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MR Imaging of Parkinson Disease with Spin-Echo and Gradient-Echo Sequences

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High-field MR with both spin-echo and gradient-echo sequences was performed in 21 patients with (idiopathic, drug-responsive) Parkinson disease. The use of gradient echoes allowed more sensitive detection than did spin echoes of susceptibility changes in the putamina and substantia nigra. No statistically significant difference in putaminal hypointensity on long TR/long TE spin-echo sequences or on T2*-weighted images using gradient-echo sequences was observed between Parkinson patients and controls. There was also no statistically significant difference in the frequency of restoration of the signal intensity of the substantia nigra between the two groups of patients. The width of the pars compacta of the substantia nigra in patients with Parkinson disease was 2.12 ± 0.82 mm (mean $\pm$ SD). This value in age- and gender-matched controls was 2.67 ± 0.5 . Comparing these two groups with an unpaired t test resulted in a p value less than or equal to .005.

Our MR study with spin-echo and gradient-echo images in Parkinson and control patients was able to substantiate and elaborate on previously described MR features of Parkinson disease.

Several investigators have described the MR imaging features of Parkinson disease (i.e., the primary or idiopathic form) and parkinsonian syndromes (i.e., secondary parkinsonism or Parkinson plus) [1–4]. Their pioneering work pointed to the utility of MR as a diagnostic tool in the evaluation of these patients. Drayer et al. [1] and Pastakia et al. [2] described an abnormal decrease in signal intensity of the putamina on long TR/long TE spin-echo sequences in multiple-system atrophy, a parkinsonian syndrome, probably due to iron (or other paramagnetic) deposition. Duguid et al. [3] found a narrowing of the signal from the pars compacta of the substantia nigra in Parkinson patients relative to controls. Rutledge et al. [4] reported a loss of the normal hypointensity on long TR/long TE spin-echo images in the dorsal lateral aspect of the substantia nigra in patients with Parkinson disease and parkinsonian syndromes. They referred to this as restoration of the signal intensity of the substantia nigra. They also observed an abnormal decrease in the signal intensity of the putamen on long TR/long TE spin-echo sequences in two patients with unclassified parkinsonism, but not in patients with Parkinson disease.

Our study used a gradient echo to emphasize the susceptibility effects (hypointensity on long TR images) noted by other investigators and prospectively included only those who met the clinical criteria for Parkinson disease. The objective was to identify which of the MR features described above are seen in a group of patients with a relatively homogeneous clinical syndrome.

Subjects and Methods

Patients were selected by three neurologists from among those under their clinical care. Inclusion criteria required classic symptoms (bradykinesia, "resting" tremor, rigidity, and festinating gait [5]) and a good response to medication. All patients meeting these criteria were asked to participate in this study. This selection process yielded 21 MR studies of

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Parkinson patients ages 41–76 years old, including 11 men and 10 women. Controls were selected by retrospectively reviewing patients scanned for reasons unrelated to movement disorders. Medical charts of control subjects were reviewed. All had received a neurologic examination. They had various neurologic deficits, but none of these controls had bradykinesia, resting tremor, rigidity, festinating gait, or other symptoms of Parkinson disease. Controls were excluded if there was evidence on MR of a mass in the midbrain distorting the anatomy of the substantia nigra. Controls with a history of radiation injury, Alzheimer disease, and multiple sclerosis (i.e., disorders that may result in abnormal concentrations of brain iron [6]) were excluded. This yielded 24 MR studies of controls.

All patients and controls were examined on a 1.5-T unit* with both spin-echo and gradient-echo sequences. The spin-echo sequences used a short TR, 600/20 (TR/TE), and a long TR, 2500/20,80 (TR/first-echo TE, second-echo TE). Acquisition time was 2.5 min and 10 min 48 sec for the short and long TR sequences, respectively.

Gradient-echo images were obtained in patients and controls by using one of two sequences. The gradient-recalled acquisition in the steady state (GRASS) technique, 200/50, used an RF pulse angle of 10°. The scanning time was approximately 45 sec per slice. The partial-saturation interleaved technique, 750/50, also used an RF pulse angle of 10°. These parameters resulted in contrast based mainly on T2* differences [7, 8]. Scanning time was approximately 3 min 48 sec for eight to 12 sections. For both spin-echo and gradient-echo sequences, section thickness was 5 mm with a 2.5-mm interval between sections. The scanning plane was axial, 0–20° degrees positive to the inferior orbitomeatal line.

