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Evaluation of the Substantia Nigra in Patients with Parkinsonian Syndrome Accomplished Using Multishot Diffusion-Weighted MR Imaging

Michito Adachi, Takaaki Hosoya, Tamami Haku, Koichi Yamaguchi, and Toru Kawanami

BACKGROUND AND PURPOSE: Although it is important to evaluate the substantia nigra in patients with parkinsonian syndrome, it is difficult to depict its anatomy, even by MR imaging. Using anatomic studies of the direction of nerve fibers around the substantia nigra, we attempted to depict this entity with multishot diffusion-weighted MR imaging to evaluate its topographic changes in patients with Parkinson's disease and secondary parkinsonism.

METHODS: We measured the substantia nigra on 72 diffusion-weighted axial MR images obtained in 36 healthy control subjects, on 47 images obtained in 25 patients with Parkinson's disease, and on 10 images obtained in five patients with secondary parkinsonism. We considered the width of the minor axis of the substantia nigra as its "thickness," which appeared as a crescent-shaped region in the midbrain.

RESULTS: Diffusion-weighted imaging portrayed the substantia nigra distinctly better than did T2-weighted imaging, because the surrounding white matter appeared as an area of high signal intensity. The mean (\pm SD) thickness values of the substantia nigra were 5.1 ± 0.89 mm in control subjects, 4.8 ± 0.75 mm in patients with Parkinson's disease, and 3.4 ± 0.53 mm in patients with secondary parkinsonism.

CONCLUSION: Multishot diffusion-weighted imaging is a better imaging technique than T2-weighted imaging for demonstrating a change in size of the substantia nigra in vivo. The substantia nigra is not reduced in size in patients with Parkinson's disease, but it is reduced in patients with secondary parkinsonism.

Although, many studies have examined the MR imaging features of parkinsonian syndrome, few have focused on the morphologic changes of the substantia nigra on MR images in patients with this disorder.

At present, no optimal MR imaging method has been established for depicting and evaluating the substantia nigra. T2-weighted MR images show the substantia nigra only faintly, owing to the susceptibility effect resulting from the accumulation of iron (1, 2). Recent advances in MR imaging technology have made it possible to image the diffusion of tissue water (ie, intravoxel incoherent motion) on the molecular level. For example, on diffusion-weighted images (3–5) of the midbrain, the substantia nigra is depicted distinctly better than it is

on T2-weighted images. Diffusion-weighted imaging has been shown to be useful for the assessment of anisotropy of nerve fibers and of cellular integrity in the context of stroke (3–5). By depicting the white matter around the substantia nigra as an area of high signal intensity, diffusion-weighted imaging shows the substantia nigra as a crescent-shaped area of low signal intensity between the tegmentum of the midbrain and the cerebral peduncle.

To clarify whether the substantia nigra is reduced in size in patients with parkinsonian syndrome, we measured the minor axis (thickness) of the substantia nigra on axial diffusion-weighted images obtained in healthy subjects and in patients with Parkinson's disease and secondary parkinsonism.

Methods

Subjects

T1-, T2-, and diffusion-weighted MR studies of the substantia nigra were obtained in patients with Parkinson's disease, in patients with secondary parkinsonism, and in control subjects who were examined at our institution between October 1996 and July 1998. All subjects were told the purpose of the MR examination, and they were enrolled in the study with their

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consent. The study protocol was approved by our institution's medical ethics committee.

The diagnosis of Parkinson's disease was based on clinical criteria, including the following neurologic signs: resting tremor, rigidity, bradykinesia, disorder of postural reflex, and/or good response to levodopa or anticholinergic therapy. Patients with abnormal MR findings (eg, abnormal high signal intensity on T2-weighted images or atrophic changes) were excluded from the study. The criteria for secondary parkinsonism included some or all of the neurologic signs of parkinsonism, abnormal findings of the lenticular nucleus on T1- or T2-weighted images or both, and documentation of the causes of secondary parkinsonism.

