSP) is a neurodegenerative disease[1] that can present with a number of different clinical phenotypes[2-6], including a speech/language phenotype where patients present with progressive apraxia of speech (AOS) and/or non-fluent/agrammatic aphasia[7, 8]. Progressive AOS is a disorder of speech motor planning or programming that affects the production of speech[9], while agrammatic aphasia is characterized by agrammatic, telegraphic or truncated spoken language[10]. The Movement Disorder Society clinical diagnostic criteria for PSP (MDS-PSP criteria) were recently published which provide criteria for different clinical variants of PSP[11]. A patient can be diagnosed as PSP with predominant speech/language disorder (PSP-SL) if they have progressive AOS or non-fluent/agrammatic aphasia, and display vertical supranuclear gaze palsy or slowing of vertical saccades[11]. Of note, the diagnostic certainty associated with PSP-SL is only "possible PSP", since other pathologies have been reported in AOS/agrammatic patients[12-16]. However, a patient could meet a probable PSP diagnosis if they developed additional clinical features, such as postural instability/falls (probable PSP-RS), bradykinesia and rigidity (probable PSP-P) or freezing of gait (probable PSP-PGF)[11].

We aimed to apply the MDS-PSP criteria to a cohort of 52 speech/language patients who have been followed longitudinally to determine which PSP symptoms most commonly develop over time and when in the disease course they develop. We also determined whether baseline features can help predict progression to probable PSP, and the associated neuroimaging

abnormalities. This study allows us to evaluate the PSP-SL criteria and will provide invaluable prognostic information to patients with these speech/language disorders.

METHODS

Patients

We identified all patients who had been recruited into an NIH-funded grant studying patients with progressive speech/language problems (PI: KAJ) who presented with either progressive AOS[17] or non-fluent/agrammatic aphasia[10, 11], and had undergone at least two serial visits in another NIH-funded grant (PI: JLW). All patients had spared single-word comprehension, object knowledge and word retrieval during sentence repetition. Patients were included if they had some PSP features at baseline, but were excluded if they met criteria for probable PSP-RS[11] or corticobasal syndrome[18] at baseline. All patients were recruited from the Department of Neurology, Mayo Clinic Rochester, MN between 7/1/2010-2/21/2017. Fifty-two patients were identified. Of these, 16 had two serial visits, 14 had three visits, 11 had four visits, 7 had five visits and four had six visits (total=177 visits). Follow-up intervals were most commonly 12 months (median=1.1yrs, range 0.7-3.0), with a total follow-up from first-to-last visit of 3.0yrs (range 0.9-6.2). Demographic features of the cohort are shown in **Table 1**.

The study was approved by the Mayo Clinic IRB (IRB# 09-008772/12-008988/15-004618) and informed consent was obtained from all patients. We confirm that we have read the Journal's

position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

Clinical assessments

All patients underwent detailed neurological examination at each visit, including the Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III)[19], the PSP Saccadic Impairment Scale (PSIS)[20], and the PSP rating scale[21]. All patients also underwent neuropsychological testing and a detailed speech/language evaluation (see **Table 1**). Quantitative scores and video recordings of the speech/language protocol were reviewed by at least two speech/language pathologists who made independent judgments about the presence/absence of aphasia, AOS and dysarthria, as previously described[22]. Agrammatism was defined as the presence of function word omissions or syntactic errors during the Western Aphasia Battery (WAB) picture description task, in general conversation, or in the narrative writing subtest of the WAB. AOS was determined based on all spoken language tasks of the WAB plus additional speech tasks that included vowel prolongation, speech alternating motion rates, speech sequential motion rates, word and sentence repetition tasks and a conversational speech sample. Of the 52 speech/language patients, at the baseline visit, 26 (50%) were judged to have AOS in the absence of aphasia and hence meet criteria for primary progressive AOS (PPAOS)[22], eight (15%) were judged to have agrammatic aphasia in the absence of AOS (PAA)[23], and 18 (35%) were judged to have mixed agrammatic aphasia and

AOS (AOS+PAA). In addition, 12 (23%) had dysarthria (6 spastic, 3 hypokinetic, 3 mixed), although severity was mild (**Table 1**).