We analyzed the intensity of the putamina in patients and controls with both the gradient-echo and spin-echo techniques on relatively T2*- and T2-weighted images (i.e., long TR/long TE sequences), respectively. Three neuroradiologists evaluated the MR images of patients and controls in a blinded fashion. Visual analysis was standardized to four discrete ratings. Grades 0–3 were variable patterns of hypointensities of the putamina relative to cortical gray matter. Grade 0 was for no hypointensity (Fig. 1); grade 1 was for hypointensity limited to the lateral margin of the putamen (Fig. 2); grade 2 was for hypointensity extending through part of the body of the putamen (Fig. 3); and grade 3 was for diffuse hypointensity of the entire putamen (Fig. 4).

The signal intensity of the substantia nigra was recorded as normal, restored, or questionably restored (i.e., loss of the normal hypointensity of the dorsal lateral aspect of the substantia nigra), as described by Rutledge et al. [4], on both spin-echo and gradient-echo sequences (Fig. 5).

Duguid et al. [3] described the anatomy of the pars compacta of the substantia nigra on MR. They found no significant change in the width of the pars compacta when the scanning plane was oriented between 0° and 20° positive to the inferior orbitomeatal line. On a long TR spin-echo sequence, the pars compacta is the relatively hyperintense band between the hypointense pars reticulata of the substantia nigra and the hypointense red nucleus (Fig. 6).

The width of the pars compacta signal in patients and controls was measured on the basis of a variation of the method described by Duguid et al. [3]. Intensity values of a straight line perpendicular to the pars compacta through the center of the red nucleus were measured on an image of the midbrain. We drew two additional parallel straight lines 1 mm to either side. At the half-height maximum intensity value between the hypointense red nucleus and relatively hyperintense pars compacta we placed one cursor. At the corresponding half-height maximum intensity value between the pars compacta and relatively hypointense pars reticulata we placed a

second cursor. The distance between the two was taken as the width of the pars compacta. We averaged three values for each pars compacta. The precision of this method was determined by repeating the measurements on three separate occasions in three different subjects. In each subject, a mean width and a standard deviation were determined. The standard deviation divided by the mean width was taken as a measure of the precision [9]. The average precision in these three patients was 3.4%.

Additional observations on MR, such as the presence of punctate hyperintense foci on long TR images in the globus pallidus and substantia nigra and presence of cortical atrophy (none, mild, moderate, and marked), were recorded.

Results

The widths of the pars compacta in both groups are listed in Table 1. Five Parkinson patients were either unable to maintain the head position in order to scan through the midbrain at 0–20° positive to the inferior orbitomeatal line or moved during scanning, and therefore were excluded. (In one of these five patients, the midbrain nuclei were not identified on MR, possibly because of the 2.5-mm gap between 5-mm slices.) The mean width in the Parkinson group was 2.12 mm (SD = 0.82). This value in the age- and gender-matched controls was 2.67 mm (SD = 0.5). There was a significant overlap between the two groups, as reflected in the relatively large standard deviations and as seen in Table 1. Nonetheless, comparing these two groups with an unpaired *t* test [9] resulted in a *p* value less than or equal to .005. In some (but not all) cases, the smaller width of the pars compacta in Parkinson patients was visibly detectable (Fig. 7A). MR in one Parkinson patient was notable for a width of 0 of the pars compacta; that is, there was complete loss of the hyperintense band between the red nucleus and the pars reticulata (Fig. 7B).

The grades of the intensities of the putamina on the spin-echo and gradient-echo images are listed in Table 2. In one Parkinson patient, putamina were graded 3 bilaterally on the spin-echo sequence (Fig. 4). This same patient and an additional Parkinson patient (whose putamina were graded 1 on the spin-echo sequence) had putamina that were graded 3 bilaterally on gradient-echo sequences. No control subject had putamina that were graded 3 on either gradient-echo or spin-echo sequences. The number of Parkinson patients and controls included in this study is not large enough to determine whether the number of patients with putamina graded 3 is statistically significant. The grades of the two groups of subjects could be compared by using a chi-square test if there were five or more putamina of each grade [9]. To achieve this, we combined grades 2 and 3. A comparison of the grades of the putamina in the Parkinson group with those in the control group by using chi-square revealed no statistically significant difference between the two groups ($\chi^2 = .693$, $p > .05$ on spin-echo sequences and $\chi^2 = .024$, $p .05$ on gradient-echo sequences).