The control group consisted of 36 subjects (19 men and 17 women) 21 to 76 years old (mean age, 48 ± 19 years) without neurologic deficit or abnormal findings on T1- or T2-weighted brain MR images. Seventy-two diffusion-weighted images of both substantia nigra were obtained in these subjects.

The group with Parkinson's disease included 25 patients (16 men and nine women) 46 to 78 years old (mean age, 63 ± 9 years) with a mean duration of disease of 7 years (range, 2 to 21 years). A total of 47 diffusion-weighted images of the substantia nigra were obtained in this group. Three patients with Parkinson's disease had had posteroventral pallidotomy, and the images of the substantia nigra ipsilateral to the pallidotomy were excluded. Severity of disease was evaluated by using the Hoehn and Yahr scale: three patients had stage 1 disease; 11, stage 2; five, stage 3; and six, stage 4.

Five patients had secondary parkinsonism, including one with Fahr's disease (a 61-year-old woman), one with carbon monoxide intoxication (a 19-year-old man), one with putaminal infarction (a 72-year-old man), one with putaminal hemorrhage (a 75-year-old man), and one with progressive supranuclear palsy (PSP) (a 65-year-old man). The mean duration of disease among this group was 5 years (range, 3 to 10 years).

Anatomic Assessment of the Direction of the Nerve Fibers around the Substantia Nigra

Measurement of the molecular diffusion of water has been possible for decades by the use of nuclear MR imaging with the application of a pair of diffusion-sensitizing magnetic field gradients to dephase and then rephase the precessing protons (6). Diffusion-weighted imaging is valuable for determining the anisotropic diffusion behavior of small molecules. In the white matter of the brain, slower water diffusion is observed when the diffusion-sensitizing gradient direction is applied perpendicularly to the long axis of white matter tracts, whereas faster diffusion occurs parallel to the long axis, owing to fewer barriers to water motion (5). Therefore, on diffusion-weighted images, the signal intensity of white matter is relatively increased when the direction of the diffusion-sensitizing gradient is parallel to the direction of the nerve fibers.

To determine the direction of the diffusion gradient, we examined the direction of the nerve fibers of the white matter around the substantia nigra. Tissue blocks of the midbrain were obtained from a 68-year-old man who had died of amyotrophic lateral sclerosis. The brain was fixed with 10% formalin, and the midbrain was cut in the axial plane and embedded in paraffin. Serial tissue sections were cut 7- μ m thick and stained with Klüver-Barrera method.

MR Imaging of the Substantia Nigra

Using a 1.5-T superconducting system, we obtained T1-, T2-, and multishot diffusion-weighted axial images of the midbrain in all patients and control subjects. The spin-echo acquisition parameters were 519/10 (TR/TE) for the T1-weighted images and 3540/105 for the T2-weighted images, the field of view (FOV) was 28×21 cm, the section thickness was 6 mm with a 1.5-mm gap, the matrix was 512×256 , the imaging time was 1 minute 47 seconds for T1-weighted sequences and 2

minutes 8 seconds for T2-weighted sequences, and the number of echoes for the T2-weighted fast spin-echo sequences was 12.

Multishot diffusion-weighted images were obtained using spin-echo echo-planar imaging with the following parameters: 3000–4000/120/6; FOV, 21×21 cm; section thickness, 5 mm with a 2.5-mm gap; matrix, 256×192 ; 16 shots; 40-millisecond duration of diffusion-sensitizing gradient pulses; 1.5 G/cm diffusion-sensitizing gradient; and a gradient attenuation factor b value of 825 s/mm². Imaging time was 5 to 6 minutes using a peripheral pulse gate. Navigator echoes were not used.

Measurement of the Substantia Nigra

Axial images of the midbrain, which included the center of the red nucleus and mammillary body, were obtained in all control subjects and patients. In the axial plane, the substantia nigra appeared as a crescent-shaped region, so we defined the width of the minor axis of the substantia nigra as its "thickness." One radiologist, who was blinded to the patient/control subject status, used a micrometer (a minimum distance of 0.1 mm) to measure the maximal thickness of the substantia nigra manually on the images in which the FOV and magnification were fixed.