Evaluation of the MDS-PSP criteria

Operational definitions were created to determine whether each patient met each level of the oculomotor (O1, O2, O3), postural instability (P1, P2, P3) and akinesia (A1, A2, A3) sections of the MDS-PSP criteria[11] at each visit (**Supplemental Table 1**). For **oculomotor dysfunction,** a patient was considered to meet O1 criteria if they scored ≥3 (absence of vertical saccades) on the PSIS and O2 if they scored 2 (slowing of vertical saccades) on the PSIS. A patient was considered to meet O3 criteria if they scored ≥2 (at least mild apraxia of eyelid opening) on item 17 of the PSP Rating Scale.

For **postural instability,** a patient was considered to meet P1 criteria (repeated unprovoked falls) if they scored ≥1 on item 5 of the PSP Rating Scale, meaning they had experienced 1-4 falls/month. If a patient was classified as having falls at baseline then they were considered to have falls at all subsequent visits to avoid the confound of patients not endorsing falling although they had progressed but were using a cane, wheelchair or walker. A patient was considered to meet P2 (tendency to fall on the pull-test) if they were not falling and if they scored 3 on item 3.12 of the MDS-UPDRS reflecting moderate postural instability. A patient was considered to meet P3 (more than two steps back on the pull-test) if they were not falling and if they scored 1 or 2 on item 3.12 of the MDS-UPDRS reflecting slight to mild postural instability.

Since we were interested in assessing the development of symptoms, we did not require that postural instability occurred within three years of disease onset.

For **Akinesia,** a patient was considered to have freezing of gait if they scored ≥1 (at least slight) on item 3.11 of the MDS-UPDRS III. A patient was considered to have bradykinesia if they scored ≥2 (at least mild) on either limb of item 3.4 (finger tapping) or 3.7 (toe tapping). A patient was considered to have rigidity if they scored ≥2 (at least mild) on any of the subcategories (neck, right or left upper or lower extremity) of item 3.3 (rigidity). A patient was considered to have axial>appendicular rigidity if the score for neck rigidity was greater than the score for either the lower or upper extremities on item 3.3. A patient was considered to have rest tremor if they scored ≥1 (at least slight tremor) on any of the subcategories (right or left upper or lower extremity or lip/jaw) of item 3.17 (rest tremor amplitude). Given these definitions, a patient was considered to meet A1 criteria if they had freezing of gait and no rigidity, A2 if they had bradykinesia and rigidity and axial greater than appendicular rigidity; and A3 if they had bradykinesia and either rigidity or rest tremor.

Each patient was assigned the highest level that they fulfilled criteria for; i.e. a patient meeting criteria for P1 was not also assigned to P2 and P3. We also determined whether the patient met criteria for possible PSP-SL (i.e. must have C1 AND O1 or O2), probable PSP-RS criteria (i.e. must have O1 or O2 AND P1 or P2), probable PSP-P (i.e. must have O1 or O1 AND A2 or A3) or probable PSP-PGF (i.e. must have O1 or O2 AND A1) at each visit. In order to determine whether baseline features can help predict whether a speech/language patient will

develop probable PSP-RS, we compared two groups of speech/language patients: 1) speech/language patients who developed probable PSP-RS during their disease course (i.e., SL-progressors, n=20) and 2) speech/language patients who did not meet criteria for probable PSP-RS, probable PSP-P or possible PSP-SL during their disease course (i.e. SL-stable, n=23).

There has been recognition that patients can meet multiple diagnostic categories according to the MDS-PSP criteria, and hence, MAX rules were recently published to provide a mechanism to eliminate multiple diagnostic allocations[24]. We applied these MAX criteria to assign one diagnostic category to each patient at their last visit.

Neuroimaging

All MRI were performed at 3T using a standardized protocol that included a magnetization-prepared rapid gradient echo (MPRAGE) acquisition[22]. Voxel-based morphometry was performed using SPM12[25] to assess patterns of grey and white matter volume loss in the SL-progressors and SL-stable cohort. For the SL-progressors, we assessed the MRI at baseline and also at the visit in which they first met criteria for PSP-RS (MRI interval=2.8[1.7, 4.6] years, PSP Rating scale=46[37,60] at follow-up). For the SL-stable cohort, we assessed the baseline MRI and the follow-up MRI was selected to best match the scan interval of the SL-progressors (2.0 [1.0, 3.1] years). Both groups were compared to 20 healthy controls age and gender matched to the SL-progressors [age=74[63,77], 65% female) and also to 20 patients with typical probable PSP-RS (four definite PSP) who had been recruited into a NIH-funded longitudinal PSP grant

(PIs: JLW & KAJ) (**Supplementary Table 1**). The matched PSP-RS patients had all been diagnosed with typical PSP-RS at presentation and none had speech/language symptoms (i.e. C1 in the MDS-PSP criteria). All MPRAGE scans were normalized to the Mayo Clinic Adult Lifespan Template[26], segmented via unified segmentation[27] and the grey and white matter images were modulated and smoothed at 8mm full-width-at-half-maximum. Voxel-wise t-tests in SPM12 were used to compare groups with results assessed uncorrected at $p<0.001$ using a 200 voxel cluster limit, and after false discovery rate correction at $p<0.01$. Midbrain volumes were calculated for all MRI scans[28] using SPM12 and divided by total intracranial volume.

