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Midbrain atrophy in patients with presymptomatic progressive supranuclear palsy-Richardson's syndrome

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ABSTRACT

Introduction: In the present study, midbrain atrophy and the pons-to-midbrain area ratio (P/M ratio) were investigated as diagnostic markers for presymptomatic progressive supranuclear palsy-Richardson's syndrome (Pre-PSP-RS).

Methods: The present study included 27 patients with probable PSP-RS who underwent brain MRI at least twice before and after the development of clinical symptoms, age- and sex-matched participants with Parkinson's disease (PD, n = 27), and healthy controls (n = 27). The midbrain area, pons area, and P/M ratio of the Pre-PSP-RS, PD, and control subjects were measured using midsagittal images from brain MRI, and the parameters were compared among the groups.

Results: The midbrain area decreased and the P/M ratio increased significantly in the Pre-PSP-RS patients compared with both the PD and control subjects (midbrain, Pre-PSP-RS *vs.* PD = 1.01 cm^2 *vs.* 1.29 cm^2, $p < 0.001$, Pre-PSP-RS *vs.* controls = 1.01 cm^2 *vs.* 1.29 cm^2, $p < 0.001$; P/M ratio, Pre-PSP-RS *vs.* PD = 5.27 *vs.* 4.03, $p < 0.001$, Pre-PSP-RS *vs.* controls = 5.27 cm^2 *vs.* 4.06 cm^2, $p < 0.001$). The P/M ratio had high sensitivity (*vs.* PD, 96.3%, *vs.* control, 88.9%) and specificity (*vs.* PD, 81.5%, *vs.* control, 96.3%) in differentiating Pre-PSP-RS patients from PD and control subjects.

Conclusion: Midbrain atrophy precedes the clinical symptoms of PSP-RS and could be a useful diagnostic imaging biomarker for Pre-PSP-RS. Furthermore, this information could play an important role in the development of future treatment strategies.

1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by postural instability, vertical gaze palsy, and akinetic-rigid and frontal dysexecutive syndromes [1]. PSP presents with a wide range of clinical phenotypes, with PSP-Richardson's syndrome (PSP-RS) being the most common subtype, remarkable for postural instability, falls, vertical supranuclear gaze palsy, and axial rigidity. PSP is one of the most frequent atypical parkinsonisms and is an incurable, progressive disease with a prevalence of 5–7 cases per 100,000 people, a mean of 2 years to become wheelchair bound, and a median survival of 7.1 years [2–4]. No effective treatments are currently available for PSP [5]. Similar to most neurodegenerative diseases, PSP has a presymptomatic phase, which has an inadequate pathologic burden to show clinical symptoms [6,7]. Detecting presymptomatic PSP (Pre-PSP) is important for the development of novel therapeutic strategies, future clinical trials, and early differential diagnosis from Parkinson's disease (PD) or other atypical parkinsonisms. However, no specific biomarker has been found for the detection of Pre-PSP.

Midbrain atrophy is a characteristic feature of PSP, and conventional brain MRI is a useful tool to determine midbrain atrophy [8]. The midbrain area and the pons-to-midbrain area ratio (P/M ratio),

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measured along the midsagittal plane of brain MRI, are considered neuroimaging diagnostic and progression biomarkers for PSP [9–12]. In our previous study, we observed a steady increase in the P/M ratio over time [13]. Considering the progressive nature of neurodegeneration, presymptomatic midbrain atrophy, which has never been studied, can be expected.

In the present study, we investigated whether midbrain atrophy, estimated by brain MRI of patients with Pre-PSP-RS, precedes the development of symptomatic PSP-RS.