Statistical Analysis

The correlation between age and thickness of the substantia nigra was tested in the control group, because the substantia nigra was expected to be reduced with age. Analysis of the distribution of samples for all groups was carried out by χ^2 -test for goodness of fit. Statistical comparisons of the thickness between the right and left substantia nigra for the control group were based on results of an unpaired Student's *t*-test. In the group with Parkinson's disease, statistical comparisons of the thickness of the substantia nigra between subgroups (as measured on the Hoehn and Yahr scale) were also tested by one-way ANOVA. Statistical comparisons of the thickness of the substantia nigra between the control and Parkinson's disease groups, between the control and secondary parkinsonism groups, and between the Parkinson's disease and secondary parkinsonism groups were based on results of an unpaired Student's *t*-test. *P* values less than .05 were considered to indicate a significant difference.

Results

Anatomy of the White Matter around the Substantia Nigra and Visualization of the Substantia Nigra on T1-, T2-, and Diffusion-Weighted Images

Based on the photomicrographs obtained, the nerve fibers of the cerebral peduncle extended in a rostrocaudal direction, and those between the substantia nigra and the red nucleus extended in an obliquely ventrodorsal direction (Fig 1). Therefore, it was considered that the diffusion gradient in the left-right direction, which was nearly perpendicular to the nerve fibers of the cerebral peduncle, the outer margin of the substantia nigra, and the fibers between the substantia nigra and the red nucleus, offered good diffusion-weighted contrast between the substantia nigra and the surrounding white matter.

We could not identify the substantia nigra on T1-weighted images of any control subject. On T2-weighted images, the substantia nigra was depicted faintly as an area of low signal intensity caused by

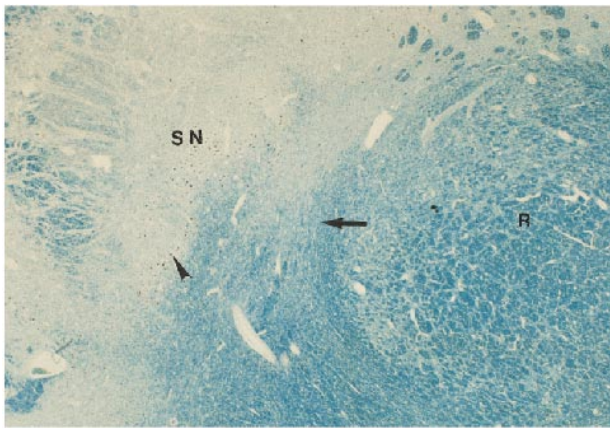


FIG 1. Photomicrograph of the midbrain shows the white matter between the red nucleus and substantia nigra, where the nerve fibers (arrow) extend in the obliquely ventrodorsal direction (Klüver-Barrera stain; original magnification, $\times 40$). R indicates red nucleus; SN, substantia nigra; arrowhead, pigmented neurons.

the susceptibility effect resulting from the accumulation of iron (Fig 2A). We could identify the whole border of the substantia nigra in 13 (18%) of 72 T2-weighted images in the control subjects. In contrast, the substantia nigra of all control subjects was clearly depicted as a crescent of low signal intensity between the tegmentum of the midbrain and the cerebral peduncle on diffusion-weighted images when the diffusion gradient was applied in the left-right direction (Fig 2B).

Diffusion-weighted imaging, which is sensitive to patient motion, takes about 5 minutes using peripheral pulse gating. In this study, motion artifacts prevented the acquisition of clear diffusion-weighted images in seven patients with Parkinson's disease, in one patient with secondary parkinsonism (who had had a midbrain contusion in a traffic accident), and in five control subjects. These images, in which the substantia nigra could not be measured, were excluded from analysis.