Restoration of the signal intensity of the substantia nigra was seen in 10 (24%) of 42 Parkinson patients and in seven (15%) of 48 control patients on spin-echo sequences (Table 3). Although restoration was more common in the Parkinson

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Fig. 1.—MR image (2500/80) of 49-year-old man with Parkinson disease. Globi pallidi (arrows) are hypointense relative to cortical gray matter. Putamina (arrowheads) are isointense. Putamina were graded 0.

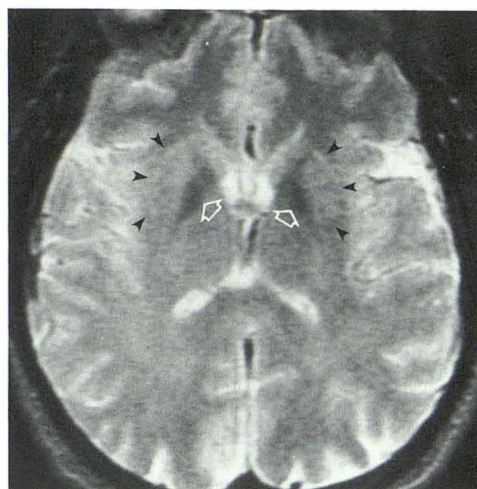


Fig. 2.—MR image (2500/80) of 76-year-old man with Parkinson disease. Hypointensity is limited to lateral aspect of putamina. (arrowheads), left side greater than right. Both were graded 1.



Fig. 3.—MR image (2500/80) of 73-year-old woman with Parkinson disease. Bilateral putaminal hypointensity involves most, but not all, of putamina. They were graded 2. Also note bilateral punctate hyperintense foci (arrowheads) in globi pallidi.

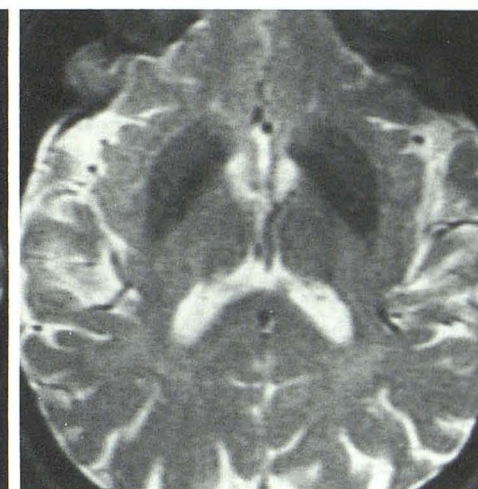
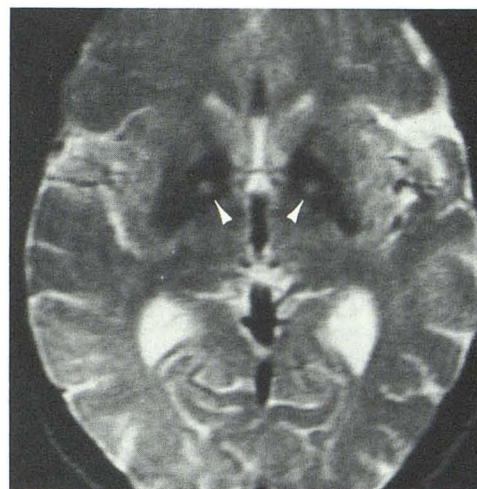


Fig. 4.—MR image (2500/80) of 68-year-old man with Parkinson disease. Hypointensity involves entire putamina diffusely. They were graded 3.



Fig. 5.—MR image (2500/80) of 64-year-old man with Parkinson disease. There is loss of normal hypointensity (arrows) of dorsal lateral aspect of substantia nigra; that is, there is restoration of signal intensity [4].

