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ORIGINAL COMMUNICATION

# MR imaging of brainstem atrophy in progressive supranuclear palsy

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**Abstract** *Background* To enhance the sensitivity and specificity of the clinical diagnosis of progressive supranuclear palsy (PSP), neuroradiological parameters established in pathologically proven cases are needed. *Methods* We examined brainstem atrophy in five pathologically confirmed PSP patients (three men, mean age at death 77 years, range 64–84 years). Time interval between symptom onset and MRI ranged from 1 to 5 years, and between MRI and death from 33 to 52 months. Only one patient had clinical diagnosis of PSP at the time of MRI. Control group consisted of 19 age- and gender-matched healthy subjects. Seventeen morphometric parameters of the midbrain and pons were measured on T1-weighted midsagittal and T2-weighted axial MRI scans with Image Analyzer. Measurements of superior cerebellar peduncle (SCP) width were performed on PSP autopsy specimens. *Results* Mean SCP width on MRI in PSP (2.7 ± 0.8 mm, 95 %CI: 2.1–3.3) was smaller than in controls (3.7 ± 0.5 mm, 95 %CI: 3.5–3.9). Mean SCP width at autopsy was 8 % smaller than mean SCP width on MRI. Midsagittal midbrain area in PSP (99.1 ± 6.9 $mm^2$, 95 %CI: 90.5–107.6) was smaller than in controls (141.0 ± 18.1 $mm^2$, 95 %CI: 132.2–149.7). Midbrain/pons area ratio in PSP was 1:5 and in controls was 1:4 ($p < 0.01$). Repeat MRI 17 months later in one PSP case revealed 30 % decrease of SCP width. *Conclusions* MR imaging with quantitative analysis may be useful in the diagnosis of early PSP and in monitoring disease course.

**Key words** atrophy · brainstem · MRI · progressive supranuclear palsy

## Introduction

Progressive supranuclear palsy (PSP) is the second most frequent parkinsonian syndrome, diagnosed clinically as probable by virtue of vertical supranuclear gaze palsy and prominent postural instability with falls within the first year of disease [12]. Although the specificity and positive predictive value of the clinical criteria of PSP are high, the diagnosis of definite PSP requires neuropathologic confirmation. It is estimated that the average patient with PSP remains undiagnosed for the first three years, i.e. approximately half of the natural history of PSP [14]. Thus, there is a clear need for biomarkers, which will improve the sensitivity and specificity of current clinical criteria and enhance early diagnosis of PSP.

Atrophy of the upper brainstem is an acknowledged radiological and pathological feature of PSP [2, 5, 6, 21, 26]. The atrophy can be assessed qualitatively or quantitatively on axial or midsagittal MR images. Atrophy of the superior cerebellar peduncles (SCP) was originally described by Steele et al. [23]. Results of our neuropathological study [24] demonstrated significant de-

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crease of SCP width in PSP, compared to other neurodegenerative diseases. Specifically, our results suggested that SCP atrophy may be useful in the differential diagnosis of PSP and corticobasal degeneration (CBD). MRI volumetric analysis showed that the mean SCP volume is significantly lower in PSP and this measurement differentiates among PSP, Parkinson's disease (PD), multiple system atrophy (MSA), and healthy control subjects [18]. However, the issue of clinical usefulness of a simple measurement of SCP width on routine MRI images in early-stage PSP was not addressed. Other authors reported utility of different radiological parameters for diagnosis of PSP, based on either visual assessment [1, 16, 20] or morphometric analysis of midbrain atrophy [11, 15, 26]. Most of these studies were cross-sectional and lack pathological confirmation. Therefore, we decided to examine upper brainstem atrophy in MRI in pathologically proven PSP cases. Our approach involved three steps: 1) assessment of whether the SCP width measured on routine MRI provides diagnostic information in patients with early-stage PSP; 2) correlation between MRI and autopsy measurements of SCP, and 3) validation of diagnostic utility of other brainstem MRI measurements.

