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ORIGINAL ARTICLE

Increased Signal in the Superior Cerebellar Peduncle of Patients with Progressive Supranuclear Palsy

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ABSTRACT

Objective The provisional diagnosis of progressive supranuclear palsy (PSP) depends on a combination of typical clinical features and specific MRI findings, such as atrophy of the tegmentum in the midbrain. Atrophy of the superior cerebellar peduncle (SCP) distinguishes PSP from other types of parkinsonism. Histological factors affect the conventional fluid-attenuated inversion recovery (FLAIR) signals, such as the extent of neuronal loss and gliosis.

Methods We investigated patients with PSP to verify the percentage of patients with various PSP phenotypes presenting a high signal intensity in the SCP. Three interviewers, who were not informed about the clinical data, visually inspected the presence or absence of a high signal intensity in the SCP on the FLAIR images. We measured the pixel value in the SCP of each patient. Clinical characteristics were evaluated using the Mann-Whitney test, followed by the χ^2 test.

Results Ten of the 51 patients with PSP showed a high signal intensity in the SCP on FLAIR MRI. Higher pixel values were observed within the SCP of patients with a high signal intensity in the SCP than in patients without a high signal intensity ($p < 0.001$). The sensitivity and specificity of the high signal intensity in the SCP of patients with PSP was 19.6% and 100%, respectively. This finding was more frequently observed in patients with PSP with Richardson's syndrome (PSP-RS) (25.7%) than other phenotypes (6.2%).

Conclusion The high signal intensity in the SCP on FLAIR MRI might be an effective diagnostic tool for PSP-RS.

Key Words Atrophy; FLAIR; Magnetic resonance imaging; Neurodegenerative disease; Progressive supranuclear palsy; Superior cerebellar peduncle.

Progressive supranuclear palsy (PSP) is characterized by postural instability, vertical supranuclear gaze palsy, axial rigidity, symmetric bradykinesia, pseudobulbar palsy, and dementia.[1] Recently, patients with atypical PSP have been classified according to the clinical phenotypes of PSP.[2] A definite diagnosis is based on the pathological findings in the brain. However, the provisional diagnosis depends on a combination of typical clinical features and specific MRI findings. Atrophy of the tegmentum in the midbrain, signal changes in the midbrain, and an increase in the size of the third ventricle are well-known morphological MRI features of PSP.

Some superior cerebellar peduncle (SCP) fibers project to the reticular and vestibular nuclei in the brainstem, which may contribute to impaired posture and balance.[3] Selective damage to SCP that impairs the smooth pursuit movements may contribute to gaze palsy in patients with PSP.[2] SCP atrophy, which

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is based on gross pathological or MRI findings, distinguishes PSP from Parkinson's disease (PD) or multiple systemic atrophy (MSA),[4-6] and the pathological microscopic changes in SCP include gliosis and demyelination.[4] In addition, the integrity of the white matter tract in the SCP on diffusion-tensor MRI correlates with the score on the clinical rating scale for PSP, although whole-brain and midbrain findings do not correlate with the score.[7] Numerous MRI studies have used advanced MRI techniques, such as quantitative volumetric MRI or diffusion-tensor imaging. Conventional MRI is useful for specifically distinguishing PSP from other parkinsonian syndromes, and it diagnoses > 70% patients with PSP.[8] Some studies have examined the SCP of individuals with PSP using conventional MRI,[9-12] and a recent meta-analysis has shown that the SCP size represents a potential diagnostic tool for PSP.[13] However, no study has evaluated the change in signal intensity within the SCP in patients with PSP. In 2006, we assessed the SCP of 12 patients with clinically probable PSP using conventional fluid-attenuated inversion recovery (FLAIR) MRI because histological factors affect the FLAIR signals, such as the extent of neuronal loss and gliosis.[14] High signal intensity in the SCP was evident in some patients with PSP but not in patients with PD and MSA with predominant parkinsonism, as well sex-matched and age-matched healthy controls.[14] The sensitivity and specificity of the high signal intensity in the SCP of individuals with PSP were 25% and 100%, respectively. However, this study included a small number of patients. Thus, we subsequently examined a large number of patients with PSP to estimate the percentage of patients in which a high signal intensity was visualized in the SCP and to verify whether the high signal intensities are evident in patients with each clinical phenotype of PSP.