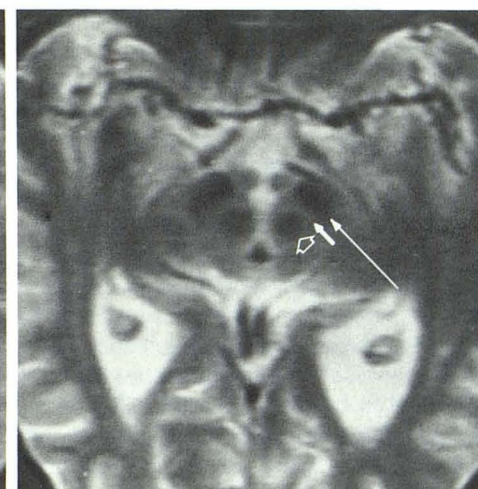
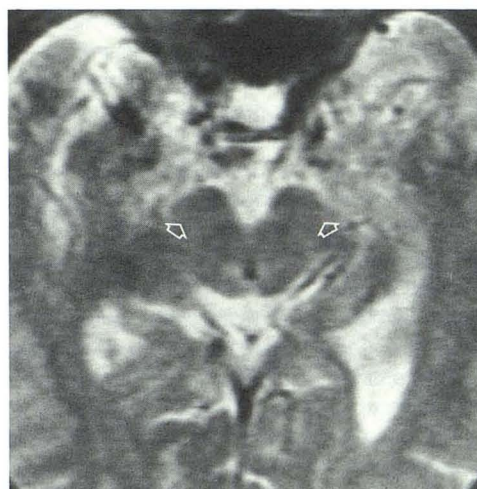


Fig. 6.—MR image (2500/80) of 60-year-old woman scanned for unrelated disorder (control subject). Scanning plane is 0–20° positive to inferior orbitomeatal line. Pars compacta of substantia nigra (short solid arrow) is the relatively hyperintense band between hypointense pars reticulata (long solid arrow) of substantia nigra and hypointense red nucleus (open arrow).



TABLE 1: Measured Widths of the Pars Compacta of Substantia Nigra in Parkinson and Control Subjects

Group: Case No.	Width (mm)	
	Right	Left
Parkinson:		
1	2.53	1.92
2	1.84	2.10
3	2.95	1.77
4	3.36	2.88
5	1.85	1.96
6	1.71	2.50
7	2.14	1.72
8	2.27	1.67
9	2.24	4.10
10	0	0
11	2.99	1.65
12	2.88	2.54
13	2.70	1.97
14	2.32	1.84
15	3.04	0.96
16	1.72	2.13
Control:		
1	1.95	2.56
2	2.78	2.79
3	2.83	4.22
4	2.51	2.61
5	2.88	2.99
6	2.78	2.91
7	2.18	2.43
8	2.20	3.08
9	2.30	2.01
10	3.71	3.50
11	2.13	1.80
12	2.61	2.24
13	3.00	3.36
14	1.86	2.15
15	2.83	2.63
16	3.09	2.67
17	3.05	2.32
18	1.97	1.92
19	3.10	2.61
20	3.31	2.72
21	2.39	2.45
22	3.04	2.98
23	2.66	2.82
24	2.85	2.98

Note.—Five of the 21 Parkinson patients are not included here because they were unable to maintain proper head position for scanning through the midbrain at 0–20° positive to the inferior orbitomeatal line, or moved during scanning.

patients, comparing the two groups with chi-square revealed the difference was not statistically significant ($\chi^2 = 2.86$, $p > .05$). On gradient-echo sequences, the substantia nigra was restored in four (10%) of 40 Parkinson patients and in two (4%) of 46 controls (Table 3). The substantia nigra was in the restored category in too few patients (less than five) on gradient-echo sequences to determine statistical significance.

Atrophy was more common in the Parkinson group than in the control group (Fig. 8) (Table 4). Comparing the two groups with chi-square revealed the difference was not statistically significant ($\chi^2 = 3.285$, $p > .05$). However, in selecting controls, we did not exclude subjects with disorders that may result in atrophy. It is possible that this difference in atrophy

would be statistically significant if it were compared with otherwise normal elderly subjects.

Three patients had bilateral hyperintense foci on the long TR spin-echo sequences in the globi pallidi (Fig. 3). One of these patients was hypertensive; the other two were neither hypertensive nor had other cardiovascular risk factors. No control subject revealed these features.