Statistical analysis

Time between visit and onset of speech/language symptoms (i.e. disease duration) was calculated for each visit for each patient. Visits were grouped by disease duration in order to assess the frequency of oculomotor (O), postural instability (P) and akinesia (A) diagnostic levels. The number/proportion of patients who first met criteria for possible PSP-SL, probable PSP-RS, or probable PSP-P in each disease duration window was calculated. This analysis allows patients to meet any of these three diagnostic categories at the same time (e.g. a patient with O1+P1+A3 would meet criteria for all three diagnoses). We used Kaplan-Meier estimates for time-to-event variables to quantify the proportion of patients at any given disease duration that experienced falls (P1), oculomotor deficits (O1 or O2), and bradykinesia and rigidity/tremor (A3), as well as the proportion of patients that met criteria for PSP-RS, stratified by age at onset. In order to

assess which PSP symptoms (O, P or A) were most likely to first develop, we identified 30 patients who had only C1 at baseline. We then recorded which PSP symptoms (O, P or A) were present at the first visit that each patient developed any of these symptoms.

Comparisons between groups were performed using Mann-Whitney U tests for continuous variables or Chi-Squared tests for categorical variables. Statistical analysis was performed in JMP version 14.1.0.

RESULTS

Symptoms assessed by disease duration

When assessing all 52 patients, few PSP symptoms were observed within two years of onset (**Table 2**). Oculomotor abnormalities (O1 or O2) and falls (P1) were first observed 2-2.9 years after onset (occurring in 10% and 25% of visits in this disease duration window, respectively), with frequency of both symptoms peaking between 6-6.9 years after onset (60% and 48%, respectively). Falls were more common than absence of vertical saccades (O1) throughout the disease course. Apraxia of eyelid opening (O3) was typically observed later in the disease course, most commonly 8 years from onset. Freezing of gait (A1) was rare, only occurring in one patient after disease duration of 7 years. In addition, few patients met criteria for A2, defined as bradykinesia with axial greater than appendicular rigidity. The frequency of bradykinesia with rigidity/tremor (A3) increased throughout the course of the disease, with highest frequency of 73% observed at disease duration 8 to 8.9 years. Differences in the development of PSP

symptoms were observed when the cohort was divided by age (**Table 2**). Patients who were over age 70 at onset more commonly developed oculomotor impairments, falls, posterior instability and bradykinesia with rigidity/tremor compared to patients ≤70. The probability of oculomotor impairment and falls was greater in patients >70 for any given disease duration, although the age effect on the probability of bradykinesia with rigidity/tremor was most noticeable later in the disease course (**Figure 1**).

Diagnostic categories

Twenty-eight (54%) patients met criteria for possible PSP-SL during follow-up. Within these 28 patients, a total of 22 (42% of the whole cohort) developed probable PSP during their disease course (18 met criteria for both probable PSP-RS and PSP-P, two for just PSP-RS and two PSP-P). The earliest patients met criterion for probable PSP was 2-2.9 years after onset with frequency peaking 6-6.9 years after onset, and the development of probable PSP was much more common in patients over age 70 (**Table 2 and Figure 1**). When applying the MAX criteria[24] to the 22 probable PSP patients, 16 had a final clinical diagnosis of PSP-RS and six had PSP-P. If we require that P1/P2 must occur within three years from onset[11], then the final diagnosis was PSP-RS in six, PSP-P in 15 and PSP-PGF in one.

Symptom progression

Of the 30 patients who had only C1 at the first research visit, seven (23%) did not develop any PSP symptoms during follow-up (average of 5 years). Of the remaining 23 (77%) patients, the most common first symptom that developed was postural instability, followed by akinesia, followed by oculomotor symptoms (**Figure 2**). However, the proportion of patients who went on to develop probable PSP-RS did not differ relative to which PSP symptoms developed first.