MATERIALS & METHODS

We assessed 51 of 76 patients with suspected PSP who were admitted to our hospital from January 2010 to August 2018. Clinical phenotypes of PSP were classified as previously described.[2,15] The following clinically probable PSP phenotypes were defined according to the Movement Disorder Society (MDS)-PSP criteria: PSP with Richardson's syndrome (PSP-RS), PSP with progressive gait freezing (PSP-PGF), PSP with predominant parkinsonism (PSP-P), PSP with predominant frontal presentation (PSP-F), PSP with predominant corticobasal degeneration, and PSP with predominant speech/language disorders. These patients, including patients with other clinical phenotypes of PSP, had supranuclear vertical gaze palsy and postural instability, and they experienced falls within 3 years after the onset of PSP symptoms (32 patients within 1 year). We excluded patients with any of the following conditions: intracranial large vessel disease, multiple lacunar infarctions, or a tumor on cranial MRI. Patients with grade 3 white matter lesions according to the Fazekas scale[16] on cranial MRI and patients with orthostatic hypotension, which is defined as a decrease in systolic blood pressure > 20 mmHg or in diastolic blood pressure > 10 mmHg upon standing, were also excluded. Patients with PSP with predominant cerebellar ataxia (PSP-C) were also included in our study.[17] Cerebellar ataxia was defined as the presence of gait ataxia and one of the following signs: cerebellar dysarthria, limb ataxia, or sustained gaze-evoked nystagmus.[18] At least two experienced neurologists assessed the neurological findings from the patients.

MRI evaluation

All MRI studies were performed on a 1.5-T or 3.0-T MRI device using turbo spin-echo sequences for T2-weighted (5-mm slice thickness, with a 1-mm interslice interval), T1-weighted (5-mm slice thickness, with a 1-mm interslice interval), and FLAIR images (5-mm slice thickness, with a 1-mm interslice interval). Twenty and 31 patients with PSP underwent 3.0-T and 1.5-T MRI, respectively. The TR and TE ranged from 4,000 to 12,000 and from 50 to 384, respectively. Three interviewers (neurologists with 18, 16, and 6 years of experience) who were not informed about the clinical data visually inspected the changes in signal intensity on the FLAIR images. The signal intensity of the SCP was evaluated at the pontine level in SCP fibers. The three interviewers evaluated the presence or absence of a high signal intensity in the SCP on the FLAIR images. The presence of a high signal intensity was confirmed only when each reviewer consistently confirmed a positive result during the first evaluation. Equivocal cases in which the first judgment of all reviewers was inconsistent were excluded. We repeatedly asked the same reviewers to evaluate the lesions that they initially considered positive to increase the accuracy of this evaluation, and the result was similar to the first evaluation. FLAIR imaging at the pontine level with SCP fibers of the patients with PD was randomized into panels of FLAIR images captured in patients with PSP (Figure 1). We measured pixel values within the SCP and calculated the relative signal intensity ratio using the pixel value of the SCP divided by the pixel value of the middle part of the pons with SCP fibers. The categories were evaluated using the Mann-Whitney U test and χ^2 test to analyze the statistical significance of differences in the clinical characteristics or MRI findings, such as the internal signal intensity in the SCP, between patients with different clinical phenotypes of PSP. The Statistical Package for the Social Sciences software (version 24 for Mac; IBM Corp., Armonk, NY, USA) was used for statistical analyses.

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Ethics statement

No investigations or interventions were performed outside of routine clinical care for these patients. This study was approved by the Medical Ethics Committee of Nara Medical University (No. 2163). Written, fully informed consent was obtained during the routine clinical care of these patients. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this study is consistent with those guidelines.