Four patients had hyperintense foci on the long TR spin-echo sequences in the substantia nigra or in adjacent structures (Fig. 9). None of these patients was hypertensive or had other cardiovascular risk factors. Three control subjects revealed similar findings. One was hypertensive while the others were neither hypertensive nor had other cardiovascular risk factors.

Discussion

Although known since ancient times, Parkinson disease, or paralysis agitans, was first described concisely by James Parkinson in 1817 [10]. The disease is relatively prevalent. Approximately 1% of the population over the age of 50 years in the United States is affected, for a total of approximately a half million people [5]. Its onset is between 40 and 70 years of age.

The neuropathologic hallmark of the disease is loss of neuromelanin-containing neurons in the substantia nigra (most marked in the central part of the pars compacta), the locus ceruleus, and the dorsal vagal nucleus [17–17]. Associated changes of gliosis occur at these sites. The remaining cells contain Lewy bodies, an eosinophilic cytoplasmic inclusion.

Our study corroborated the results described by Duguid et al. [3] regarding a decreased width in the pars compacta of the substantia nigra in Parkinson patients. As those authors commented, this MR appearance probably reflects the atrophy of this structure described in the neuropathologic literature, but possibly may be due to increased iron in this region.

Of interest are the four parkinsonian patients who, in addition to a decreased breadth of the pars compacta, revealed punctate hyperintense foci of the substantia nigra on long TR spin-echo sequences (Fig. 9). This may represent the gliosis that accompanies the cell loss of the pars compacta. Similar punctate hyperintense foci of the substantia nigra in three control subjects, however, illustrate the lack of specificity of this latter observation.

Gradient-echo images are more sensitive than spin-echo images to local magnetic field inhomogeneity [18]. This greater sensitivity accounts for the higher grading of the putamen and lower incidence of restoration of the substantia nigra in both Parkinson patients and controls on gradient-echo compared with spin-echo images (Tables 2 and 3). We were unable to detect a statistically significant difference in the grading of the putamen in the Parkinson group compared with the control group on either spin-echo or gradient-echo sequences. However, we did observe grade 3 in both putamina of one Parkinson patient with the spin-echo technique (Fig. 4) and in an additional patient with the gradient-echo technique, but in no control patient with either technique. Our

Fig. 7.—A, MR image (2500/80) of 76-year-old woman with Parkinson disease (same patient as in Fig. 2). Observe narrowed hyperintense band (pars compacta of left substantia nigra) between hypointense pars reticulata of left substantia nigra and left red nucleus. Right pars compacta is not affected as markedly.

B, MR image (2500/80) of 73-year-old woman with Parkinson disease (same patient as in Fig. 3). Note complete loss of normal hyperintense band between pars reticulata of substantia nigra and red nuclei bilaterally.

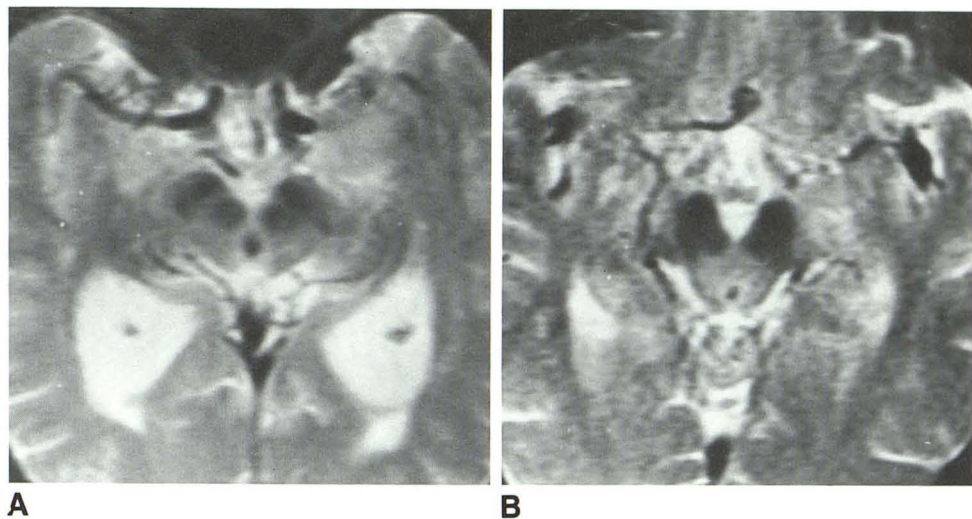


TABLE 2: Putaminal Intensities in Parkinson and Control Patients on Spin-Echo and Gradient-Echo Sequences