Comparisons of SL-progressors versus SL-stable

The SL-progressors did not differ from SL-stable in turns of demographics, except disease duration at the final visit was longer and there was a trend for older age in the SL-progressors (**Table 1**). However, SL-progressors performed worse on the MDS-UPDRS III, PSIS, WAB limb apraxia and ASRS at baseline compared to SL-stable (**Table 1**). Furthermore, there was a trend for a difference in speech/language diagnoses, with SL-stable having a higher proportion of patients with PAA (**Table 1**).

At baseline, both groups showed grey matter loss in premotor and motor cortex, with white matter loss underlying these regions and in body of the corpus callosum (**Figure 3**). However, at follow-up, different patterns were seen. The SL-progressors showed more severe volume loss in the regions identified at baseline but also additional volume loss in striatum and midbrain. The SL-stable group showed more widespread grey matter loss at follow-up with involvement of prefrontal cortex and anterior temporal lobes, with white matter loss underlying these regions and involvement of genu of the corpus callosum. The typical PSP-RS patients

showed dramatic white matter loss throughout brainstem, superior cerebellar peduncle and cerebellar dentate (**Figure 3**). These results were very similar when assessed after FDR correction, except the baseline grey matter findings in the speech/language groups did not survive. SL-progressors had smaller midbrain volumes compared to controls and SL-stable at baseline ($p=0.047$ and $p=0.05$) and follow-up ($p<0.0001$ and $p=0.005$) (**Figure 4**). Typical PSP-RS showed smaller midbrain volumes than all other groups ($p<0.0001$ for all).

DISCUSSION

This study uses the MDS-PSP criteria to describe the emergence of PSP symptoms in speech/language patients. During follow-up, 54% of patients met criteria for possible PSP-SL and 42% met criteria for probable PSP; both were more common in patients over age 70 years.

The development of PSP symptoms is, therefore, fairly common in patients with progressive AOS and/or agrammatic aphasia. While we and others have previously noted the development of PSP in speech/language patients[7, 12-15], this is the largest longitudinal cohort reported to date and the first to apply the MDS-PSP criteria. It is clear that a large proportion of patients that meet possible PSP-SL criteria will go on to meet criteria for probable PSP-RS or probable PSP-P, with most patients meeting criteria for both diagnoses. We found that patients were most likely to first meet possible PSP-SL or probable PSP criteria 6-6.9 years after disease onset, demonstrating that it typically occurs relatively late in the disease. The fact that the frequency of these diagnoses declined after this point may reflect patient drop-out and suggests

that those patients who are able to return may be progressing more slowly or not developing PSP symptoms that would make it more difficult to return or more likely that they may die. When the MAX criteria were applied to the cohort, we found that patients most commonly developed a probable PSP-RS diagnosis. However, a consideration when discussing PSP-RS within the context of speech/language abnormalities is how one should define the onset of PSP-related features since this is a stipulation within the postural instability criteria (i.e. that falls should be within three years from onset)[11]. It is not clear whether the onset of speech/language symptoms should be counted as the onset of PSP-related features. When we required that P1 and P2 occur within three years of the first speech/language symptom, we found that a final diagnosis of PSP-P was then more common than PSP-RS. However, the issue of whether these patients should at that point be labelled probable PSP-P or PSP-RS could be debated. On-one-hand, these diagnoses provide a higher level of diagnostic certainty, but on the other-hand, it may be important to not lose sight of the fact that these patients started with speech/language symptoms and that speech/language symptoms are equally severe and equally likely to affect daily function. A speech/language patient labelled as probable PSP-P or probable PSP-RS is also likely to be very different clinically and anatomically from a patient with a typical presentation of either of these probable PSP diagnoses, and hence combining them in studies may be counter-productive. The diagnosis of PSP-P, in particular, was first used to describe patients which had a Parkinson's disease like presentation for many years before the onset of PSP symptoms[3]; this is not the case in the speech/language patients and hence a label of PSP-P may not be appropriate. Ultimately,

autopsy confirmation will be needed to determine whether the probable PSP diagnoses do indeed increase specificity for PSP pathology.