Measurement of the Substantia Nigra in Control Subjects

The mean (\pm SD) thickness of the substantia nigra in the control group ($n = 72$) was 5.1 ± 0.89

mm, with a range of 3.1 to 7.6 mm. The mean (\pm SD) thickness of the right substantia nigra ($n = 36$) was 4.9 ± 0.73 mm, and that of the left substantia nigra ($n = 36$) was 5.1 ± 0.98 mm. By unpaired Student's *t*-test there was no significant difference between the right and left substantia nigra ($P > .05$). No correlation was detected between the thickness of the substantia nigra and age by one-way ANOVA.

Measurement of the Substantia Nigra in Patients with Parkinson's Disease

In the patients with Parkinson's disease ($n = 47$), the mean (\pm SD) thickness of the substantia nigra was 4.8 ± 0.75 mm, with a range of 3.4 to 6.5 mm. No correlation was detected between thickness of the substantia nigra and severity of disease (as measured on the Hoehn and Yahr scale) by one-way ANOVA. A comparison of the thickness of the substantia nigra between the control subjects and the patients with Parkinson's disease with an unpaired Student's *t*-test revealed no significant difference ($P > .05$) (Fig 3). No abnormal signal intensity was observed in the substantia nigra on T2- or diffusion-weighted images in this group (Fig 4).

Measurement of the Substantia Nigra in Patients with Secondary Parkinsonism

A significant reduction in the thickness of the substantia nigra was observed in the patients with secondary parkinsonism (Figs 5–7). Thickness values in these five patients were 4.0 and 3.1 mm (right and left, respectively) in the patient with Fahr's disease; 2.9 and 3.7 mm in the patient with carbon monoxide intoxication; 3.1 and 2.3 mm in the patient with putaminal infarction; 4.0 and 3.2 mm in the patient with putaminal hemorrhage; and 3.8 and 3.6 mm in the patient with PSP. The mean (\pm SD) thickness ($n = 10$) was 3.4 ± 0.53 mm, with a range of 2.3 to 4.0 mm.

Using an unpaired Student's *t*-test, comparison of the thickness of the substantia nigra between the control subjects and the patients with secondary parkinsonism revealed a significant difference (P

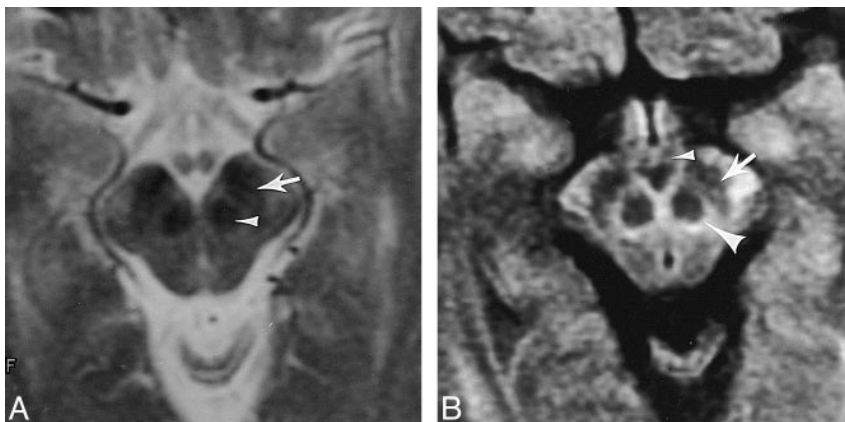


FIG 2. 41-year-old male control subject.

A, Axial T2-weighted image (3540/105) of the midbrain barely depicts the substantia nigra (arrow). The red nucleus (arrowhead) is depicted as a round area of low intensity resulting from the accumulation of iron.

B, Diffusion-weighted image with a left-right direction diffusion-sensitizing gradient shows a distinct crescent of low signal intensity (arrow) between the cerebral peduncle and the tegmentum. Large arrowhead indicates substantia nigra; small arrowhead, mammillary body.