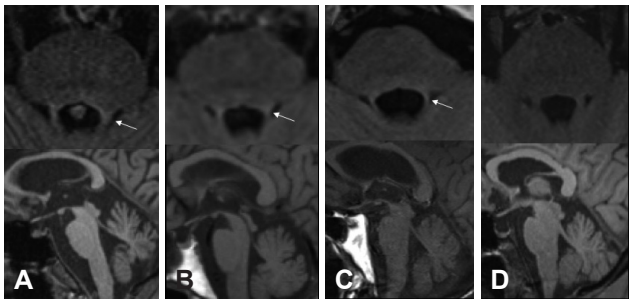

Figure 1. Conventional fluid-attenuated inversion recovery MRI at the pontine level with superior cerebellar peduncle (SCP) fibers. Patients with progressive supranuclear palsy with Richardson's syndrome showed high signals in the SCP on the axial view and atrophy of the SCP on the sagittal view (arrows) (A-C). Patients with Parkinson's disease (D) showed no changes in the signal and atrophy of the SCP.

RESULTS

The clinical characteristics and MRI findings of 51 patients with PSP are summarized in Table 1 and 2, respectively. The 35 patients with PSP-RS had the most common phenotype, and 16 patients had other phenotypes, including PSP-P (n = 4), PSP-F (n = 4), PSP-PGF (n = 2), PSP-C (n = 2), PSP with predominant corticobasal degeneration (n = 1), PSP presenting as primary lateral sclerosis (n = 2), and PSP with predominant speech/language disorders (n = 1). The duration from disease onset to MRI examinations in all patients was 3.5 ± 2.0 years. The disease duration in 35 patients with PSP-RS (2.9 ± 1.8 years) was similar to patients with PSP-P (3.3 ± 1.0 years, p = 0.460) and patients with PSP-F (3.5 ± 2.3 years, p = 0.672). The disease duration in patients with PSP-RS was shorter than the 16 patients with PSP who had other phenotypes (4.2 ± 2.2 years, p = 0.035). However, no significant difference was observed in terms

Table 1. Baseline characteristics of patients with PSP

	All (n = 51)	PSP-RS (n = 35)	Others (n = 16)*	p-value†	PSP-P (n = 4)	PSP-F (n = 4)	Other clinical phenotypes§ (n = 8)
Age (years) (SD)	72.2 (6.2)	73.0 (5.2)	70.5 (7.1)	0.238	68.5 (8.3)	70.7 (7.9)	71.5 (7.0)
Men (n, %)	35 (68.6)	22 (62.8)	8 (50)	0.541	3 (60)	2 (50)	3 (37.5)
Duration (SD) (years‡)	3.5 (2.0)	2.9 (1.8)	4.2 (2.2)	0.035‡	3.3 (1.0)	3.5 (2.3)	5.1 (2.5)
Mean frequency values of falls on PSP rating scale (mean, median) (n)	2.92, 2.97 (50)	2.79, 2.78 (34)	3.19, 3.31 (16)	0.134	3.5, 3.5 (4)	3, 3 (4)	3.1, 3.3 (8)
Dysphagia on PSP rating scale (mean, median) (n)	0.78, 0.53 (50)	0.79, 0.56 (34)	0.75, 0.46 (16)	0.735	0.75, 0.67 (4)	0, 0 (4)	1.13, 0.67 (8)
MMSE (SD) (n)	23.5 (4.5) (40)	23.7 (4.4) (26)	23.0 (4.8) (14)	0.754	22.5 (6.1) (4)	26.3 (3.0) (3)	22 (4.7) (7)

*all clinical phenotypes except for PSP-RS; †comparison of patients with PSP-RS and patients with other clinical phenotypes; ‡p < 0.05; §PSP with progressive gait freezing (n = 2), PSP with predominant cerebellar ataxia (n = 2), PSP with predominant corticobasal degeneration (n = 1), PSP presenting as primary lateral sclerosis (n = 2), PSP with predominant speech/language disorders (n = 1). PSP-RS: progressive supranuclear palsy (PSP) with Richardson's syndrome, PSP-P: PSP with predominant parkinsonism, PSP-F: PSP with predominant frontal presentation, MMSE: Mini-Mental State Examination.