Application of the MDS-PSP criteria also allowed us to assess the frequency of specific PSP symptoms. We showed that falling was more common than vertical supranuclear gaze palsy throughout the disease course, with both symptoms first emerging relatively early in the disease after two years. The frequency of these symptoms peaked between 6-6.9 years from onset; explaining why the diagnosis of probable PSP was also most common in this time window. Optic apraxia was very rarely observed and, hence, does not appear to be a feature of PSP-SL. We also did not observe many patients who had a tendency to fall on the pull test (i.e. met P2 criteria) who did not actually report falls; hence this category did not add much to the diagnosis of these patients. Bradykinesia and rigidity/akinesia commonly developed in our patients, although we did not observe many patients who displayed axial greater than appendicular rigidity and freezing of gait was also not common in our cohort; only one patient would have met diagnostic criteria for PSP-PGF[11]. Our patients, therefore, only commonly met A3 criteria. In this cohort, axial rigidity was most commonly equal to appendicular rigidity, and in some cases, particularly later on in the disease course, appendicular rigidity was greater than axial rigidity, likely reflecting that speech/language patients also commonly develop features of corticobasal syndrome[12, 18]. A striking finding from our study was that the development of PSP symptoms was strongly associated with older age; patients who were ≤70 at onset rarely developed many PSP features or met criteria for probable PSP during their disease course. This could suggest a

slower more indolent course in younger patients or that PSP pathology may be more common in older patients. Regardless, it is clear that older age is an important predictor of the development of PSP symptoms; a finding that will be crucial to help guide prognostic estimates for these patients.

Our results also showed that it was most common for patients to first develop postural instability/falls, followed by akinesia, and oculomotor impairment was the least common. Furthermore, the order that a patient developed these symptoms did not influence the probability that they would eventually meet criteria for probable PSP-RS. Postural instability may, therefore, be the earliest sign of PSP in these patients. This does not quite align with how the criteria were designed, where oculomotor impairment was given more weight for increasing the confidence in a PSP diagnosis. However, the criteria for P3 will pick up relatively mild postural instability and may, hence, be over sensitive.

Our analysis of the SL-progressors and SL-stable cohort highlighted potential predictors of progression in speech/language patients and provided insight into the neuroanatomical underpinnings of progression. First, we found that the SL-progressors already showed worse parkinsonism, limb apraxia, and oculomotor impairment at baseline compared to the SL-stable patients; and hence the presence of these features may increase the likelihood that a patient will go on to develop probable PSP. Indeed, more severe parkinsonism at baseline has been associated with faster rate of decline in parkinsonism in progressive AOS patients[29]. There were also differences in speech/language features, with the SL-progressors showing worse AOS at

baseline, and the SL-stable cohort showing a higher proportion of PAA patients (29% versus 1%). This concurs with our previous study suggesting that PAA patients have a different disease course compared to patients with AOS[23]. Second, while both SL groups showed typical patterns of premotor and motor atrophy at baseline[12, 22, 30, 31], the SL-progressors showed a greater degree of midbrain atrophy, both at baseline and follow-up, overlapping with findings in typical PSP-RS. Midbrain atrophy has been previously reported in PPAOS[31] and shown to be associated with the development of a PSP-like syndrome[12]. Midbrain atrophy has also been associated with autopsy confirmed PSP in a speech/language cohort[14]. It, therefore, appears that atrophy of the midbrain is associated with the development of PSP symptoms and could be a potential predictor.

The results of this study serve as important prognostic guidelines for patients with progressive AOS and/or agrammatic aphasia and provide a neuroanatomical explanation for the development of PSP symptoms in these patients.

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Table 1: Demographics, clinical and neuroimaging data

