The Combination of Hypointense and Hyperintense Signal Changes on T2-Weighted Magnetic Resonance Imaging Sequences

A Specific Marker of Multiple System Atrophy?

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Objective: To compare the frequency and specificity of hypointense magnetic resonance imaging (MRI) signal changes alone with the frequency and specificity of a pathological MRI pattern consisting of a hyperintense lateral rim and a dorsolateral signal attenuation on T2-weighted MRIs in patients with parkinsonism of various origins.

Patients: Ninety patients with Parkinson disease (PD) (n = 65), progressive supranuclear palsy (PSP) (n = 10), and multiple system atrophy (MSA) of the striatonigral degeneration type (n = 15) underwent MRI.

Setting: University medical center.

Results: Nine of the 15 patients with MSA showed the pattern with hyperintense lateral rim and a dorsolateral hypointense signal attenuation on T2-weighted images within the putamen. This pattern was not found in the 65 patients with PD, nor in the 10 patients with PSP. Only hypointense changes in the putamen were found in 6 patients (9%) with PD, 4 patients (40%) with PSP, and 5 patients (36%) with MSA.

Conclusions: Our data suggest that the pattern consisting of hypointense and hyperintense T2 changes within the putamen is a highly specific MRI sign of MSA, while hypointensity alone remains a sensitive, but nonspecific MRI sign of MSA. In clinically doubtful cases, the appearance of a hypointense and hyperintense signal pattern on MRI makes the diagnosis of PD very unlikely, while hypointense signal changes alone do not exclude idiopathic PD.

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The differential diagnosis of patients with parkinsonism very often remains a challenging task for neurologists and may require additional investigations. The most important alternative diagnoses of Parkinson disease (PD) are progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). In the early course of the disease, both PSP and MSA may be clinically difficult to distinguish from PD, but this distinction has important prognostic and therapeutic implications. In contrast to PD, in which degeneration does not involve striatal or pallidal neurons, cell degeneration is found in those areas in PSP and MSA. Most cases of MSA of the striatonigral degeneration (SND) type reveal a prominent degeneration of the putamen. Thus, magnetic resonance imaging (MRI) may be helpful in differentiating PD from MSA or PSP by identifying putaminal involvement. Nevertheless, the specific role of MRI in the differential diagnosis of parkinsonism has yet not been established, for several reasons. First, hypointense signal changes on T2-weighted MRI sequences in the putamen, which have been proposed as an indicator of nonidiopathic parkinsonism, have been shown to be clearly age dependent and therefore misleading or nonspecific. Second, the amount of pathological MRI findings in patients with MSA varies in the literature from 35% to 100%. Recently, we described a pattern consisting of hypointense and hyperintense signal changes within the putamen in 2 patients with MSA of the SND type, as well as the corresponding neuropathological findings. Other authors have also reported similar findings. One of the studies, however, was conducted on lower-field strength, which is known to influence the pathological signal changes within the basal ganglia. None of the prior studies compared the frequency of hypointense areas in the putamen with the combination of hyperintense and hypointense changes in patients with PD, MSA, and PSP. Therefore, the aim of this study was to compare the frequency and specificity of hypointense signal changes alone with those of the combination of hypointense and hyperintense signal changes in the putamen in...
PATIENTS AND METHODS

The study included 90 patients with parkinsonism of different origins. None of these patients had a history of treatment with dopamine receptor antagonists that cross the blood-brain barrier, such as neuroleptics and metoclopramide hydrochloride. Clinically, the patients were diagnosed as having MSA of the SND type, PD, or PSP.

PARKINSON DISEASE

Sixty-five patients (mean age, 58 years; mean duration of disease, 5 years) were clinically diagnosed as having PD. All of these patients showed 2 of the 3 cardinal motor signs of the akinetic rigid type. Also, 9 of these 15 patients had severe autonomic dysfunction, 8 had a cerebellar syndrome, and 13 exhibited pyramidal tract signs. The diagnosis was confirmed by postmortem analysis in 2 patients (details of the pathological findings are described elsewhere17).