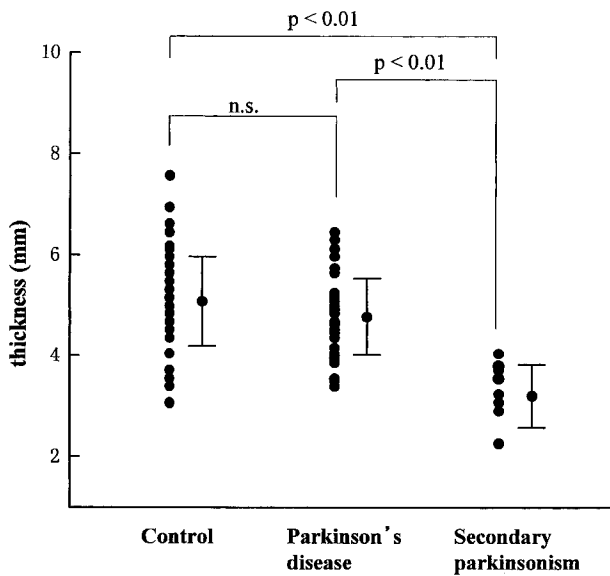


FIG 3. Thickness of the substantia nigra in the control subjects, the patients with Parkinson's disease, and the patients with secondary parkinsonism. The mean (\pm SD) thickness of the substantia nigra in the control group ($n = 72$) was 5.1 ± 0.89 mm, that in the group with Parkinson's disease ($n = 47$), 4.8 ± 0.75 mm; and that in the group with secondary parkinsonism ($n = 10$), 3.4 ± 0.53 mm. There was a significant difference between the group with Parkinson's disease and the group with secondary parkinsonism by unpaired Student's *t*-test ($P < .01$).

$< .01$) (Fig 3). Comparison of the thickness of the substantia nigra between the patients with Parkinson's disease and those with secondary parkinsonism by using an unpaired Student's *t*-test also revealed a significant difference ($P < .01$) (Fig 3).

Discussion

Movement disorders that accompany parkinsonian syndrome (consisting of resting tremor, rigidity, bradykinesia, and postural instability) are found with both Parkinson's disease and secondary parkinsonism. Differentiating Parkinson's disease from secondary parkinsonism is important in predicting response to levodopa or anticholinergic therapy. Although many studies have described the MR imaging features of parkinsonian syndrome, especially Parkinson's disease and multisystem atrophy, it is not easy to distinguish these diseases by routine MR imaging.

In patients with PSP, T2-weighted images reportedly show increased signal and atrophic changes in the periaqueductal and tectal regions, while moderate to marked decrease in signal intensity, reflecting increased iron concentration, is observed in the putamen, globus pallidus, and substantia nigra (7-9).

In patients with Parkinson's disease, low signal intensity has been reported in the putamen, globus

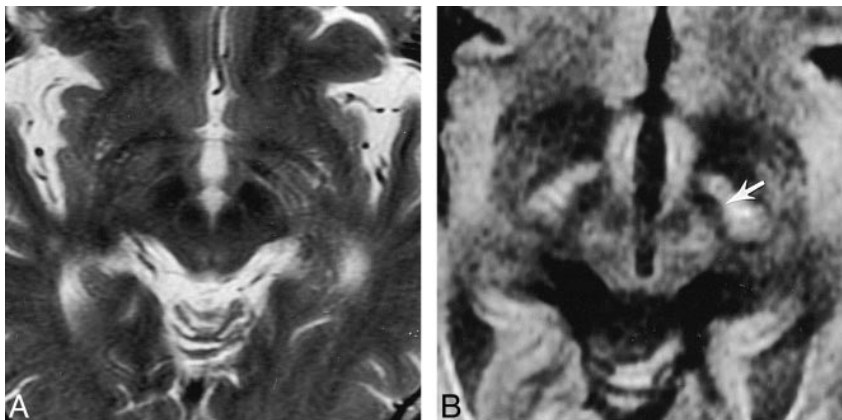


FIG 4. 67-year-old man with Parkinson's disease (Hoehn and Yahr scale, 4).