## Material and methods

### Patients and control group

This study was conducted with Mayo Foundation Institutional Review Board approval. Five patients (3 men, mean age at death: 77 years; range: 64–84) with pathologically confirmed PSP were studied retrospectively. A pathologic diagnosis was made by one neuropathologist (DWD), according to consensus criteria [7]. The database of the Mayo Clinic Jacksonville (MCJ) was searched for subjects with histopathological diagnosis of PSP, and who were seen by MCJ neurologists. This search revealed seventeen individuals. MRI scans were available for five. Demographic and clinical data of these patients are given in Table 1.

A control group consisting of 19 subjects (12 men, mean age at MRI examination: 75 years; range: 64–87) was selected from the MCJ patients who had MRI performed with an indication for the study defined as "headache". Neurological examination in the control group was normal and MRI did not show any abnormalities except for age-related cerebral atrophy and signal abnormality consistent with small vessel disease.

### Autopsy study

Five fixed PSP brains were subjected to measurement of the SCP. Brains were submitted with one hemibrain fixed in formaldehyde and the other frozen. In 3 cases the left hemibrain and in two the right was examined. Brains were dissected on average 2 to 3 weeks after death. The method of morphometric evaluation of SCP was described in detail previously [24]. Briefly, digital images of the transverse brainstem sections cut at the level of the trigeminal nerve (Fig. 1E) were transferred to the workstation. The distance between the outer and inner borders of SCP was measured interactively at three levels (along the dorso-ventral axis) on four times magnified images and the mean SCP width was calculated. Image analysis software (MetaMorph, version 6.3r3, Molecular Devices, Downington, PA) was utilized for line measurements, calibrating for length, by measuring a 1 cm segment on a ruler included in each digital picture. Because of the suboptimal quality of anatomical detail in most of the autopsy midsagittal sections, they were not included in morphometric analysis.

### MRI analysis of the midbrain and pons

All MRI exams were performed on 1.5-Tesla units (GE Medical Systems, Milwaukee, WI or Siemens, Erlangen, Germany). MRI exams were performed between 1997 and 2005. The sequences included sagittal T1-weighted images [repetition time (TR) range/echo time (TE) range, 516–665 ms/15–17 ms, number of excitations (Nex), 1–2)] and axial T2-weighted images (TR range/TE range, 3950–6390 ms/94–108 ms; Nex, 1). Section thickness was uniformly 5 mm; intersection gap was 1 mm for all sequences and all patients, except for the T2-weighted sequence for patient #3, with spacing of 2.5 mm.

T1-weighted midsagittal (Fig. 1A) and T2-weighted axial MR images (Fig. 1D) taken at the level of SCP were imported to the workstation and studied with an image analysis software, using the same equipment and technique used for analysis of autopsy specimens. Line measurements of SCP width (Fig. 2A) and area measurements of series of pre-defined brainstem regions were performed interactively on four times magnified MR images. For measurements in midsagittal plane, the two approaches described previously [11, 15] were applied (Fig. 2B, C). We also measured the anteroposterior diameter of the aqueduct, superior and inferior colliculi and tectal plate length and elongation. All measurements were done by one author (JS), who was blinded to the clinical data. The measurements were performed three times for each patient and the mean values were used for statistical analysis.

### Coregistration of images

Anatomical subregions (midsagittal section of the brainstem and transverse section of the pons at the level of SCP) from high resolution autopsy photographs were manually segmented and visually co-registered (Analyze 7.0, Biomedical Imaging Resource, Mayo Clinic Foundation, Rochester, MN) to the anatomy on the MR image of the corresponding patient. The segmented autopsy image was scaled, rotated, translated and displayed in a false translucent color to achieve the best visual co-registration with the MR anatomy (Fig. 1A–F).

### Statistical analysis

The Mann-Whitney U test with Bonferroni post-hoc analysis was used for comparison of the mean values of examined parameters between PSP patients and the control group. Intrarater variability was measured by a coefficient of variation (CV), of 5 consecutive measurements performed for each parameter. Correlation between measured parameters and patient age at MRI and disease duration was evaluated with the Spearman rank order test. Data were expressed as the mean ± SD and 95 % confidence interval (95 % CI). A $p$ value $< 0.05$ was considered significant.

## Results

Mean disease duration was six years (range 4–8 years). Mean time interval between symptom onset and MRI was 2.4 years (range 1–5 yr), and between MRI and autopsy was 45 months (range 33–52 months). There was a high correlation between intraobserver measurements, both in axial and midsagittal planes (CV $\leq$6 %).