2. Methods

2.1. Participants

Eligible participants were identified by searching the databases at six university hospitals in South Korea for patients seen between January 2010 and December 2017. Patients from each hospital who met the criteria for probable PSP-RS at the time of their most recent visit to the neurology clinic were included. The clinical diagnosis was made based on the PSP criteria from the Movement Disorder Society [1]. Patients who underwent brain MRI from 12 to 48 months prior to the development of clinical symptoms of PSP were selected. We reviewed the clinical charts of patients with PSP and excluded those who had any clinical symptoms or complaints of subjective symptoms that suggested PSP before the time of their first brain MRI. We confirmed that none of our subjects had any clinical symptoms suggesting PSP. The clinical symptoms of PSP were defined as ocular motor dysfunction (vertical supranuclear gaze palsy, apraxia of eyelid opening, slow saccades), postural instability (spontaneous falls, fall on pull test, or more than 3 steps on pull test), parkinsonism (freezing of gait, axial predominant rigidity, bradykinesia, rigidity, resting tremor), and cognitive dysfunction (apraxia of speech, non-fluent aphasia, frontal/behavioral cognitive presentation, and cortico-basal syndrome) as described in the diagnostic criteria [1]. Age- and sex-matched patients with idiopathic PD consistent with the United Kingdom Parkinson's Disease Brain Bank Criteria [14] and age- and sex-matched healthy participants with no neurologic illness at the time of imaging were included in the study. We included patients with PD who had been followed by a Movement Disorder Clinic for more than 5 years without any red flag signs that suggested atypical parkinsonism [15]. Brain MRI was obtained from the healthy controls and from PD patients within 4 years of symptom onset. Patients who had structural brain lesions affecting the brainstem structure were excluded. The midbrain area, pons area, and P/M ratio were measured along the midsagittal plane of brain MRI from all four groups: control subjects, PD patients, and PSP-RS patients at the Pre-PSP stage, and after development of clinical symptoms. Clinical information (age, sex, Unified Parkinson's Disease Rating Scale (UPDRS) part III, and Hoehn and Yahr (H&Y) scale at the time of diagnosis) was collected from PSP and PD patients. Age of onset, age when MRI was first performed, age at diagnosis, and reason for performing brain MRI were also collected. The time interval between the date of the brain MRI and the date of clinical symptom onset was calculated based on that information. This study was approved by the Institutional Review Board of the six participating hospitals. Informed consent was obtained from all subjects.

2.2. Measurements of brainstem structures

All the measurements were performed on a picture archiving and communication system (PACS; GE Healthcare Integrated IT Solutions, Barrington, IL, USA.) using a mouse point cursor and automated computer calculations for distance and angle. The method of Oba et al. was used to measure the midbrain area, pons area, and P/M ratio [16]. Measurements were performed by two different neurologists blinded to clinical information. To evaluate intra-rater reliability, the same person measured the midbrain and pons areas twice on different days.

2.3. Statistical analyses

Data were evaluated for normality using the Shapiro-Wilk test. Clinical features and measured values were compared using Student's *t*-tests, one-way analysis of variance (ANOVA), or the Kruskal-Wallis test, depending on the nature of the variable, followed by Tukey's post-hoc test for multiple comparisons. Diagnostic accuracy was determined in differentiating Pre-PSP from PD or controls and in differentiating PSP from PD or controls using the optimal cut-off values determined through a receiver operating characteristic (ROC) curve analysis with 95% confidence intervals (95% CI). The value resulting in the highest sum of sensitivity and specificity was considered to be the optimal cut-off. Pearson correlations were calculated to evaluate the relationship between the measured values and duration of the presymptomatic stage, baseline midbrain area, baseline P/M ratio, age of onset, UPDRS, and H&Y scale. Corrected *p*-values for multiple testing are based on the Bonferroni correction. The intra- and inter-rater reliability were assessed by calculating the intraclass correlation coefficients. All tests were two-tailed, and the α level was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS for Windows (version 25.0; IBM Inc., Armonk, NY, USA).

3. Results

3.1. Demographics and clinical features

In this study, we evaluated 27 patients with probable PSP-RS who underwent brain MRI at least twice before and after the development of clinical symptoms, 27 age- and sex-matched patients with PD, and 27 healthy controls. Demographic and clinical data for the patients and controls are shown in Table 1. The mean age of onset and the mean age when diagnostic MRI was first performed in patients with PSP-RS did not differ from that of the PD patients or controls. The mean interval between performing presymptomatic MRI and MRI after the development of subjective symptoms was 41.6 months (range, 14–86 months). The mean interval between presymptomatic MRI and the onset of symptoms was 28.4 months (range, 12–48 months). The mean UPDRS score and H&Y scale were higher in the PSP-RS group than in the PD group. The most common reason for performing brain MRI in Pre-PSP-RS patients was health screening (n = 11, 40.7%), followed by dizziness (n = 7, 25.9%), headache (n = 6, 22.2%), cancer work-up (n = 1, 3.7%), concussion (n = 1, 3.7%), and transient weakness (n = 1, 3.7%). Twelve patients with PSP-RS presented with gait disturbance (44.4%), and 9 patients had postural instability (33.3%) as initial symptoms. Cognitive decline (7.4%), frequent falling (7.4%), and resting tremor (7.4%) were each the first symptom in 2 patients.