A, On T2-weighted image (3540/105), the substantia nigra is difficult to identify. There are no abnormal signal changes in the midbrain.

B, On diffusion-weighted image, the substantia nigra (arrow) is depicted clearly as a crescent of low signal intensity. No atrophy of the substantia nigra is seen.

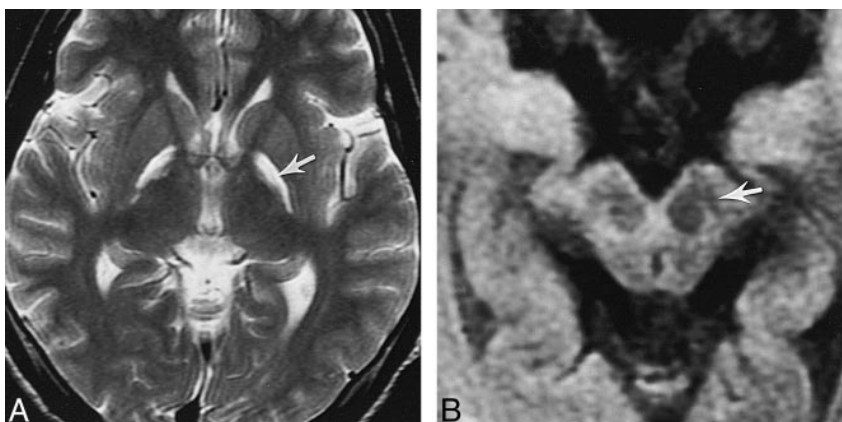


FIG 5. 19-year-old man with secondary parkinsonism (carbon monoxide intoxication) 3 years after onset.

A, On T2-weighted axial image (3540/105), a hyperintense lesion (arrow) is observed in the globus pallidus; a result of carbon monoxide poisoning.

B, Diffusion-weighted axial image of the midbrain shows atrophy of both substantia nigra (arrow). The signal intensity is relatively higher than that in the control subjects.

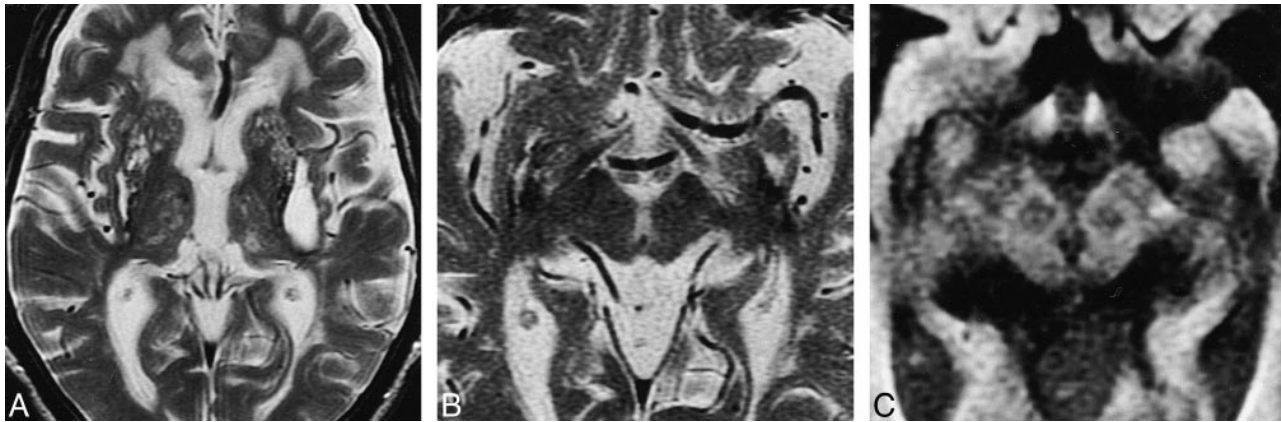


FIG 6. 75-year-old man with secondary parkinsonism after bilateral putaminal hemorrhage.