**Table 1** Demographic and clinical data of five patients with progressive supranuclear palsy

| | Case 1a* | Case 1b* | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|---|
| Sex | M | | F | M | M | F |
| Brain weight (g) | 1080 | | 1200 | 1100 | 1340 | 1140 |
| Side of brain available for autopsy | L | | R | L | L | R |
| Age at onset (yr) | 67 | | 73 | 74 | 60 | 79 |
| Symptom duration (yr) | 7 | | 6 | 8 | 4 | 5 |
| Age at MRI (yr) | 68 | 70 | 75 | 79 | 61 | 80 |
| Time interval between MRI and autopsy (months) | 65 | 48 | 49 | 33 | 42 | 52 |
| Physician's impression at MRI examination | early PD | PD, Dx of PSP two years later | suggest PSP | FTD, Dx of PSP one year later | PD/PSP, Dx of PSP three years later | CBD |
| Vertical supranuclear ophthalmoparesis I | 0 | 1 | 0 | 0 | 0 | 1 |
| Vertical supranuclear ophthalmoparesis II | 1 | 1 | 1 | 0 | 1 | 1 |
| Slow vertical saccade I | 0 | 1 | 1 | 1 | 0 | 1 |
| Slow vertical saccade II | 1 | 1 | 1 | 1 | 1 | 1 |
| Postural instability I | 0 | N/A | 1 | 1 | 1 | 1 |
| Postural instability II | 0 | 1 | 1 | 1 | 1 | 1 |
| Parkinsonism I** | 1 | 1 | 1 | 1 | 1 | 1 |
| Parkinsonism II** | 1 | 1 | 1 | 1 | 1 | 1 |
| Levodopa response I | N/A | N/A | 1 | N/A | 0 | 0 |
| Levodopa response II | 1 | 1 | 1 | N/A | 0 | 0 |
| Cognitive disturbances I | 1 | 1 | 1 | 1 | 0 | 0 |
| Cognitive disturbances II | 1 | 1 | 1 | 1 | 0 | 0 |
| Apathy I | 1 | 1 | 0 | 0 | 1 | 0 |
| Apathy II | 1 | 1 | 0 | 0 | 1 | 0 |
| Disinhibition I | 0 | 0 | 1 | 1 | 0 | 0 |
| Disinhibition II | 0 | 0 | N/A | 1 | 0 | 0 |
| Depression I | 0 | 0 | 0 | 0 | 0 | 0 |
| Depression II | 0 | 0 | 0 | 0 | 0 | 0 |
| Dystonia I | 0 | 0 | 0 | 0 | 0 | 1 |
| Dystonia II | 0 | 0 | 1 | 0 | 0 | 1 |
| Pyramidal signs I | 0 | 0 | 0 | 0 | 0 | 0 |
| Pyramidal signs II | 0 | 0 | 0 | 0 | 0 | 0 |
| Cerebellar signs I | 0 | 0 | 1 | 1 | 0 | 1 |
| Cerebellar signs II | 0 | 0 | N/A | 1 | 0 | 1 |
| Dysautonomia I | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysautonomia II | 0 | 0 | 1 | 0 | 0 | 0 |
| Dysarthria/Dysphagia I | 1 | 1 | 1 | 1 | 1 | 1 |
| Dysarthria/Dysphagia II | 1 | 1 | 1 | 1 | 1 | 1 |

* Patient #1 had two MRI examinations, 1a refers to the data at the first MRI, 1b – to the data at the repeat MRI; ** akinetic-rigid syndrome
*1* clinical feature is present; *0* clinical feature is absent
*I* refers to the clinical examination prior to MRI; *II* refers to the clinical examination after MRI
*CBD* corticobasal degeneration; *Dx* diagnosis; *FTD* frontotemporal dementia; *N/A* not available or could not examine; *PD* Parkinson's disease; *PSP* progressive supranuclear palsy

Anatomical details seen on MR images corresponded well with those observed at autopsy (Fig. 1 A–F).