	Whole patient cohort	Patients that developed probable PSP-RS (SL-progressors)	Patients that did not develop probable PSP-RS (SL-stable)	P
Demographics				
N	52	20	24	
% female	28 (54%)	12 (60%)	14 (58%)	0.91
Handedness (right/left/ambi)	86/12/2%	85%/10/5%	83/17/0%	0.38
Education, years	15 (12, 16)	15 (12, 16)	15 (12, 18)	0.66
Age at baseline, years	70 (62, 76)	73 (71, 76)	66 (58, 75)	0.06
Age at onset, years	67 (57, 73)	70 (68, 73)	63 (55, 74)	0.10
Time from onset to baseline, years	3 (2, 5)	3 (2, 4.2)	2 (2, 4)	0.70
Time from onset to final visit, years	7 (5, 9)	8 (6, 9)	5 (4, 8)	0.03
Number of visits	3 (2, 4)	4 (2, 5)	3 (2, 3)	0.12
Speech/language diagnosis at baseline				
PPAOS	26 (50%)	10 (50%)	11 (46%)	0.07
AOS + PAA	18 (35%)	9 (45%)	6 (25%)	
PAA	8 (15%)	1 (5%)	7 (29%)	
Neurological and neuropsychological results at baseline				
MoCA (/30)	25 (24, 28)	24 (23, 27)	25 (24, 29)	0.25
Frontal Assessment Battery (/18)	16 (14, 17)	16 (13, 17)	16 (14, 17)	0.54
CDR-SB (/18)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.90
Neuropsychiatric Inventory Q (/36; 0=best)	2 (0, 3.5)	1 (0, 2.8)	2 (0.5, 3.5)	0.60
WAB apraxia (/60)	57 (54, 59)	56 (49, 57)	58 (56, 59)	0.01
MDS-UPDRS III (/132)	9.5 (5.8, 18.5)	15.5 (6.8, 22.5)	8 (4, 11)	0.04
PSP Saccadic Impairment Scale (/5)	0 (0, 1)	1 (0, 1)	0 (0, 1)	0.01
PSP Rating Scale (/100)	9 (3, 21)	17 (4, 25)	4 (3, 15)	0.28
CVLT long term % retention MOANS*	12 (9, 14)	13 (10, 15)	11 (10, 13)	0.23
Trail Making Test A MOANS*	8 (6, 11)	8 (6, 10)	10 (7, 11)	0.41
DKEFS card sort scaled score*	9 (7, 13)	8 (7, 12)	11 (8, 13)	0.15
WOSS letters raw score (/20)	20 (19, 20)	20 (19, 20)	19 (19, 20)	0.17
Speech and language results at baseline				
WAB-Aphasia Quotient (/100)	95.2 (85.4, 97.5)	94.2 (84.9, 96.6)	95.5 (87.8, 97.3)	0.76
WAB – information content (/10)	10 (9, 10)	10 (9, 10)	10 (9, 10)	0.81
WAB – fluency (/10)	9 (6, 10)	9 (6, 10)	9 (6, 9)	0.86
WAB – AV comprehension (10)	10 (9.6, 10)	9.9 (9.6, 10)	10 (9.6, 10)	0.90
WAB – repetition (/10)	9.4 (9.0, 9.8)	9.4 (9.1, 9.7)	9.4 (9.0, 9.6)	0.75
Token Test (/22)	19 (17, 21)	20 (17.5, 21.3)	19 (16.8, 20)	0.26
Northwestern Anagram Test (/10)	9 (6, 10)	9 (2, 9)	8.5 (6.3, 10)	0.43
FTSRS (/64; 0=best)	16 (10, 24)	20.5 (11.5, 27.5)	14 (6, 17)	0.03
Motor Speech Disorders severity scale (/10)	7 (6, 8)	7 (6, 7)	8 (6, 9)	0.15

Dysarthria severity (0-4)	0 (0, 0)	0 (0, 0.1)	0 (0, 0.1)	1.00
Action fluency	11 (7.8, 15)	9 (7, 12)	13 (8, 16)	0.07
Letter fluency	20.5 (11, 26.5)	15 (10, 22.5)	22 (14, 28)	0.15
Boston Naming Test, short form (/15)	14 (12, 15)	14 (13, 15)	14 (11, 15)	0.86
Pyramids and Palm Trees (/52)	51 (49, 51)	50 (48, 51)	51 (50, 51)	0.62
Non-verbal oral apraxia (/32, 32=best)	29 (/21, 31)	26 (19, 31)	29 (25, 31)	0.26

Data shown as number (%) or median (1st and 3rd quartiles); MoCA = Montreal Cognitive Assessment Battery; CDR-SB = Clinical Dementia Rating Scale sum of Boxes; WAB = Western Aphasia Battery-Revised; MDS-UPDRS = Movement Disorder Society Sponsored revision of the Unified Parkinson's Disease Rating Scale; AVLT = Auditory Verbal Learning Test; MOANS = Mayo older adult norms; DKEFS = Delis–Kaplan Executive Function System; VOSP = Visual Object and Space Perception Battery; AV = Auditory Verbal; ASRS = Apraxia of Speech Rating Scale; PPAOS = primary progressive apraxia of speech; PAA = progressive agrammatic aphasia

*test scores are constructed to have a mean of 10 and standard deviation of 3 in cognitively healthy participants