3.2. MRI results

Scatterplots summarizing the results from the midbrain area, pons area, and P/M ratio for each group are shown in Fig. 1. The mean pons area did not differ significantly among the Pre-PSP-RS, PD, and control groups (Pre-PSP-RS = 5.24 cm^2, 95% CI = 5.06–5.42, SD = 0.45; PD = 5.18 cm^2, 95% CI = 4.95–5.42, SD = 0.60; control = 5.17 cm^2, 95% CI = 4.97–5.40, SD = 0.54; Pre-PSP-RS *vs.* PD, $p = 0.973$; Pre-PSP-RS *vs.* control, $p = 0.973$). The mean pons area in the PSP-RS group was 5.07 cm^2 (95% CI = 4.91–5.22, SD = 0.39), which did not differ from the PD or control groups (PSP-RS *vs.* PD, $p = 0.835$; PSP-RS *vs.* control, $p = 0.835$). The mean midbrain area in the Pre-PSP-RS and PSP-RS groups was 1.01 cm^2 (95% CI = 0.95–1.07, SD = 0.15) and 0.87 cm^2 (95% CI = 0.80–0.93, SD = 0.16), respectively. These midbrain areas were smaller than the midbrain areas in the PD and control groups (Pre-PSP-RS *vs.* PD = 1.01 cm^2 vs. 1.29 cm^2, $p < 0.001$; Pre-PSP-RS *vs.* control = 0.87 cm^2 vs. 1.29 cm^2, $p < 0.001$; PSP-RS *vs.* PD, $p < 0.001$; PSP-RS *vs.* control, $p < 0.001$). The P/M ratio in the Pre-PSP-RS group was higher than that in the PD and control groups (Pre-

Table 1
Clinical characteristics of subjects in the PSP-RS, PD, and control groups.

	PSP-RS (n = 27)	PD (n = 27)	Control (n = 27)	*p*-value
Age of onset (years)	71.6 (59–81)[a]	68.2 (41–78)[a]	–	0.082[b]
Sex (male), n (%)	22 (81.5)	22 (81.5)	22 (81.5)	1.000[c]
UPDRS	30.9 (4–70)[a]	17.2 (6–26)[a]	–	< 0.001[b]
H&Y scale	3 (2.5–4)[a]	1.9 (1–2.5)[a]	–	< 0.001[b]
Age at MRI, (years)	69.5 (48–80)[a,d] 73.0 (53–83)[a,e]	69.9 (45–81)[a]	70.3 (48–80)[a]	0.914[c,d] 0.264[c,e]
Presymptomatic MRI to symptom onset (months)	28.4 (12–48)[a]	–	–	–
Symptom onset to diagnostic MRI (months)	12.8 (0–40)[a]	14.4 (0–48)[a]	–	0.157[b]
Presymptomatic to diagnostic MRI (months)	41.6 (14–86)[a]	–	–	–

PSP-RS = progressive supranuclear palsy-Richardson syndrome; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; H&Y = Hoehn and Yahr.
[a] Data are expressed as mean (range).
[b] Statistical analysis using Student's *t*-test.
[c] Statistical analysis using analysis of variance.
[d] Age at presymptomatic MRI in the patients with PSP-RS.
[e] Age at diagnostic MRI in the patients with PSP-RS.

PSP-RS = 5.27, 95% CI = 4.98–5.55, SD = 0.72; PD = 4.03, 95% CI = 3.85–4.22, SD = 0.47; control = 4.06, 95% CI = 3.93–4.19, SD = 0.33; Pre-PSP-RS *vs.* PD, $p < 0.001$, Pre-PSP-RS *vs.* control, $p < 0.001$). This difference became more prominent when comparing the PSP-RS group with the PD and control groups (PSP-RS = 5.99, 95% CI = 5.64–6.34, SD = 0.89; PSP *vs.* PD, $p < 0.001$, PSP *vs.* control, $p < 0.001$). Intra-rater and inter-rater measurements showed excellent correlation. The intra-rater intraclass correlation coefficient was 0.95 for the midbrain area and 0.94 for the pons area ($p < 0.001$). The inter-rater intraclass correlation coefficient was 0.94 for the midbrain area and 0.95 for the pons area ($p < 0.001$).