## Axial measurements

In PSP patients, the mean left and right SCP width was 2.8 ± 0.8 mm and 2.6 ± 0.9 mm, respectively. In controls, the mean left and right SCP width was 3.8 ± 0.5 mm and 3.5 ± 0.5 mm. The differences between the two sides in PSP and control subjects were not significant. Comparison between PSP and control subjects showed that both left and right SCP were significantly smaller in patients with PSP (Table 2, Fig. 3A). One patient (case #1) had a second brain MRI repeated after a 17-month interval. On the first examination, the left SCP measured 2.9 mm and the right 3.2 mm; on the repeat examination, similar measurements were 2.0 and 2.3 mm, respectively (Table 3). At autopsy, three left and two right SCPs were examined, and their mean width was 2.4 ± 0.3 mm. The differences between SCP diameters obtained from MRI and at autopsy were not significant, with good radiographic-anatomical correlation (Fig. 1D–F). In four cases, the difference between MRI and autopsy mea-

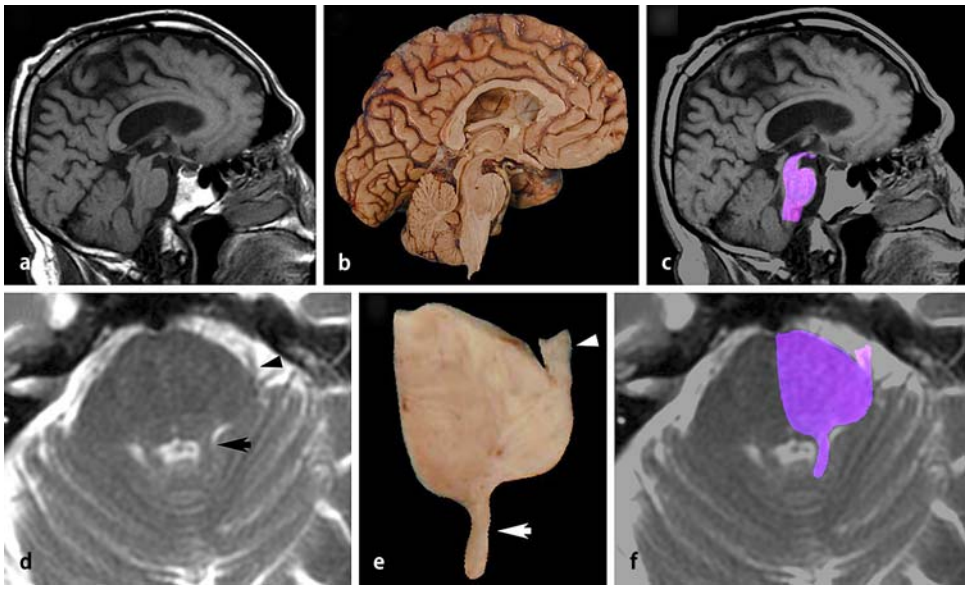


**Fig. 1** Representative radiological and autopsy images of the brain and brainstem of two progressive supranuclear palsy (PSP) cases: **A** Case 3. Midsagittal T1-weighted MRI of the brain shows pronounced atrophy of the midbrain as well as mild generalized cerebral atrophy. The midbrain area in this case measured 89 $mm^2$ and the midbrain/pons area ratio was 0.172. **B** Corresponding autopsy specimen from the same case. **C** The brainstem from high resolution autopsy photograph was manually segmented (shown in pink) and visually co-registered to anatomy in the MR image of the corresponding patient. MRI study was obtained nearly three years before patient's death at age 82 years. **D** Case 1. Axial T2-weighted MRI of the brainstem at the level of the left trigeminal nerve (arrowhead) shows atrophy of the superior cerebellar peduncles (SCP, arrow). The left SCP width in this case was 2.0 mm and the right SCP was 2.3 mm. **E** Corresponding autopsy specimen of the left half of the pons. Trigeminal nerve (arrowhead) and SCP (arrow) are seen. **F** The left half of the pons (including SCP) from autopsy photograph was segmented (shown in violet) and co-registered to the axial MR image of the same patient. MRI study was obtained four years before patient's death at age 74 years. Good radiologico-anatomical correlation is evident in both cases