A, T2-weighted image shows a large hyperintense area in the left putamen and a slitlike hyperintensity in the right putamen. Multiple spotty areas of hyperintensity are also seen in both putamen. The margins of the large area of hyperintensity and of the slitlike hyperintensity are hypointense owing to susceptibility effects resulting from the accumulation of iron (hemosiderin).

B, On T2-weighted image (3540/105) of the midbrain, the substantia nigra is not distinguishable. There are no abnormal signal changes in the midbrain.

C, On diffusion-weighted image, both substantia nigra are reduced in size. This image shows hyperintensity in the substantia nigra, which might reflect neuronal degeneration and gliosis.

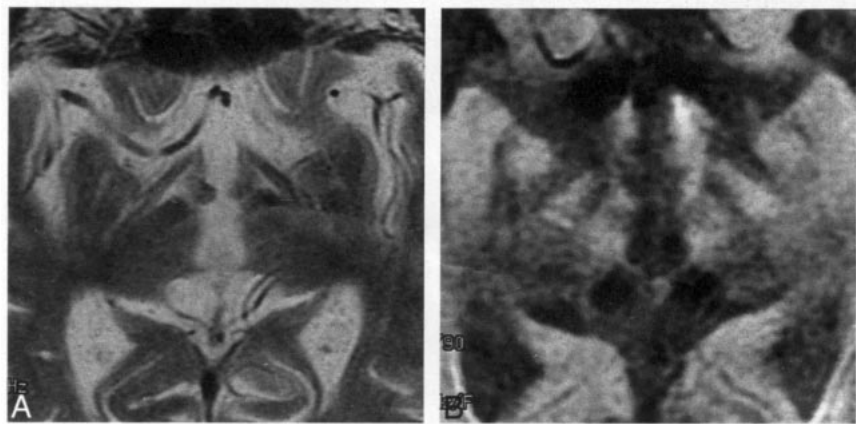


FIG 7. 65-year-old man with progressive supranuclear palsy.

A, T2-weighted image (3540/105) shows atrophic changes of the midbrain; however, no abnormal signal intensity is evident.

B, Diffusion-weighted image shows the substantia nigra to be reduced in size.

pallidus, and substantia nigra on T2-weighted images, resulting from the accumulation of iron (10, 11). Other investigators have reported the reduction of a hyperintense band of tissue on T2-weighted images between the dark region corresponding to the red nucleus and the more ventrally lying dark area of the pars reticularis (12–14). Rutledge et al (7) described a restoration of signal in the dorsal lateral substantia nigra, which may be caused either by a depletion of iron (due to increased cellular metabolic activity) or by local cell death, resulting in an expansion of the extracellular space.

A divergence of opinions, however, exists regarding these MR imaging features. Braffman et al (13) found no significant differences in putaminal hypointensity between patients with Parkinson's disease and control subjects on long-TR/long-TE spin-echo sequences or on T2*-weighted images obtained with gradient-echo sequences. They also reported no significant difference in the frequency of restoration of signal intensity of the substantia nigra between these two groups. Regarding the ac-

cumulation of iron, Antonini et al (10) stated that, owing to the overlap of measured T2 signal between healthy subjects and patients with Parkinson's disease, T2 shortening could not serve as an absolute distinguishing feature. Galazka et al (15) reported no difference in the total amount of iron in the substantia nigra of the brains of patients with Parkinson's disease as compared with the brains of control specimens. Regarding reduction of the white band, which was said to consist of the pars compacta of the substantia nigra, the question arises as to whether all or part of this band consists of the white matter between the red nucleus and substantia nigra (ie, nigrostriatal fibers, not the pars compacta of the substantia nigra) (11).