3.3. ROC curve

The ROC curve analyses are shown in Fig. 2. The midbrain area for patients in the Pre-PSP-RS and PSP-RS groups showed high sensitivity and specificity in differentiating them from the PD and control groups. The P/M ratio also showed high sensitivity and specificity for the Pre-PSP-RS group, allowing for differentiation from the PD and control groups. In the PSP-RS group, the midbrain area and P/M ratio showed higher sensitivity and specificity than in the Pre-PSP-RS group for differential diagnosis from the PD and control groups (Table 2).

3.4. Longitudinal change in the P/M ratio

The midbrain area decreased 0.048 cm^2 (range, 0.003–0.111 cm^2) during the period from Pre-PSP-RS to PSP-RS and did not correlate with age of onset (r = −0.243, $p = 0.222$), disease duration (r = −0.198, $p = 0.326$), baseline midbrain area (r = −0.150, $p = 0.455$), UPDRS part III score (r = 0.184, $p = 0.358$), or H&Y scale (r = 0.198, $p = 0.323$). The mean changes in the P/M ratio between Pre-PSP-RS and PSP-RS patients was 0.25 annually (range, 0.01–0.60). Statistical correlation was not observed between the reduction rate and the age of onset (r = 0.24, $p = 0.904$). Correlations were not found between presymptomatic duration (r = −0.197, $p = 0.326$), baseline P/M ratio (r = 0.381, $p = 0.051$), UPDRS part III score (r = 0.106, $p = 0.600$), or H&Y scale (r = 0.184, $p = 0.359$).

4. Discussion

To the best of our knowledge, this is the first study to investigate midbrain atrophy in patients with Pre-PSP-RS. We analyzed the midbrain area, pons area, and P/M ratio of patients with Pre-PSP-RS who were eventually diagnosed with probable PSP-RS. Our results show that midbrain atrophy preceded the clinical symptoms of PSP-RS and could therefore be a useful diagnostic imaging biomarker for Pre-PSP-RS.

In this study, patients with Pre-PSP-RS had a decreased midbrain area and increased P/M ratio compared with PD patients and normal control subjects. To date, reliable biomarkers for Pre-PSP-RS are unavailable. The presymptomatic stage of PSP has been reported in only a few studies. Piccini and colleagues reported that 33% of asymptomatic relatives of patients with familial PSP showed abnormal 18F-dopa uptake and lower striatal glucose metabolism in a pattern similar to that of their affected relatives [17]. Pathological studies found PSP pathology in 2.1%–4.2% of clinically healthy elderly subjects, providing evidence for neuropathological change that could begin much earlier than clinical symptoms [6,7]. Unlike previous pathologic and functional studies, we demonstrated a significant temporal evolution of midbrain atrophy in individual patients, highlighting the P/M ratio as a practical surrogate marker.

The P/M ratio had high sensitivity and specificity as a diagnostic marker for Pre-PSP-RS, making it a useful tool within conventional brain MRI to distinguish PSP from PD, multiple system atrophy, and healthy controls [9–11,16,18–25] and establish an early clinical diagnosis of PSP [26]. Currently, disease-modifying treatments for PSP have not been discovered, so early diagnosis cannot change the clinical course of PSP. However, various treatments have been attempted for PSP, such as modulating tau phosphorylation, targeting other tau post-translational modifications, and the use of microtubule stabilizers, tau aggregation inhibitors, and anti-tau immunotherapy [27]. Hoglinger and colleagues reported that tideglusib reduced the progression of brain atrophy in PSP patients, especially in the parietal and occipital lobes, where the disease progressed the least [28]. This result showed that early neuroprotective intervention could change disease progression. Early diagnosis and treatment is thus significant in PSP, and the P/M ratio could be an important factor in identifying those patients.

