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Cerebellar dentate nucleus in progressive supranuclear palsy

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ABSTRACT

Objectives: Some patients with progressive supranuclear palsy (PSP) present with cerebellar dysfunction. Severe degeneration of the cerebellar dentate nucleus (CDN) was evident in these patients. We evaluated signal intensity on MRI in the CDN of PSP patients with or without cerebellar ataxia.
Patients and methods: We reviewed the clinical histories and brain MRI studies of 28 patients with clinically probable PSP. Three disease control groups were studied: a group of 28 sex- and age-matched patients with Parkinson's disease (PD), a group of 15 patients with multiple system atrophy with predominant parkinsonian features (MSA-P), and 15 control subjects. Turbo spin-echo sequences for T2-weighted images were used using a 1.5 T magnetic resonance imager.
Results: Eight patients with PSP (28%) and one patient with MSA-P (6%) had heterogeneous regions in the CDN. This finding was not evident in the patients with PD or controls. Three out of four PSP patients with cerebellar ataxia had heterogeneous regions in the CDN and other one patient with cerebellar ataxia as the initial and principal symptoms had no heterogeneous regions in the CDN.
Conclusion: Heterogeneous regions in the CDN on MRI do not always reflect cerebellar ataxia in PSP patients, and this finding might be an additional marker to support a probable diagnosis of PSP.

1. Introduction

Progressive supranuclear palsy (PSP) is characterized by postural instability and supranuclear gaze palsy [1]. Postural instability has been suggested to be responsible for grumose degeneration in the cerebellar dentate nucleus (CDN) [2,3]. This pathological change is characterized by eosinophilic, granular, and amorphous material around dentate neurons in the CDN in PSP patients and is associated with myelinated fiber loss, tau pathology, and microgliosis in the dentatorubrothalamic tract [2,3]. A recent study reported evidence of such degeneration in the CDN of PSP patients, some of whom had cerebellar dysfunction as an initial principal symptom [4]. We recently reported that patients with clinically probable PSP showed increased signals in the superior cerebellar peduncle on conventional magnetic resonance imaging (MRI) [5]. Such signals were absent in patients with Parkinson's disease (PD) or multiple system atrophy with predominant parkinsonian features (MSA-P) [5]. We hypothesized that pathological degeneration in the CDN might contribute to increased signal intensity on MRI in PSP patients. When increased MRI signal intensity is evident in the CDN, it remains unclear whether this finding is useful for differential diagnosis from other parkinsonian syndromes or whether it is specific to PSP with cerebellar ataxia. We thus evaluated signal intensity on MRI in the CDN of PSP patients with or without cerebellar ataxia.

2. Materials and methods

We reviewed the clinical histories and brain MRI studies of 28 patients with clinically probable PSP (15 men, 13 women; age range 56–79 years, mean 70.5 ± 4.9 years) according to the National Institute of Neurologic Disorders and Stroke-SPSP diagnostic criteria [2]. Three disease control groups were studied: a group of 28 sex- and age-matched patients with PD, a group of 15 patients who had MSA-P (age range 57–83 years, mean 68.6 ± 7.0 years), and 15 control subjects (age range 58–78 years, mean 69.4 ± 5.0 years). Clinically definite PD was diagnosed according to both the Calne and Gelb criteria [6,7]. Clinically possible MSA-P was diagnosed according to recent diagnostic criteria [8]. All patients with MSA-P had orthostatic hypotension, defined as a drop in systolic blood pressure of more than 20 mmHg or a drop in diastolic blood pressure of more than 10 mmHg on standing up. The heart-mediastinum ^{123}I-metaiodobenzylguanidine uptake ratio was significantly decreased in all patients with PD, but not decreased in all patients with MSA-P [9]. The control subjects had no history of central nervous system

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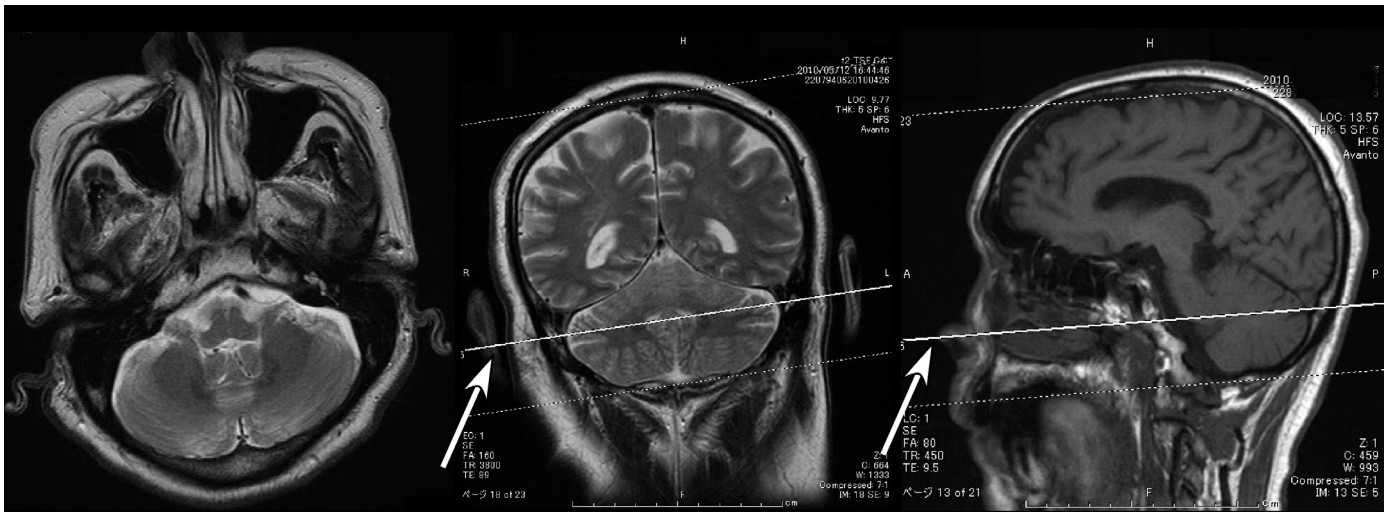