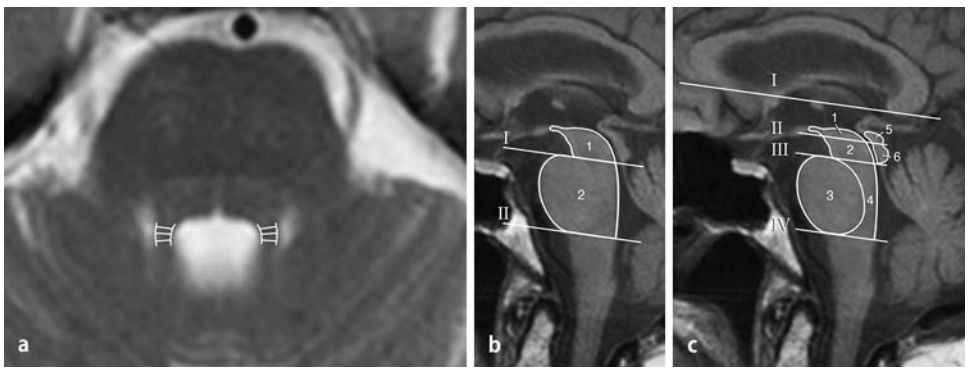


**Fig. 2** Scheme for the measurements of the brainstem on axial and midsagittal MRI images: **A** T2-weighted axial MRI at the level of trigeminal nerves. The distance between the outer and inner borders of SCP was measured at three levels (along the dorso-ventral axis) on four times magnified images. **B** T1-weighted midsagittal MRI of the brainstem. The method of Oba et al. [15]. The midbrain and pons were separated by a line (I) passing through the superior pontine notch and the inferior edge of the tectal plate. The lower border of the pons was limited by a line (II) drawn parallel to the first, passing through the inferior pontine notch. The area of the midbrain [1] and pons [2] was measured, and a ratio of the midbrain area to the pons area was calculated. **C** The method of Kato et al. [11]. The reference line (I) passes through the base of the genu and splenium of the corpus callosum. The two parallel lines (III and IV) separate the pons from the midbrain superiorly and the medulla inferiorly. Additional parallel line (II), divides the midbrain into rostral and caudal part through a mid-collicular plane. The area of the rostral midbrain [1], caudal midbrain [2], basis pontis [3], tegmentum pontis [4], superior colliculus [5] and inferior colliculus [6] were measured

surements was 10 % or less. In one case (#3), SCP width measured on MRI was 40 % larger than at autopsy (Table 3).

## Sagittal measurements

Comparison of midsagittal MRI between PSP and control patients showed significant brainstem atrophy in PSP. The atrophy was most evident with regard to the