The midbrain atrophy in Pre-PSP-RS patients was significant compared with the PD and control subjects. These differences became more prominent over time, whereas the pons area was relatively preserved. In previous longitudinal MRI change studies, the mean decrease of P/M ratio in PSP patients was reportedly 0.22, with 2.2%–3.5% of volume lost annually [13,29,30]. Those results are similar to the results from the present study, which show a decrease of 0.25 cm^2 (SD = 0.19) in the midbrain area and 0.048 (SD = 0.030) in P/M ratio per year. No correlation between the duration of the presymptomatic stage of PSP and change in the midbrain area or P/M ratio was observed. In other words, the rate of midbrain atrophy did not change with disease progression. In a previous study, the suggested trajectory atrophy model for PSP showed that midbrain volume declined linearly [31], which is in agreement with our results. Nevertheless, estimating the beginning of

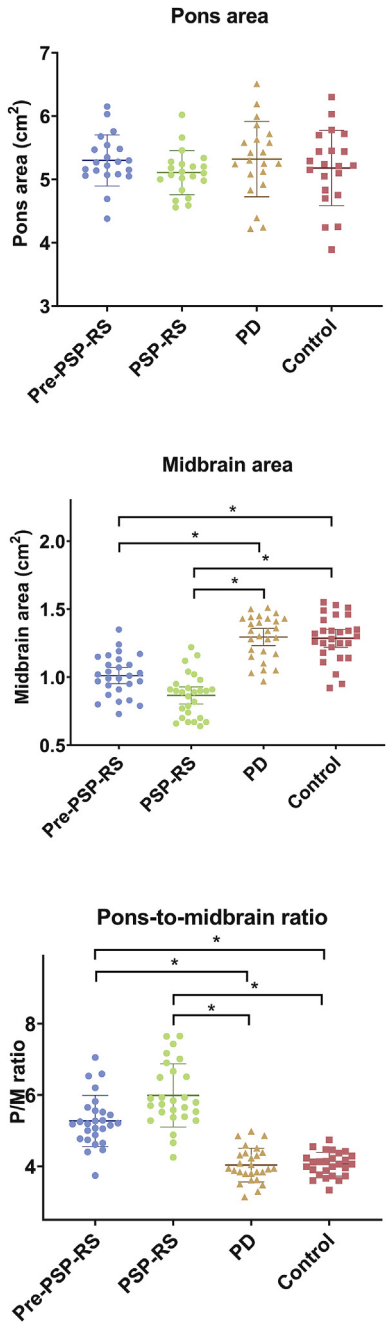

Fig. 1. Scatterplots illustrating the pons area (cm^2), midbrain area (cm^2), and pons-to-midbrain ratio (P/M ratio) in the Pre-PSP-RS, PSP-RS, PD, and control groups. Pre-PSP-RS = presymptomatic progressive supranuclear palsy-Richardson's syndrome; PSP-RS = progressive supranuclear palsy-Richardson's syndrome; PD = Parkinson's disease; P/M ratio = pons-to-midbrain area ratio* $p < 0.001$.

structural change is difficult because the decrement rate varies between individuals, and many factors, including environmental, genetic, and disease subtype, could affect midbrain atrophy. Further studies with many participants are needed to explain this issue.

Most patients in our study underwent brain MRI for health screening purposes, dizziness, headache, cancer work-up, concussion, and transient weakness. Taking brain MRI for health screening without any neurologic symptom is common among elderlies in South Korea. Consequently, the mean age of onset among the participants with Pre-PSP was higher than in epidemiologic studies [32–34]. We included participants who were diagnosed with PSP based on their most recent visit to the Neurology Clinic to reduce the possibility of misdiagnosis. The mean duration from onset to the time of diagnosis was 64.6 months in PSP patients. Therefore, all PSP patients included in this study had clinical symptoms of PSP-RS and were classified as this subtype. Ten of our 27 patients were diagnosed with another subtype of PSP (not RS) at their initial visit to the Movement Disorder Clinic. There was no difference in the P/M ratio according to the initial clinical diagnosis, and all of those patients were finally diagnosed with probable PSP-RS (P/M ratio; suggestive vs. possible vs. probable = 4.94 vs. 5.75 vs. 5.38, $p = 0.287$). Our result coincides with a previous study that suggested midbrain atrophy as a biomarker for the development of vertical supranuclear palsy [35] and a hypothetical model of the clinical trajectories of PSP showing that clinical symptoms of variant PSP syndrome eventually progress into PSP-RS [36].

There have been discussions about how to define the onset of neurodegenerative disease [37]. It is difficult to clearly define the onset of neurodegenerative disease, because the pathologic change of neurodegenerative disease begins much earlier than clinical symptoms. Moreover, there is no consensus or reasonable clinical data to identify prodromal or presymptomatic PSP, as well. To minimized this limitation, we defined PSP-related symptoms subsequently progresses during the clinical course in absence of other identifiable cause, based on the diagnostic criteria [1].