Fig. 1. All evaluated axial T2-weighted magnetic resonance images (left panel) were obtained at the level of the cerebellar dentate nucleus on coronal (middle panel) or sagittal magnetic resonance images (right panel) (white arrows). This patient showed heterogeneous regions in the cerebellar dentate nucleus.

disorders, abnormal neurological signs, or abnormal cranial MRI findings. We excluded patients who had any of the following conditions: another atypical parkinsonian syndrome such as normal pressure hydrocephalus and large vessel disease, infarction, multiple lacunar infarctions, or tumor on cranial MRI. Patients with an infarct in the cerebellar lobes or with white matter lesions of grade 3 according to Fazekas scale [10] on cranial MRI were also excluded. There was no different in age and sex between patients with PSP and patients with MSA-P ($P = 0.307$ and 0.343, respectively) or controls ($P = 0.492$ and 1.0, respectively). Cerebellar ataxia was defined as the presence of gait ataxia plus at least either of cerebellar dysarthria, limb ataxia or sustained gaze-evoked nystamgus [8]. Neurological findings were assessed by at least two experienced neurologists.

3.1. MRI evaluation

Patients were examined with a 1.5-T magnetic resonance imager. Because two patients with PSP and one patient with MSA-P were studied retrospectively, various techniques were used for imaging, but the scan slice thickness and interslice gap were similar in all patients. These patients did not show signal changes in the CDN as described as below, and the two patients with PSP had no cerebellar ataxia. In the other 26 patients with PSP and 14 patients with MSA-P and in all patients with PD and all controls, conventional imaging techniques were used as follows: turbo spin-echo sequences for T2-weighted images (T2WI) (TR 4400 ms; TE 110 ms; 5-mm slice thickness, with a 1-mm interslice gap), FLAIR images (TR 9000 ms; TE 120 ms; TI 2200 ms; 5-mm slice thickness, with a 1-mm interslice gap), and T1-weighted images (T1WI) (TR 450 ms; TE 9 ms; 5-mm slice thickness, with a 1-mm interslice gap) using a 1.5 T magnetic resonance imager. Signal intensity changes on these axial MRI scans were assessed by visual inspection by two experienced reviewers who were blinded to the clinical data and diagnosis, and agreement was reached by consensus. These axial images were obtained at the level of CDN as shown in Fig. 1. Heterogeneous regions in the CDN were defined as some apparent high-signal intensities mixed on a background of low-signal intensities in the CDN on T2WI, as shown in Fig. 2. These MRI images were analyzed in a blinded, randomized fashion to control for bias. When the reviewers unanimously agreed that there were heterogeneous regions in the CDN, the reviewers were also requested to indicate whether the lesions were apparent by marking a position

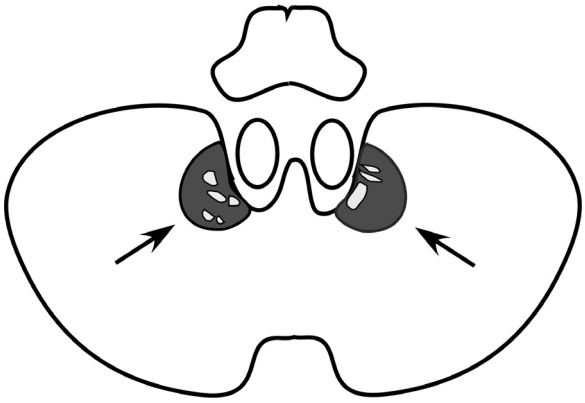

Fig. 2. Schema of the heterogeneous regions in the cerebellar dentate nucleus on a T2-weighted magnetic resonance image. Some high-intensity regions were imposed against a background of low intensity in the cerebellar dentate nucleus.

along a continuous 50-mm horizontal visual analog scale line (left [0 mm], absolutely not detectable; right [50 mm], absolutely apparent) as described previously [11,12]. A detailed description of the bar chart is provided in the supplemental material. Increased signals of the superior cerebellar peduncle on FLAIR were defined as previously [5]. In patients with PSP, midbrain atrophy on mid-sagittal and axial T1-weighted images was assessed by an experienced neuro-radiologist. The interval between the onset of neurological symptoms and MRI examinations in PSP was 41.4 ± 32.7 months. For statistical analysis, differences were examined with the use of unpaired *t*-tests or Fisher's exact probability tests for categorical data (SPSS software, version 18). *P* values of less than 0.05 were considered to indicate statistical significance.

3. Results

Eight patients with PSP (28%) and one patient with MSA-P (6%) had heterogeneous regions in the CDN. This finding was not evident in the patients with PD or controls (Fig. 3). The sensitivity and specificity of heterogeneous regions in the CDN for PSP were 28% and 98%, respectively. There was no difference in the duration of disease between PSP patients with and those without heterogeneous regions in the CDN (48.0 ± 29.8 vs. 40.1 ± 34.5 months, $P = 0.579$). The heterogeneous regions in the CDN showed the same findings on FLAIR and on T2WI, and TIWI showed iso-signal intensity.