At present, no optimal imaging technique for depicting the substantia nigra has been established. In this study, the frequency of identification of the whole border of the substantia nigra on T2-weighted images was only 18%. Recent advances in MR technology have made it possible to image the diffusion of tissue water. Diffusion-weighted imaging

is useful for the assessment of the anisotropy of nerve fibers (5), and we obtained satisfactory images of the substantia nigra using axial multishot diffusion-weighted imaging. The substantia nigra was most clearly depicted when the diffusion gradient was applied in the left-right direction, which offered good diffusion-weighted contrast between the substantia nigra and the surrounding white matter, because anatomically the nerve fibers of the cerebral peduncle extend in the rostrocaudal direction, and those between the substantia nigra and the red nucleus extend in the obliquely ventrodorsal direction.

Using this imaging technique, we evaluated 72 images of the substantia nigra obtained from 36 control subjects, 47 images from 25 patients with Parkinson's disease, and 10 images from five patients with secondary parkinsonism. We previously speculated that the thickness of the substantia nigra in the patients with Parkinson's disease or secondary parkinsonism would be smaller than those of the control subjects; however, we found no significant difference in the size of the substantia nigra between the control subjects and the patients with Parkinson's disease. To our knowledge, there are few reports measuring the size of the substantia nigra. Ma et al (16) demonstrated that in Parkinson's disease, the number of pigmented neurons in the whole substantia nigra was about 24% of control values. Wakabayashi et al (17) showed that in Parkinson's disease, the average number of pigmented neurons in the substantia nigra and locus ceruleus was 28% and 19%, respectively, of those of control subjects. They also showed that the number of non-pigmented neurons in the substantia nigra was not reduced in patients with Parkinson's disease. The substantia nigra consists of the pars compacta, within which pigmented neurons condense, and the pars reticularis, including nonpigmented neurons. The pars reticularis, which occupies the ventrolateral part of the substantia nigra, is larger than the pars compacta. Neuropathologically, it is known that gliosis in the substantia nigra is less significant in Parkinson's disease than in multisystem atrophy; for example, in PSP, gliosis is shown in the whole substantia nigra. It is therefore possible that the volume of the substantia nigra does not markedly decrease even if pigmented neurons disappear from the pars compacta of the substantia nigra.

On the other hand, the mean thickness of the substantia nigra of the five patients with secondary parkinsonism was less than that of the average of the control group. Tamura et al (18) reported that following occlusion of the middle cerebral artery in rats, marked atrophy was observed in the ipsilateral substantia nigra during and after the second week, and that the mechanism of this neuropathologic change might be explained by a transsynaptic, neurotransmitter-mediated disinhibition as a result of infarction of the striatum. These authors also described neuronal loss, gliosis, and marked atrophy in the ipsilateral substantia nigra pars reticularis.

Forno (19) reported that with massive unilateral infarction of the basal ganglia, slight to moderate nerve cell loss was present in the ipsilateral substantia nigra. And Ogawa et al (20) suggested that a hyperintense area in the substantia nigra was degenerative after striatal infarction on T2-weighted MR images, which might be attributable to excessive excitation due to a loss of inhibitory γ -aminobutyric acid. These authors also found that the hyperintense area of the substantia nigra became less intense and smaller 3 months later. In patients with secondary parkinsonism of long duration, the striatonigral pathway could be damaged and the whole volume of the substantia nigra reduced. Indeed, we observed a reduced size of the substantia nigra on the diffusion-weighted images in such patients.

The distinction between Parkinson's disease and secondary parkinsonism is difficult, particularly in the early stages. Diagnostic accuracy, however, is important in predicting prognosis and expected response to pharmacotherapy. Our results, indicating the ability to distinguish between these diseases on diffusion-weighted images, could be valuable for accurate diagnosis of parkinsonian syndrome.

Conclusion

Multishot diffusion-weighted MR imaging with the left-right direction diffusion gradient is a better imaging technique than T2-weighted imaging for depicting a change in the size of the substantia nigra in vivo. We found that in patients with Parkinson's disease, the substantia nigra is not reduced in size, but it is diminished in patients with secondary parkinsonism, whose striatonigral pathway could be damaged.

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