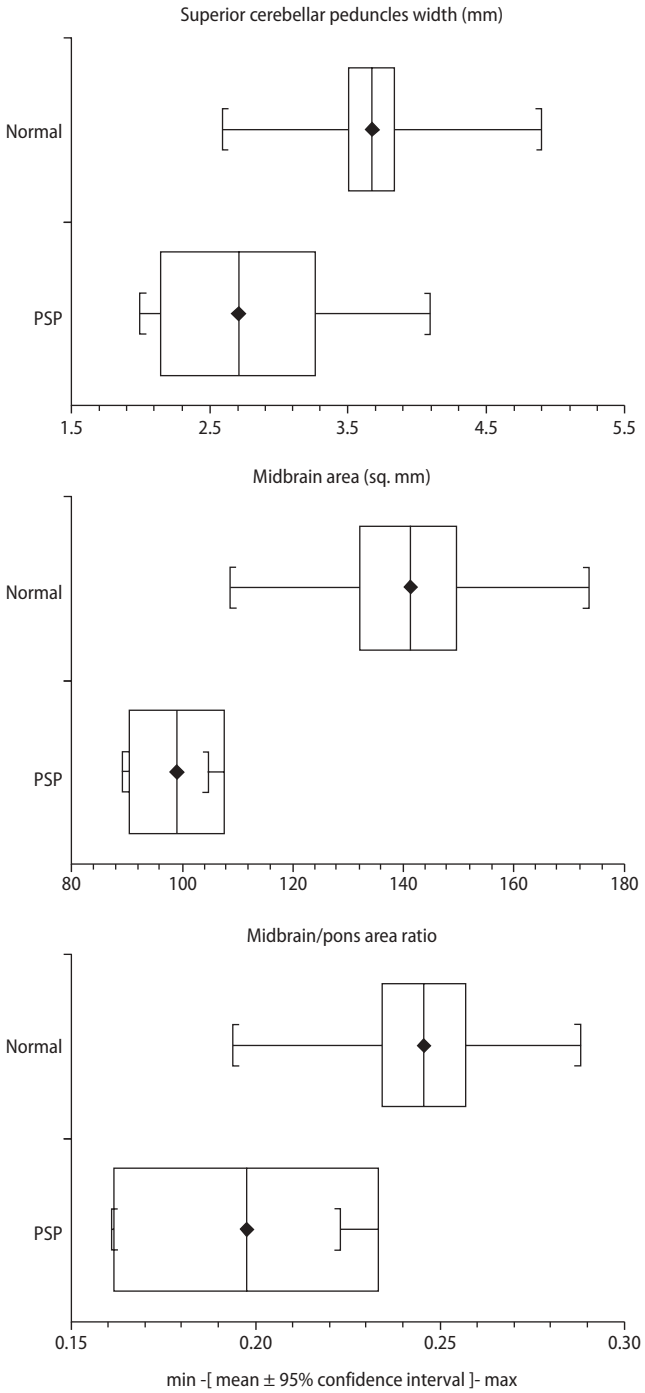


**Fig. 3** Box plot (mean, 95 %CI, and range) of the superior cerebellar peduncles width, the area of the midbrain and the ratio of the area of the midbrain to the area of the pons, for patients with PSP and normal controls. The mean values of all presented parameters were significantly smaller in PSP patients compared to controls. Midbrain area was the only one parameter which did not show overlap of values between the two studied groups

area of the midbrain ($99.1 \pm 6.9\,mm^2$ in PSP vs. $141.0 \pm 18.1\,mm^2$ in controls, $p = 0.01$), and the ratio of the area of the midbrain to the area of the pons ($0.198 \pm 0.029$ vs. $0.246 \pm 0.024$, $p = 0.04$) (Table 2, Fig. 3B, C). Analysis of 95 %CI showed that SCP width, midbrain area and rostral midbrain area in PSP and controls were fully separated (Table 2, Fig. 3A–C). In the control group, a sex difference with regard to the area of the pons and basis pontis was observed, with larger values in men than in women ($p < 0.05$). None of the examined parameters showed significant correlation with patient age at time of MRI or symptom duration before radiologic examination.

## Discussion

Despite standardization and optimization of diagnostic criteria, the differential diagnosis of parkinsonian syndromes remains difficult. Previous studies showed that diagnostic accuracy in parkinsonism may be surprisingly low, with up to one-third of cases misdiagnosed [9, 13]. Clinicopathological analysis of 143 cases of parkinsonism, performed by Hughes and coworkers [8], revealed that more than 60 % of cases with the final diagnosis of a parkinsonian syndrome other than PD had their diagnosis changed over the course of disease. The mean time to revision of the clinical diagnosis was 5.4 years. Therefore, there is a need for biomarkers, able to assist early identification of particular parkinsonian syndromes (high sensitivity) and to differentiate them from the other disorders (high positive predictive value). Because PSP is a rare disease, a low sensitivity of diagnostic tests makes it more difficult to identify cases for therapeutic trials and epidemiologic studies [13].

The results of our investigations, which included quantitative analysis of multiple radiological parameters characterizing upper brainstem atrophy, may potentially enhance the early diagnosis of PSP. Our results showed that SCP width, midbrain area, and the midbrain/pons area ratio measured on routine MRI are significantly decreased in PSP patients presenting for examination approximately two and a half years after symptom onset. Different approaches have been applied for assessment of brain atrophy in PSP. They include linear measurements of anteroposterior midbrain diameter [22, 26], visual [28], or volumetric [18] analysis of SCP atrophy and volumetric analysis of the entire brain [3–5, 10, 17]. However, most authors focused on the analysis of brainstem regions, especially the midbrain, on the midsagittal MRI. All studies confirmed midbrain atrophy in PSP emphasizing its utility for differential diagnosis from CBD, MSA, PD and other parkinsonian disorders [1, 2, 4, 11, 15, 20, 21, 27].