Table 2. MRI findings in patients with PSP

	All (n = 51)	PSP-RS (n = 35)	Others (n = 16)*	p-value†	PSP-P (n = 4)	PSP-F (n = 4)	Other clinical phenotypes§ (n = 8)
Humming bird sign	51 (100)	35 (100)	16 (100)		5 (100)	4 (100)	8 (100)
Morning glory sign	7 (13.7)	7 (20)	0	0.040‡	0	0	0
Mickey Mouse sign	9 (20)	7 (20)	2 (12.5)	0.456	1 (25)	0	1 (12.5)
High signals on FLAIR in SCP	10 (19.6)	9 (25.7)	1 (6.2)	0.142	0	0	1 (12.5)

Values are presented as n (%). *all clinical phenotypes except for PSP-RS; †comparison of patients with PSP-RS and patients with other clinical phenotypes; ‡p < 0.05; §PSP with progressive gait freezing (n = 2), PSP with predominant cerebellar ataxia (n = 2), PSP with predominant corticobasal degeneration (n = 1), PSP presenting as primary lateral sclerosis (n = 2), PSP with predominant speech/language disorders (n = 1). PSP-RS: progressive supranuclear palsy (PSP) with Richardson's syndrome, PSP-P: PSP with predominant parkinsonism, PSP-F: PSP with predominant frontal presentation, FLAIR: fluid-attenuated inversion recovery imaging, SCP: superior cerebellar peduncle.

of age (p = 0.238) or gender (p = 0.541). All patients presented both vertical gaze palsy and postural instability during every consultation, and they also had a history of falls. Based on the available clinical data, the mean frequency of falls on subitems 1−5 or dysphagia on subitems 3−13 of the PSP rating scale[19] were 2.92 (median: 2.97) and 0.78 (0.53), respectively. The frequency of falls in 34 patients with PSP-RS (mean: 2.79, median: 2.78, and range: 1−4) and in 16 patients with other phenotypes (mean: 3.19, median: 3.31, and range: 1−4) did not differ significantly (p = 0.134). Dysphagia on subitems 3−13 did not significantly differ between patients with PSP-RS (mean: 0.79, median: 0.56, and range: 0−4) and patients with other phenotypes (mean: 0.75, median: 0.46, and range: 0−4; p = 0.735). The Mini-Mental State Examination (MMSE) score of 40 patients and the Front Assessment Battery (FAB) score of 37 patients were 23.5 ± 4.5 and 11.1 ± 4.1, respectively. The MMSE scores of 26 patients with PSP-RS (23.7 ± 4.4) and 14 patients with other phenotypes (23.0 ± 4.8) did not differ significantly (p = 0.754). Moreover, no significant difference was observed in the FAB scores between the 24 patients with PSP-RS (median: 10.6 and range: 5−18) and the 13 patients with the other phenotypes (median: 9 and range: 3−18; p = 0.654). In the two patients with PSP-C, cerebellar ataxia persisted for 13−20 months, and the two patients presented typical PSP features after the cerebellar ataxia resolved.[17] All patients with PSP had midbrain atrophy on midsagittal and axial T1-weighted and T2-weighted images. All patients presented the humming bird sign on MRI. The Mickey Mouse and morning glory signs were evident on MRI of 9 of 45 patients (seven patients with PSP-RS, one with PSP-P, and one with other phenotype) and seven patients with PSP-RS, respectively.

The nine patients with PSP-RS and one patient with PSP-C showed a high signal intensity in the SCP on FLAIR MRI (Figure 1). The results of the assessments of all reviewers revealed 10 patients with PD who did not present a high signal intensity. The sensitivity and specificity of the high signal intensity in the SCP of individuals with PSP were 19.6% and 100%, respectively. This finding was more frequently observed in patients with PSP-RS (9/35 patients, 25.7%) than in patients with other phenotypes of PSP (1/16 patients, 6.2%) (Table 2). However, this result was not significant (p = 0.142).

