Brain Magnetic Resonance Imaging in Multiple-System Atrophy and Parkinson Disease

A Diagnostic Algorithm

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Background: Brain magnetic resonance imaging (MR imaging) offers the potential for objective criteria in the differential diagnosis of multiple system atrophy with predominant parkinsonism (MSA-P) and Parkinson disease (PD), since it frequently shows characteristic abnormalities in patients with MSA-P and is believed to be normal in patients with PD.

Objective: To determine concordance between clinical and MR imaging–based diagnoses of MSA-P and PD.

Design: Two neuroradiologists identified and rated striatal and infratentorial abnormalities in 39 brain MR images and assigned a diagnosis of PD, MSA-P, or MSA with additional marked cerebellar ataxia (MSA-C).

Setting: Academic medical center.

Patients: Thirty-nine patients with parkinsonism, including 21 with a clinical diagnosis of PD, 14 with MSA-P, and 4 with MSA-C.

Results: All patients with MSA and 14 (67%) of 21 patients with PD had some abnormality on brain MR imaging. Brainstem atrophy was seen in patients with MSA-P and MSA-C. Putaminal atrophy was seen only in MSA-P. Putaminal hypointensity and lateral slitlike hyperintensity were seen in both PD and MSA-P but were always mild in PD. Cerebellar abnormalities, seen in all patients with MSA-C and 11 patients with MSA-P, were also identified in 6 patients with PD, albeit always rated as mild. Nonconcordance between clinical and radiological diagnosis occurred in 2 patients with PD, 5 with MSA-P, and 1 with MSA-C.

Conclusion: Since several features on brain MR imaging are seen only in MSA-P, a simple diagnostic algorithm may improve the MR imaging diagnosis of MSA-P and PD.

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MULTIPLE-SYSTEM atrophy (MSA) and Parkinson disease (PD) are the 2 most prevalent neurodegenerative disorders that exhibit features of parkinsonism and autonomic dysfunction. Many patients with MSA have, in addition to parkinsonism, cerebellar ataxia, and this combination is referred to as MSA-C.

In the most frequent type of MSA, referred to as MSA-P, patients have mostly parkinsonian and few, if any, cerebellar signs. Accordingly, the clinical distinction between MSA-P and PD is often difficult. Clinical history may be helpful because, in patients with MSA-P, symptoms of autonomic failure frequently precede parkinsonism but, not infrequently, parkinsonism is the presenting feature. Complicating matters further, although patients with PD usually present with parkinsonism, they may also have severe autonomic failure in a later phase of the disease, making the distinction from MSA-P extremely difficult. The availability of new surgical and pharmacologic therapies that may be effective only in patients with PD has heightened the need for precise diagnosis.

In addition to clinical criteria, several tests are proposed to distinguish between these disorders. The most commonly used is the therapeutic response to dopaminergic agents, the lack of which suggests a diagnosis of MSA-P. However, pharmacologic challenge is not specific, as many patients with MSA-P may initially respond to dopaminergic drugs. Other tests include neuroendocrine responses to hypotension or centrally acting adrenergic agonists, which are blunted in patients with MSA-P but preserved in patients with PD because brainstem-hypothalamic-pituitary pathways are affected only in MSA-P.

Similarly, sphincter electromyogram...
PATIENTS AND METHODS

Thirty-nine patients with parkinsonism, who were followed up at the Mount Sinai Medical Center, New York, NY, participated in this study. Eighteen patients had a diagnosis of probable MSA according to published criteria (13 men and 5 women; age, 59 ± 11 years [range, 39-74 years]; disease duration, 5 ± 2 years [range, 1-10 years]; all ages and disease durations are expressed as mean ± SD). Fourteen had predominantly parkinsonian signs and were classified as having MSA-P (9 men and 5 women; age, 59 ± 11 years [range, 39-71 years]; disease duration, 5 ± 3 years [range, 1-10 years]). Four had predominantly cerebellar features and were classified as having MSA-C (all men; age, 57 ± 12 years [range, 45-74 years]; disease duration, 4 ± 2 years [range, 3-6 years]). Twenty-one patients had a diagnosis of PD (15 men and 6 women; age, 64 ± 11 years [range, 40-81 years]; disease duration, 7 ± 6 years [range, 1-20 years]) according to United Kingdom PD Brain Bank criteria. No patient with PD had clinical evidence of autonomic dysfunction. Patients with PD, MSA-P, and MSA-C had a similar age. The male-female ratio was 15:6 in PD, 5:1 in MSA-P, and 4:0 in MSA-C.

All patients underwent 1.5-T MR imaging, with a protocol that included sagittal T1-weighted images (repetition time/echo time, 600/14 seconds; slice thickness, 5 mm), axial intermediate and T2-weighted sequences (repetition time/echo time, 2500/90-90 seconds; slice thickness, 5 mm), and inversion recovery axial T1 images (repetition time/echo time/inversion time, 2500/20/800 seconds; slice thickness, 4 mm).

Two experienced neuroradiologists (B.D. and B.E.), blind to the clinical diagnosis, visually rated the MR images for changes previously described in brain MR images of patients with PD, MSA-P, and MSA-C. These included (1) putaminal signal hypointensity relative to the globus pallidus on T2-weighted images, (2) linear slit-like hypointensity in the postero-lateral margin of the putamen on T2-weighted images, (3) putaminal atrophy, (4) cerebellar atrophy (vermis and cerebellar hemispheres), (5) brainstem atrophy (midbrain,pons,medulla), (6) decreased width of the substantia nigra pars compacta, and (7) abnormal signal intensity in the middle cerebellar peduncles. Images were rated on a scale from 0 to 3, where 0 was normal, 1 mild, 2 moderate, and 3 severe abnormalities.