Table 2: The appearance of PSP symptoms by disease duration

Disease Duration (years)	0~.9	1~1.9	2~2.9	3~3.9	4~4.9	5~5.9	6~6.9	7~7.9	8~8.9	9~9.9
WHOLE COHORT (n=52)										
N visits	0	7	20	27	23	23	25	20	15	10
N subjects	0	6	19	27	22	23	24	19	14	10
Only C1	n/a	5 (71%)	11 (55%)	8 (30%)	9 (39%)	8 (35%)	6 (24%)	2 (10%)	3 (20%)	2 (20%
O1	n/a	0 (0%)	1 (5%)	1 (4%)	3 (13%)	2 (9%)	6 (24%)	3 (15%)	2 (13%)	4 (40%)
O2	n/a	0 (0%)	1 (5%)	4 (15%)	1 (4%)	6 (26%)	6 (24%)	4 (20%)	4 (27%)	1 (10%)
O3	n/a	0 (0%)	0 (0%)	2 (7%)	2 (9%)	2 (9%)	1 (4%)	2 (10%)	3 (20%)	2 (20%)
P1	n/a	0 (0%)	5 (25%)	10 (37%)	5 (22%)	6 (26%)	15 (60%)	9 (45%)	6 (40%)	5 (50%)
P2	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	2 (10%)	0 (0%)	0 (0%)
P3	n/a	1 (14%)	2 (10%)	7 (26%)	6 (26%)	3 (13%)	1 (4%)	3 (15%)	4 (27%)	0 (0%)
A1	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
A2	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (5%)	1 (7%)	1 (10%)
A3	n/a	1 (14%)	4 (20%)	10 (37%)	7 (30%)	12 (52%)	11 (44%)	9 (45%)	11 (73%)	6 (60%)
Poss. PSP-SL*	0 (0%)	0 (0%)	1 (2%)	5 (10%)	2 (4%)	5 (10%)	7 (13%)	2 (4%)	2 (4%)	4 (8%)
Prob. PSP-RS*	0 (0%)	0 (0%)	1 (2%)	3 (6%)	1 (2%)	2 (4%)	8 (15%)	1 (2%)	1 (2%)	2 (4%)
Prob. PSP-P*	0 (0%)	0 (0%)	1 (2%)	2 (4%)	1 (2%)	3 (6%)	6 (12%)	0 (0%)	4 (8%)	3 (6%)
PATIENTS ≤70 YEARS (n=25)										
N visits	0	1	10	11	10	11	10	8	8	6
N subjects	0	1	10	11	10	11	10	8	8	6
Only C1	n/a	1 (100%)	6 (60%)	4 (36%)	3 (30%)	6 (54%)	4 (40%)	1 (13%)	3 (38%)	2 (33%)
O1	n/a	0 (0%)	0 (0%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)
O2	n/a	0 (0%)	0 (0%)	2 (18%)	1 (10%)	3 (27%)	2 (20%)	1 (13%)	1 (13%)	0 (0%)
O3	n/a	0 (0%)	0 (0%)	1 (9%)	1 (10%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (17%)
P1	n/a	0 (0%)	1 (10%)	4 (36%)	2 (20%)	1 (9%)	4 (40%)	2 (25%)	1 (13%)	3 (50%)
P2	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
P3	n/a	0 (0%)	1 (10%)	2 (18%)	3 (30%)	0 (0%)	1 (10%)	2 (25%)	3 (38%)	0 (0%)
A1	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
A2	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
A3	n/a	0 (0%)	2 (20%)	4 (36%)	4 (40%)	3 (27%)	2 (20%)	3 (38%)	4 (50%)	2 (33%)
Poss. PSP-SL*	0 (0%)	0 (0%)	0 (0%)	2 (8%)	1 (4%)	2 (8%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Prob. PSP-RS*	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Prob. PSP-P*	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)
PATIENTS > 70 YEARS (n=27)										