The design of our study differs from those published previously. We retrospectively analyzed MR images in subjects with pathological diagnosis of PSP; however, at the time of MRI their diagnosis was not clear. In most

**Table 2** Summary of the morphometric analyses performed on axial and midsagittal brainstem MR images in five patients with PSP and in nineteen healthy control subjects

| Parameter (unit) | PSP patients Mean ± SD (95 % CI) n = 5 | Control subjects Mean ± SD (95 % CI) n = 19 |
|---|---|---|
| Axial measurements | | |
| Left SCP width (mm) | 2.8 ± 0.8 (1.7–3.9)[a] | 3.8 ± 0.5 (3.6–4.1) |
| Right SCP width (mm) | 2.6 ± 0.8 (1.6–3.6)[a] | 3.5 ± 0.5 (3.3–3.8) |
| Total SCP[b] (mm) | 2.7 ± 0.8 (2.1–3.3)[a] | 3.7 ± 0.5 (3.5–3.9) |
| Midsagittal measurements | | |
| Midbrain area ($mm^2$) | 99.1 ± 6.9 (90.5–107.6)[a] | 141.0 ± 18.1 (132.2–149.7) |
| Pontine area ($mm^2$) | 506.4 ± 50.0 (444.3–568.4) | 574.5 ± 57.5 (546.7–602.2) |
| Midbrain/pontine area ratio | 0.198 ± 0.029 (0.162–0.234)[a] | 0.246 ± 0.024 (0.234–0.257) |
| Rostral midbrain area ($mm^2$) | 32.2 ± 1.6 (30.1–34.2) | 41.1 ± 11.8 (35.4–46.8) |
| Caudal midbrain area ($mm^2$) | 82.4 ± 20.8 (56.56–108.2) | 109.0 ± 22.8 (98.0–120.0) |
| Basis pontis area ($mm^2$) | 343.4 ± 42.6 (290.6–396.3) | 390.8 ± 36.2 (373.4–408.2) |
| Tegmentum pontis area ($mm^2$) | 159.8 ± 16.2 (139.8–180.0) | 189.5 ± 29.1 (175.4–203.5) |
| Superior colliculus area ($mm^2$) | 21.9 ± 2.3 (19.1–24.7) | 22.0 ± 5.6 (19.3–24.8) |
| Inferior colliculus area ($mm^2$) | 19.8 ± 1.6 (17.8–21.8) | 20.4 ± 2.8 (19.1–21.8) |
| Aqueduct A-P diameter (mm) | 1.5 ± 0.2 (1.2–1.8) | 1.4 ± 0.2 (1.3–1.6) |
| Superior colliculus AP diameter (mm) | 3.9 ± 0.5 (3.2–4.5) | 4.0 ± 0.5 (3.7–4.2) |
| Inferior colliculus AP diameter (mm) | 3.4 ± 0.4 (2.9–4.0) | 3.3 ± 0.5 (3.0–3.5) |
| Mean AP diameter of the colliculi (mm) | 3.6 ± 0.4 (3.2–4.1) | 3.6 ± 0.4 (3.4–3.8) |
| Tectal plate length (mm) | 11.3 ± 1.0 (10.1–12.6) | 12.0 ± 0.7 (11.7–12.3) |
| Tectal plate elongation[c] | 3.15 ± 0.49 (2.5–3.8) | 3.35 ± 0.38 (3.2–3.5) |

[a] $p < 0.05$; compared with control (with Bonferroni correction for multiple comparisons)
[b] total SCP width was defined as a mean of the left and right SCP width
[c] Tectal plate elongation was defined as a ratio of the tectal plate length to the mean width of the colliculi
*AP* anteroposterior; *PSP* progressive supranuclear palsy; *SCP* superior cerebellar peduncle