Sequence: Intensity Grade	No. (%)	
	Parkinson	Control
Spin-echo 2500/80:		
0	5 (12)	6 (13)
1	30 (71)	36 (75)
2	5 (12)	6 (13)
3	2 (5)	0
Gradient-echo:		
0	6 (15)	3 (7)
1	17 (43)	24 (52)
2	13 (33)	19 (41)
3	4 (10)	0

Note.—Grade 0 = no hypointensity; 1 = hypointensity limited to the lateral margin of the putamen; 2 = hypointensity extending through part of the body of the putamen; 3 = diffuse hypointensity of the entire putamen.

TABLE 3: Restoration of the Signal Intensities [4] of the Substantia Nigra in Parkinson and Control Patients on Spin-Echo and Gradient-Echo Sequences

Sequence: Signal Intensity	No. (%)	
	Parkinson	Control
Spin-echo 2500/80:		
Restored	10 (24)	7 (15)
Normal	32 (76)	41 (85)
Gradient-echo:		
Restored	4 (10)	2 (4)
Normal	36 (90)	44 (96)

patient and control populations were not large enough to determine whether these one or two patients whose putamina were graded 3 constitute a statistically significant group.

Drayer et al. [1] reviewed the literature regarding brain iron and Parkinson disease. Earle [16] found that measurements of brain tissue iron concentration by X-ray fluorescent spectrographic analysis in 11 formalin-fixed brains of subjects with Parkinson disease were increased by a factor of 2 or more

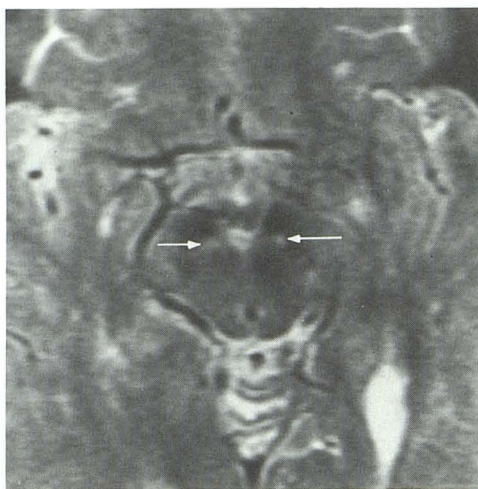
as compared with normals. Earle noted a generalized shift of this element rather than a focal deposition of this substance. Other authors have reported a localized deposition of iron. Rojas et al. [19] found an increase in glial and neuronal intracytoplasmic iron pigments in the ventrolateral thalamic, lentiform, and caudate nuclei, but not in the cerebral cortex in Parkinson patients (four idiopathic, two "arteriosclerotic," one postencephalitic). Five of these subjects who either had autopsy or had a needle biopsy of the liver also had a systemic siderosis. Unlike the description of Rojas et al. of no iron in the cerebral cortex, Kingo [20] described a positive iron reaction in the frontal cortex and substantia nigra in Parkinson patients. Lhermitte et al. [21] observed increased iron in the globus pallidus in one case of postencephalitic parkinsonism. Barbeau and Boileau [22] demonstrated an increase in urinary iron excretion in Parkinson patients following a single muscular injection of iron chelates, suggesting an increase in body storage of mobile iron in Parkinson disease. In a recent study, Rutledge and Schallert [23] evaluated the effect of administering a catecholaminergic neurotoxin to rats. On MR, these subjects revealed an abnormal hypointensity in the striato-nigral tract. The authors suggested this may be due to ferritin deposition.

The conclusive role of iron or another paramagnetic substance (striatal, nigral, and/or other) in Parkinson patients awaits further investigation. On the basis of our study, however, most patients with Parkinson disease do not demonstrate a pattern of putaminal hypointensity on long TR/long TE spin-echo images or on T2*-weighted images (gradient-echo sequences) that differs from that of controls. Alternatively, patients with the parkinsonian syndromes of multiple-system atrophy, Shy-Drager syndrome, and progressive supranuclear palsy may reveal more marked putaminal hypointensity on these sequences than do either Parkinson patients or normals [1, 2]. Therefore, MR may serve as an adjunct to the clinical examination in differentiating Parkinson disease from certain parkinsonian syndromes.