MSA OF THE SND TYPE

Fifteen patients (mean age, 58 years; mean duration of disease, 6 years) were clinically diagnosed as having probable MSA of the SND type according to the criteria established by Quinn.16 All 15 had predominant symmetrical parkinsonism of the akinetic rigid type. Also, 9 of these 15 patients had severe autonomic dysfunction, 8 had a cerebellar syndrome, and 13 exhibited pyramidal tract signs. The diagnosis was confirmed by postmortem analysis in 2 patients (details of the pathological findings are described elsewhere17).

PROGRESSIVE SUPRANUCLEAR PALSY

Ten patients (mean age, 67 years; mean duration of disease, 4 years) were diagnosed as having PSP according to the criteria proposed by Lees.20 All 10 patients had symmetrical parkinsonism of the akinetic rigid type, along with down-gaze palsy, frequent falls, axial rigidity, and square-wave jerks on the electroneystagmogram.

MAGNETIC RESONANCE IMAGING

Brain MRI was performed in all patients using the same scanning protocol at 1.5 T, including proton density and T2-weighted spin echo sequences (repetition time, 2500 milliseconds; echo time, 22-90 milliseconds) (Magnetom scanner, Siemens, Erlangen, Germany). Nineteen slices, 3 mm thick, were collected in axial and coronal orientation without an interslice gap. The field of view was 25 cm and the matrix size was 256 × 256. A standard quadrature head coil was used in all patients. All images were analyzed by 2 experienced neuroradiologists (T.V. and T.P.) who were blinded to the clinical diagnosis of the patients. The images were evaluated independently by each one of them. In the cases with differing opinion, the scans were reevaluated together and consensus was reached. The putamen was visually assessed for hypointense signal changes, hyperintense signal changes, or the combination of both. Hypointense signal changes on T2-weighted images were defined as areas of signal intensity equal or lower to signal intensity of the globus pallidus according to prior studies on putaminal hypointensities in parkinsonism.3,10,11 Hypointense signal changes were evaluated only on the T1-weighted images, while proton density images were also used to assess hyperintense signal changes within the putamen. The protocol did not include gradient echo sequences.

| Signal Changes Within the Putamen in 90 Patients With Parkinsonism of Various Origins* |
|---------------------------------|----------------|----------------|----------------|----------------|
| MRI (Putamen) | Normal | Only Hypointense | Hypointense and Hyperintense | Total |
| MSA | 1 | 5 | 9 | 15 |
| PSP | 6 | 4 | 0 | 10 |
| PD | 59 | 6 | 0 | 65 |

* MRI indicates magnetic resonance imaging; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; and PD, Parkinson disease.

In this study, we focused on signal changes in the putamen on T2-weighted and proton density sequences. Hypointense signal changes in the putamen (mostly in the dorsolateral part) were detected in 24 patients. A combination of hypointense and hyperintense signal changes in the putamen were seen in 9 patients (Table). Fourteen (93%) of 15 patients diagnosed as having MSA showed pathological signal changes in the dorsolateral putamen. Nine of them showed a band of hyperintensity at the lateral border of the putamen. These findings were bilateral in 6 patients (Figure 1) and were limited to 1 side in the other 3 patients (Figure 2). These signal changes were seen as a band of hypointensity not only on T2-weighted images but also on proton density images. All the patients with the band of hypointensity in the lateral putamen on T2-weighted images also had this finding on proton density images (Figure 3). In patients with this pattern, the dorsolateral part of the putamen also appeared to be shrunken, whereas in the subjects with hypointense putaminal lesions this was not the case. All patients diagnosed as having MSA had a symmetrical akinetic rigid syndrome. The 3 patients with unilateral findings had a shorter duration of disease (2 or 3 years) than the other 6 patients, who had disease durations ranging from 4 to 9 years. The remaining 5 patients showed only pathological hypointense lesions, and all 5 patients had bilateral hypointense signal changes. Computed tomographic scans were available in 7 of the 15 patients diagnosed as having MSA of the SND type. Four of the 7 were patients who had hypointense and hyperintense signal patterns on their MRIs. None of the 7 patients showed hyperdense areas within the basal ganglia consistent with calcification. Also, none of the 15 patients diagnosed as having MSA of the SND type had hyperintense white matter lesions suggestive of small-vessel disease. Hypointense signal changes like those
found in the 5 patients with MSA were also found in 4 of the 10 patients diagnosed as having PSP. These findings were bilateral in all 4 patients. Of the 65 patients diagnosed as having PD, 6 (9%) exhibited bilateral (n = 4) or unilateral (n = 2) hypointense signal changes in the dorsolateral putamen. A band of hyperintensity in the putamen was not observed on T2-weighted or proton density images in any of the patients with PD or PSP. Comparing the occurrence of the signal changes within the putamen revealed a high frequency of hypointense changes in patients diagnosed as having MSA or PSP, but the hypointense and hyperintense combination of signal changes in the putamen was found only in patients with the clinical diagnosis of MSA, suggesting a specificity of 100% in the patient population studied.