**Table 3** Comparison of SCP width measured on axial T2-weighted MR images and at autopsy in five patients with PSP. Note that only one side of the brainstem was available for autopsy

| | L SCP width at MRI (mm) | R SCP width at MRI (mm) | SCP width at autopsy (mm, side) | Time interval between MRI and autopsy (months) |
|---|---|---|---|---|
| Case 1a* | 2.9 | 3.2 | | 65 |
| Case 1b* | 2.0 | 2.3 | 2.2 (L) | 48 |
| Case 2 | 2.3 | 2.1 | 2.2 (R) | 49 |
| Case 3 | 4.1 | 4.0 | 2.5 (L) | 33 |
| Case 4 | 2.4 | 2.1 | 2.3 (L) | 42 |
| Case 5 | 3.2 | 2.6 | 2.9 (R) | 52 |
| Mean (± SD) | 2.8 ± 0.8 | 2.6 ± 0.8 | 2.4 ± 0.3 | 45 ± 8 |

* Patient #1 had MRI performed two times. Only the results of the second MRI examination were used for statistical analysis. *L* left; *R* right; *SCP* superior cerebellar peduncle

studies, patients are enrolled on the basis of clinical diagnosis of PSP without pathological confirmation [1, 3, 11, 15, 16, 18, 20]. In our study, at the time of MRI, the diagnosis of PSP was suspected in only one patient. Others were diagnosed with PD (3 cases) and CBD (1 case) (Table 1). In three cases, the diagnosis of PSP was made from 1 to 3 years after MRI and one patient remained diagnosed as CBD until death.

Longitudinal observation available in one patient (#1) showed rapid atrophy of SCP within less than two years after initial MRI, which was performed in the early stage of the disease (about 12 months after symptom onset). Interestingly, SCP width was the parameter that showed the largest decrease (about 30 %) between consecutive examinations, suggesting that repeated measurements of SCP width may assist in monitoring the course of PSP.

In four cases, despite an average interval of 4 years between MRI and death, there was a close correlation between radiological and autopsy measurements. Although most of our observations suggest the early occurrence of SCP atrophy in the course of PSP with its later stability over time, one patient (#3) had a 40 % decrease in SCP width between MRI and death, an interval of less than 3 years. To assess the actual rate of brain and brainstem atrophy in PSP, longitudinal studies with multiple serial MRI exams were recently reported [10, 17]. Both of these studies confirmed selective midbrain at-

rophy in PSP by means of volumetric analysis. The mean midbrain atrophy rate in PSP was seven times greater than in healthy controls [17].

The strength of our study was that all patients had MRI done in the early phase of the disease and their diagnosis was confirmed pathologically by the same neuropathologist, using the same criteria. Availability of autopsy SCP specimens allowed correlation of radiological and pathological images and assessment of disease progression. MRI was done at the same institution, using nearly identical neuroimaging technique. Furthermore, assessment of MR and autopsy images was performed by a single blinded investigator with the same image analysis system.

Limitations of this study were the small number of cases and the lack of a disease control group. Because the utility of midbrain atrophy in differentiating the later stages of PSP from other parkinsonian syndromes was confirmed earlier, we focused on the possibility of detection of early-stage PSP by using routine MR examination. Thus, the current study indicates sensitivity of MR findings (brainstem atrophy) in the early diagnosis of PSP, rather than its usefulness in the differential diagnosis of PSP and other parkinsonian syndromes (i.e. positive predictive value). We assumed that if a particular parameter does not differentiate between PSP and normal subjects, it is unlikely to be useful in the differentiation of PSP from other neurodegenerative disorders.

The small number of patients in our study does not permit addressing the issue of correlation between different clinical phenotypes of PSP and their radiological biomarkers. One may expect that some radiological parameters may vary between different subgroups of PSP (e.g. Richardson's syndrome and PSP-parkinsonism), which differ in clinical course and the tau isoform composition of pontine neurofibrillary tangles [Williams 2005]. Indeed, the heterogeneity of clinical phenotype of PSP is evident even in our small group of patients (Table 1).

In summary, we demonstrated SCP and midbrain atrophy on routine MRI of pathologically proven PSP cases; MRI was obtained early in the disease course. Further prospective studies are needed to confirm the value of routine MRI in the diagnosis and delineation of PSP from other neurodegenerative disorders.

## Conclusions

MRI is helpful in making a diagnosis of PSP. Longitudinal brainstem MRI studies may provide a useful biomarker for monitoring disease progression. Therefore, MRI could be potentially used in therapeutic trials for PSP patients.

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