In atypical parkinsonian disorders, a mismatch between pathologic diagnosis and clinical symptom makes it difficult to identify of candidate for clinical trial. For this reason, Eimeren and colleagues recently proposal the neuroimaging biomarker utility system for atypical parkinsonian disorders, the E-S-P methodology (Early-Specific-Progression) for future clinical trials [38]. They graded neuroimaging biomarker according to the ability to accurately identify an intension-to-treat patient population early in the disease (Early), to accurately detect a specific underlying pathology (Specific), and the ability to monitor disease progression (Progression). They also suggested positive predictive value (PPV) and negative predictive value (NPV) is most useful quantifications of diagnostic test performance, which were not presented in our study, because of small sample size of the study and a low prevalence of PSP. However, we firstly present the value of P/M ratio as an presymptomatic neuroimaging biomarker of PSP-RS. A large, prospective study is needed to confirm our result and to present PPV and NPV.

The present study has several limitations. First, the study was retrospective in design; therefore, adequate clinical data about the patients could not be collected. However, investigating Pre-PSP-RS patients prospectively is impossible because PSP is an extremely rare neurodegenerative disease, and diagnostic biomarkers for the presymptomatic stage of PSP-RS have not yet been determined. Furthermore, no reliable data suggest how to estimate the time required to progress from presymptomatic to possible or probable PSP. Recently, Ali and colleagues reported the sensitivity and specificity of new MDS-PSP diagnostic criteria, and they assumed that 6 months was the smallest period in which clinical changes could be recognized [39]. Therefore, we decided on 12 months before the development of clinical symptoms as the presymptomatic stage. Second, we investigated patients clinically diagnosed with PSP, not patients whose diagnoses had been pathologically confirmed. Thus, it is possible that some of our patients had a pathology other than PSP, such as cortico-basal degeneration, Lewy body disease, or multiple system atrophy. To overcome that shortcoming, we included only probable PSP-RS patients with a long follow-up duration whose diagnoses had been based on MDS-PSP criteria shown to have high sensitivity and specificity [39]. Third, we included only PSP-RS patients; therefore, we cannot be certain that other phenotypes of PSP show midbrain atrophy prior to their clinical symptoms. Fourth, we obtained clinical data through chart review and there were no PSP-related symptoms and signs at the time of the first MRI. However, since patients were evaluated by general neurologists, not by movement disorders specialists, it is not possible to exclude that subtle