N visits	0	6	10	16	13	12	15	12	7	4
N subjects	0	5	9	16	12	12	14	11	6	4
Only C1	n/a	4 (67%)	5 (50%)	4 (25%)	6 (46%)	2 (17%)	1 (7%)	1 (8%)	0 (0%)	0 (0%)
O1	n/a	0 (0%)	0 (0%)	1 (6%)	1 (8%)	2 (17%)	6 (40%)	2 (17%)	2 (29%)	2 (50%)
O2	n/a	0 (0%)	1 (10%)	3 (19%)	0 (0%)	3 (25%)	4 (27%	3 (25%)	3 (49%)	1 (25%)
O3	n/a	0 (0%)	0 (0%)	1 (6%)	1 (8%)	2 (17%)	1 (7%)	1 (8%)	3 (49%)	1 (25%)
[illegible]	n/a	0 (0%)	4 (40%)	7 (44%)	2 (15%)	5 (42%)	11 (73%)	7 (58%)	5 (71%)	2 (50%)
[illegible]	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (7%)	1 (8%)	0 (0%)	0 (0%)
P3	n/a	1 (17%)	1 (10%)	5 (31%)	3 (23%)	3 (25%)	0 (0%)	1 (8%)	1 (14%)	0 (0%)
[illegible]	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)
A2	n/a	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (67%)	1 (8%)	1 (14%)	1 (25%)
A3	n/a	1 (17%)	2 (20%)	7 (44%)	2 (15%)	9 (75%)	9 (60%)	5 (42%)	7 (100%)	3 (75%)
[illegible]ss. PSP-SL*	0 (0%)	0 (0%)	1 (4%)	3 (11%)	1 (4%)	3 (11%)	7 (26%)	2 (7%)	1 (4%)	3 (11%)
Prob. PSP-RS*	0 (0%)	0 (0%)	1 (4%)	2 (7%)	1 (4%)	2 (7%)	8 (30%)	1 (4%)	1 (4%)	1 (4%)
[illegible]b. PSP-P*	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	3 (22%)	6 (22%)	0 (0%)	3 (11%)	2 (7%)

Symptom frequency is shown as % of the number of visits for that disease duration; diagnoses (poss. PSP-SL and prob. PSP-RS) are shown as % of the total number of patients. One patient with disease duration of 16 years was excluded from the table because they were the only patient with disease duration >10 years. This patient met criteria for PSP-RS at the very last visit 16 years after onset.

*Each patient was only counted when they first met the criteria for possible PSP-SL or probable PSP-RS, and hence the values are shown as percentages of the total cohort (n=52) or the total number of patients ≤70 years (n=25) or >70 (n=27) years.

Figure Legends

Figure 1: Kaplan Meier curves depicting the probability of a speech/language patient developing oculomotor impairment, falls, bradykinesia with rigidity/tremor and probable PSP-RS according to age at onset. Since a speech/language patient that develops oculomotor impairment (O1 or O2) also meets criteria for possible PSP-SL, then the oculomotor plot also provides the probabilities of a patient developing possible PSP-SL.

Figure 2: Diagram illustrating the first PSP symptoms that developed in patients who only had speech/language symptoms at their baseline visit. Of 30 patients that only had speech/language symptoms (i.e. C1 on the PSP criteria) at baseline, seven did not develop any PSP symptoms at any visit (after a median of 5 years follow-up from onset). Of the 23 that developed PSP symptoms, the combination of O, P and A symptoms that were first present at follow-up are depicted. A total of 16 patients fulfilled criteria for postural instability (P1, P2 or P3) at the first visit that they developed PSP symptoms, with seven of these only developing postural instability without any akinesia or oculomotor impairment. Ten patients developed akinesia (A1, A2 or A3), with four developing akinesia without any postural instability of oculomotor impairment. Seven developed oculomotor impairment (O1, O2 or O3), with only two developing isolated oculomotor impairment. No patients had all three (O, P and A) symptoms at

the first visit that PSP symptoms were present. The % of patients from each O, P or A category that went on to meet criteria for probable PSP-RS is shown.

Figure 3: Voxel-level maps depicting grey and white matter loss. Results are shown for the SL-stable and SL-progressors at both baseline and follow-up compared to controls. Maps of grey and white matter volume loss are also shown for a matched group of 20 patients who presented with typical probable PSP-RS compared to controls. Results are shown uncorrected for multiple comparisons with 200 voxel cluster limit.

Figure 4: Box-plots of midbrain volume. Boxes represent 25th percentile, median and 75th percentile, with whiskers showing extending to the most extreme data points. * = significantly different from controls; ** significantly different from SL-stable base; *** significantly different from SL-stable follow-up; **** significantly different from SL-progressors base; ***** significantly different from SL-progressors follow-up

Supplemental Table 1: Operational definitions

Supplemental Table 2: Demographics and clinical data for the 20 typical probable PSP-RS patients Data shown as number (%) or median (1st and 3rd quartiles); MoCA = Montreal

Cognitive Assessment Battery; MDS-UPDRS = Movement Disorder Society Sponsored revision of the Unified Parkinson's Disease Rating Scale