**COMMENT**

In this study, we performed MRI with T2-weighted and proton density sequences in 90 patients with parkinsonism. Hypointense and hyperintense signal changes in the putamen were compared with the clinical diagnoses. Hypointense signal changes were found in 24 patients. Most of them (n = 14) were diagnosed as having MSA of the SND type. The remaining were diagnosed as having PSP (n = 4) or PD (n = 6). The combination of hypointense signal changes in the dorsolateral or entire putamen with a band of hyperintense signal changes at the lateral putamen was exclusively seen in 9 of 15 patients diagnosed as having MSA of the SND type.
PUTAMINAL HYPOINTENSITIES AND PARKINSONISM

Hypointense signal changes in the putamen have been proposed as a marker of MSA of the SND type or at least of levodopa-unresponsive parkinsonism. However, hypointense putaminal changes are not specific for one disease and are clearly related to normal aging. Consequently, hypointense changes were not described but are clearly visible on the T2-weighted image. Our results confirm that this combination of signal changes occurs in patients clinically diagnosed as having MSA of the SND type (probable MSA according to Quinn). In addition to the signal changes, atrophy of the putamen has been described, especially in the dorsolateral putamen. This finding was also present in some of our patients, especially in those with the combination of the signal changes. Atrophy would be consistent with neuronal loss known to occur in this area.

HISTOPATHOLOGICAL CORRELATE OF MRI SIGNAL CHANGES

The histopathological changes that induce signal changes on MRI in the putamen are not fully understood. Many authors have proposed that an increase of iron in the putamen results in hypointense signal changes in patients with parkinsonism. However, the comparison of MRI and tissue iron content in the same individuals showed that the area with the highest iron content did not correspond to the area with the most prominent hypointensity on T2-weighted images. The pathophysiological processes underlying the hypointense signal changes is unclear. Neuropathological studies in patients with MSA have shown that there is a marked increase of reactive astroglial and microglial cells in the area of neuronal degeneration in the putamen. In a clinicopathological study, the area with the most prominent increase of reactive gliosis corresponded to the area of hypointense signal changes on MRI. Thus, gliosis may, at least in part, lead to the band of hypointense signal changes in the lateral putamen of patients with MSA of the SND type. However, many factors seem to induce MRI signal changes. Iron and gliosis are only 2 of them. A further possible source for pathological signal changes includes calcification of the basal ganglia. Although not all our patients underwent computed tomography to exclude this possibility, it seems very unlikely to be the cause of the signal changes observed in the present study, given that none of the 7 computed tomographic scans available in these patients revealed hyperdense areas within the basal ganglia.

In conclusion, the combination of hypointense and hyperintense signal changes in the putamen seems to be highly specific for the clinical diagnosis of MSA of the SND type. These changes may be seen in the majority of these patients. Although unlikely, hypointense signal changes alone may occur in patients with levodopa-responsive parkinsonism (most likely PD), while the combination of hypointense and hyperintense signal changes in the putamen practically excludes a diagnosis of PD.

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REFERENCES