Although we found restoration of the signal intensity of the substantia nigra to be more frequent in Parkinson patients



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Fig. 8.—MR image (2500/20) of 76-year-old man with Parkinson disease. Observe marked cortical and central parenchymal loss with enlarged subarachnoid spaces, particularly of parietooccipital lobes, and enlarged lateral ventricles.

Fig. 9.—MR image (2500/20) of 67-year-old woman with Parkinson disease. Observe bilateral punctate hyperintense foci (arrows) in substantia nigra. One lesion is at junction of left pars reticulata and pars compacta; the other is in right pars compacta.

TABLE 4: Cortical Atrophy in Parkinson and Control Patients

Degree of Cortical Atrophy	No. (%)	
	Parkinson	Control
Normal	0	3 (13)
Mild	10 (48)	13 (54)
Moderate	6 (28)	6 (25)
Marked	5 (24)	2 (8)

than in controls, it was not a statistically significant difference. Rutledge et al. [4] suggested the restoration of signal intensity may be due to depletion of iron by increased cellular metabolic activity or local cell death resulting in expansion of the extracellular space, which overwhelms the T2* effect and increases the signal.

The significance of pallidal lesions in Parkinson disease is controversial. Pakkenberg [24] described a paleness of the cytoplasm of pallidal cells in Parkinson patients. Denny-Brown [25] observed pallor in myelin-stained preparations of the globus pallidus in these subjects. Lipkin [26] reported atrophy of the globus pallidus in these patients compared with age-matched controls. However, other investigators found no difference in the pallidi of Parkinson patients compared with controls [13, 14, 27–29]. Oppenheimer [17] commented that the above-described pathologic changes of the basal ganglia are seen in elderly people not suffering from parkinsonism. In our study, bilateral pallidal hyperintense foci on long TR spin-echo images were noted in three of the 21 Parkinson patients (Fig. 3) and in none of the 24 controls. This suggests there may be an increased incidence of such lesions in Parkinson patients. Rutledge et al. [4] observed similar findings in four of their seven patients with Shy-Drager syndrome. They suggested that the appearance of the globus pallidus may allow distinction between olivopontocerebellar degeneration and Shy-Drager syndrome on MR. Our observation of this change in three patients with Parkinson disease implies that it may not allow such differentiation.

We found moderate or marked atrophy in 52% of our patients and in 33% of our controls. Although the difference was not statistically significant, in selecting controls we did not exclude those with other processes that may result in atrophy. Alvord [15] stated that atrophy probably is significant and beyond what one would expect for age. Rutledge et al. [4] found generalized atrophy in 86% of patients with parkinsonism and in 56% of age-matched controls.

The progress in our understanding the features of Parkinson disease on MR may parallel the experience of F. H. Lewy, as described and quoted by Alvord [15]. After a lifetime of study of Parkinson disease, Lewy said, "When I had investigated my first two dozen cases, . . . I was convinced that I knew where the cause of tremor and rigidity was located. When I had examined pathologically the seventh dozen, . . . I was completely confused because you seemed to be able to prove just as well one theory as the contrary one."

Our data confirm certain MR features of Parkinson disease:

1. There is a statistically significant decrease in the width of the pars compacta [3]. This probably reflects selective loss of neuromelanin-containing cells of the pars compacta of the substantia nigra, but may also be due to iron deposition. This may be the characteristic feature of the disease on MR. In some cases, accompanying hyperintense foci may be seen that may represent the concomitant gliosis.

2. Most Parkinson patients do not show a pattern of putaminal hypointensity on long TR/long TE spin-echo images or on T2*-weighted images (gradient-echo sequences) that differs from that of controls.

3. Although restoration of the signal intensity of the substantia nigra [4] occurred more often in Parkinson patients than in controls, it was not statistically significant in our study.

4. Moderate and marked cortical atrophy occurred more often in Parkinson patients than in controls; however, the difference was not statistically significant.

5. Pallidal lesions, which may be the same lesions described in elderly patients without the disease, may occur more often in patients with Parkinson disease.

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