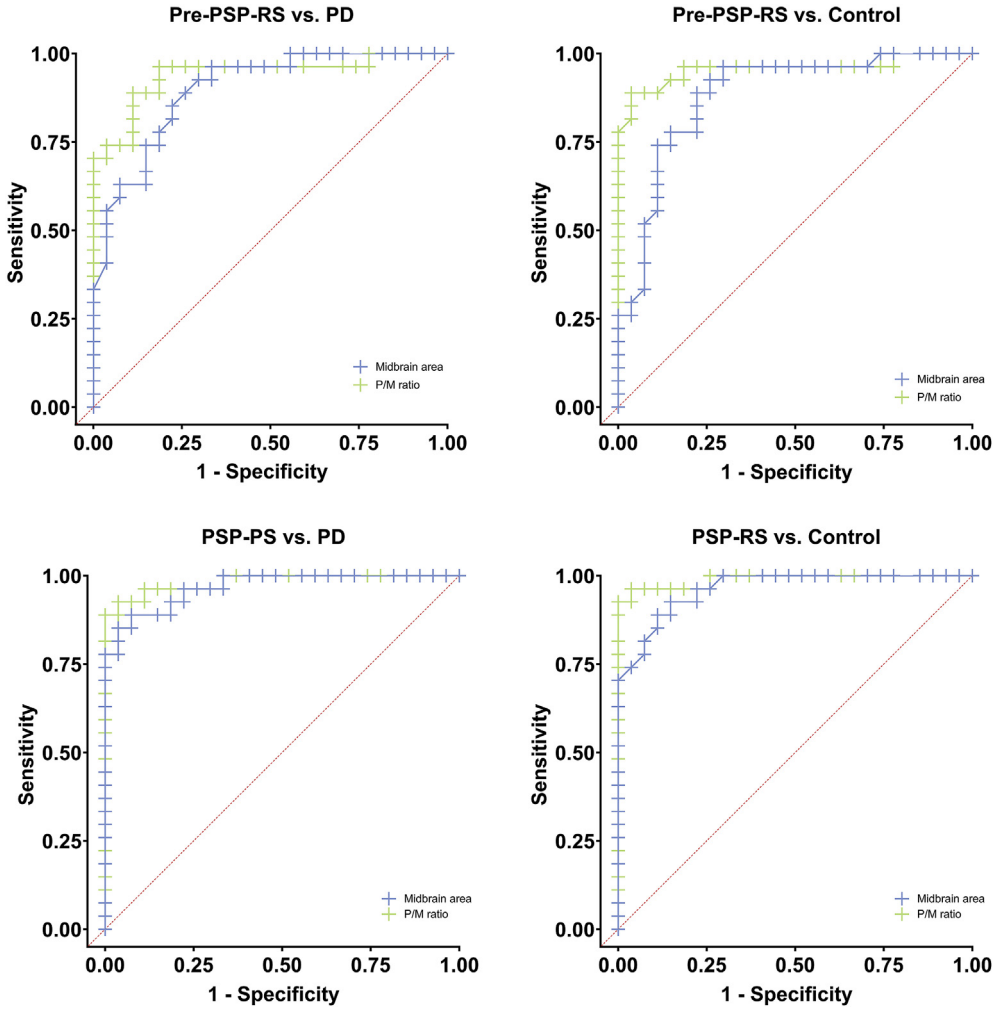

Fig. 2. Receiver operating characteristic curve analysis comparing groups: Pre-PSP-RS *vs*. PD, Pre-PSP-RS *vs*. control, PSP-RS *vs*. PD, and PSP-RS *vs*. control. Pre-PSP-RS = presymptomatic progressive supranuclear palsy-Richardson's syndrome; PSP-RS = progressive supranuclear palsy-Richardson's syndrome; PD = Parkinson's disease; P/M ratio = pons-to-midbrain area ratio.

features of PSP (e.g. slow saccades) were overlooked or not routinely assessed on neurological exam, therefore it is possible that patients meeting criteria for "Suggestive of PSP" were included. Last, no standardized method has been reported to measure P/M ratio, and the MRI data were not obtained in the same medical center or MRI equipment. Therefore, the MRI acquisition was not uniform; however, we minimized this bias by using midsagittal images, a relatively standardized method, to obtain the brain MRI data.

To the best of our knowledge, this is the first study to assess midbrain atrophy in presymptomatic PSP-RS patients and our study could pave the way for finding a presymptomatic biomarker for PSP-RS. Midbrain atrophy could be an important indicator for the application of

Table 2
Cut-off values, sensitivity, specificity, and accuracy of the P/M ratio for differentiation of patients with Pre-PSP-RS, PSP-RS, PD and control groups.

Midbrain area				
	Cut-off values (cm^2)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Accuracy (%)
Pre-PSP-RS *vs*. PD	< 1.10	74.1 (55.3–86.8)	85.2 (67.5–94.1)	79.6
Pre-PSP-RS *vs*. Control	< 1.21	92.6 (76.6–98.7)	74.1 (55.3–86.8)	85.2
PSP-RS *vs*. PD	< 0.96	77.8 (59.2–89.4)	100.0 (87.5–100.0)	88.9
PSP-RS *vs*. Control	< 0.94	74.1 (55.3–86.8)	96.3 (81.7–99.8)	85.2
P/M ratio				
	Cut-off values	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Accuracy (%)
Pre-PSP-RS *vs*. PD	> 4.40	96.3 (81.7–99.8)	81.5 (63.3–91.8)	88.9
Pre-PSP-RS *vs*. Control	> 4.58	88.9 (71.9–96.2)	96.3 (81.7–99.8)	92.6
PSP-RS *vs*. PD	> 5.13	88.9 (71.9–96.2)	100.0 (87.5–100.0)	94.4
PSP-RS *vs*. Control	> 4.81	92.6 (76.6–98.7)	100.0 (87.5–100.0)	96.3

Pre-PSP-RS = presymptomatic progressive supranuclear palsy-Richardson's syndrome; PSP-RS = progressive supranuclear palsy-Richardson's syndrome; PD = Parkinson's disease; P/M ratio = Pons-to-midbrain area ratio.

disease-modifying therapy to patients with PSP-RS and the understanding of this tragic disease.

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Conflicts of interest

Nothing to report.

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