The patients with PSP presenting with and without a high signal intensity in the SCP did not differ significantly in terms of duration from the onset of disease to MRI examination (p = 0.224), age (p = 0.208), or gender (p = 0.772). Moreover, 3.0-T and 1.5-T MRI showed a high signal intensity in the SCP of 2 (10%) of 20 patients and 8 (25.8%) of 31 patients, respectively. However, the result was not significantly different (p = 0.280). The TR in patients with a high signal intensity in the SCP (mean: 8,100, median: 8,375, and range: 4,000−12,000) did not differ from patients without a high signal intensity in the SCP (mean: 9,569, median: 9,400, and range: 4,800−12,000) (p = 0.191). No significant difference was observed in the TE between patients with and without a high signal intensity in the SCP (mean: 109, median: 107, and range: 91−125; mean: 135, median: 114, and range: 50−384, respectively) (p = 0.216). Higher pixel values were observed in the SCP of patients with a high signal intensity in the SCP (mean: 474.4, median: 474.5, and n = 10) than in patients without the high signal in the SCP (mean: 423.1, median: 331.0, and n = 35) (p < 0.001). Moreover, the relative signal intensity ratio between the SCP and middle part of the pons with SCP fibers significantly differed between patients presenting with and without a high signal intensity (1.53 ± 0.20 and 1.23 ± 0.18, respectively, p < 0.001). The width of the SCP in patients with a high signal intensity in the SCP (1.67 ± 0.41 mm) was significantly smaller than in patients without the high signal intensity (2.05 ± 0.40 mm) (p = 0.003). Of the patients with a high signal intensity in the SCP, all presented the humming bird sign, one presented the morning glory sign (p = 0.506), and two presented the Mickey Mouse sign (p = 0.655). However, the result did not differ between patients with and without a high signal intensity in the SCP.

DISCUSSION

The estimate of the high signal intensity in the SCP of patients with PSP on FLAIR MRI was low; however, the specificity was extremely high, which is similar to the results of our previous study.[14] A high signal intensity in the SCP was frequently observed in patients with PSP-RS, despite the significantly shorter duration than patients with other clinical phenotypes of PSP. Patients with PSP who present different clinical symptoms exhibit different distributions of atrophic changes based on a voxel-based morphometry analysis.[5,20] Namely, typical midbrain atrophy on MRI is less frequently observed in patients with PSP-P or PSP-PGF.[21] Atrophy in the globus pallidus and thalamus is observed in individuals with PSP-PGF.[22] Asymmetric atrophy of the frontal lobe and cerebral peduncle with relative sparing of the midbrain is a characteristic finding of PSP-CBS.[23,24] Regarding SCP, the atrophy is less severe in patients with PSP-P,[5] and this finding supports the less frequent observation of a high signal intensity in the SCP of individuals with other clinical phenotypes in our study. One patient with PSP-C presented a high signal intensity in the SCP. Structural images of patients with pathologically proven PSP-C show no obvious cerebellar and pontine atrophy.[25] However, these patients are in the early stages of PSP.[25] Direct evidence for a correlation between atrophy of the SCP and a high signal intensity on FLAIR

MRI was not observed in patients with PSP. In patients with PSP presenting with an atrophied SCP, many tau-immunoreactive inclusions are observed in oligodendroglial cells throughout the dentatorubrothalamic tract, and oligodendrocyte tauopathy may contribute to the primary degeneration of the SCP, including gliosis or demyelination.[4] These pathological changes, which may lead to SCP atrophy, may reflect FLAIR signals in the SCP.

The present study had several limitations. First, the MRI techniques were inconsistent, i.e., our study used both 1.5-T and 3.0-T MRI. Hara et al.[26] reported a high signal intensity in the SCP in 9 (45%) of 20 patients with PSP on 3.0-T axial MRI imaging, which is a significantly higher value than in our study. Although a high signal intensity in the SCP on 3.0-T MRI was also observed in 5 (20%) of 20 patients with PD and 2 of 13 (15.4%) patients with MSA-P,[26] the estimated percentage of patients presenting a high signal intensity in the SCP in our study will increase with the consistent use of 3.0-T MRI. Second, not all patients were diagnosed based on biopsy results. However, we selected patients with the typical clinical characteristics of PSP who had supranuclear vertical gaze palsy, including a downward gaze, postural instability, numerous falls, and typical midbrain atrophy (humming bird sign) on MRI. We assessed these patients for several years. Our study also included patients with PSP-C. Patients experienced persistent cerebellar ataxia for 13–24 months. However, when the cerebellar ataxia resolved, all patients presented typical PSP features.[17] Third, this study employed a retrospective design.

In patients with PSP, the high signal intensity on FLAIR MRI might reflect SCP atrophy, which has been reported as a useful marker of PSP based on pathological or neuroradiological studies. Based on our findings, a high signal intensity on FLAIR MRI might be an effective diagnostic tool for patients with PSP-RS.

Conflicts of Interest

The authors have no financial conflicts of interest.

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