The raters gave a radiological diagnosis of PD, MSA-P, or MSA-C to each MR image. A radiological diagnosis of MSA-P was based on findings of moderate to severe putaminal abnormalities or mild putaminal change together with brainstem or cerebellar abnormality. A radiological diagnosis of PD was based on near-normal MR images, with few or no abnormalities, or the presence of only mild abnormality in the putamen, brainstem, or cerebellum. A radiological diagnosis of MSA-C was given if cerebellar changes in the brainstem or cerebellum were moderate or severe regardless of putaminal change. In addition, the neuroradiologists used their overall impression to assign a diagnosis.

Statistical analysis was performed with Fisher exact t test for qualitative MR imaging variables and t test for analysis of unpaired quantitative independent variables. Significance was set at P = .05.

Table 1. Brain MR Imaging Findings in Patients Clinically Diagnosed With MSA-P, PD, and MSA-C*

<table>
<thead>
<tr>
<th></th>
<th>MSA-P, No. (%)</th>
<th>PD, No. (%)</th>
<th>P Value†</th>
<th>MSA-C, No. (%)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>6 (43)</td>
<td>0</td>
<td>.002</td>
<td>0</td>
<td>.25</td>
</tr>
<tr>
<td>Low signal (body)</td>
<td>11 (79)</td>
<td>6 (29)</td>
<td>.006</td>
<td>3 (75)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Low signal (body) &gt;1</td>
<td>6 (43)</td>
<td>0</td>
<td>.002</td>
<td>0</td>
<td>.25</td>
</tr>
<tr>
<td>Lateral slitlike hyperintensity</td>
<td>11 (79)</td>
<td>11 (52)</td>
<td>.16</td>
<td>2 (50)</td>
<td>.53</td>
</tr>
<tr>
<td>Lateral slitlike hyperintensity &gt;1</td>
<td>5 (36)</td>
<td>1 (5)</td>
<td>.006</td>
<td>0</td>
<td>.28</td>
</tr>
<tr>
<td>Brainstem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy midbrain</td>
<td>5 (36)</td>
<td>0</td>
<td>.006</td>
<td>3 (75)</td>
<td>.28</td>
</tr>
<tr>
<td>Atrophy pons</td>
<td>6 (43)</td>
<td>0</td>
<td>.002</td>
<td>2 (50)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Atrophy medulla</td>
<td>6 (43)</td>
<td>0</td>
<td>.002</td>
<td>2 (50)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>“Hot-cross bun” sign</td>
<td>1 (7)</td>
<td>0</td>
<td>.002</td>
<td>2 (50)</td>
<td>.11</td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy vermis</td>
<td>7 (50)</td>
<td>6 (29)</td>
<td>.29</td>
<td>4 (100)</td>
<td>.12</td>
</tr>
<tr>
<td>Atrophy hemispheres</td>
<td>6 (43)</td>
<td>3 (14)</td>
<td>.11</td>
<td>3 (75)</td>
<td>.58</td>
</tr>
<tr>
<td>Signal change, middle cerebellar peduncle</td>
<td>3 (21)</td>
<td>0</td>
<td>.05</td>
<td>2 (50)</td>
<td>.53</td>
</tr>
</tbody>
</table>

*MR indicates magnetic resonance; MSA-P, multiple-system atrophy with predominant parkinsonism; PD, Parkinson disease; and MSA-C, MSA-P with marked cerebellar ataxia. Rating scale for MR imaging abnormalities is as follows: 0, normal; 1, mild abnormality; 2, moderate abnormality; and 3, severe abnormality.
†MSA-P vs PD.
‡MSA-P vs MSA-C.
the striatum, brainstem, and cerebellum in patients with MSA-P.5-22 Therefore, MR imaging may be a useful aid to clinical diagnosis. In this study, neuroradiologists who were blind to the clinical diagnosis rated brain MR images of patients with clinically diagnosed PD, MSA-P, and MSA-C. On the basis of previously published characteristic MR imaging abnormalities,5-22 neuroradiologists assigned a diagnosis of PD, MSA-P, or MSA-C to each MR image. The concordance between the clinical and MR imaging diagnosis was then assessed and an algorithm was devised to improve radiological diagnosis.

RESULTS

MR IMAGING FINDINGS

Putamen

No patient with PD had atrophy of the putamen, but 11 had slitlike hyperintensity of its posterolateral margin and 6 had hypointensity of its body relative to the globus pallidum, always graded as mild (grade 1) (Table 1; Figure 1) with the exception of 1 patient, in whom slitlike hyperintensity was graded as moderate. Patients with
PD with putaminal rim hyperintensity were significantly older than those without this finding (68±10 vs 59±10 years; \( P = .02 \)). Six patients with MSA-P had atrophy of the putamen (\( P = .002 \) vs PD); 11 had slitlike hyperintensity of its posterolateral margin (\( P = .16 \) vs PD); and 11 had hypointensity of its body (\( P = .006 \) vs PD), graded as mild in 6 and moderate or severe in 5 (\( P = .006 \) vs PD). No patient with either MSA-P or MSA-C had radiological changes in the substantia nigra.

**Substantia Nigra**

Decreased width of the substantia nigra pars compacta was identified in 1 of 21 patients with PD and “smudging” of its posterior border in 2. No patient with either MSA-P or MSA-C had radiological changes in the substantia nigra.

**Brainstem Findings**

No patient with PD had brainstem atrophy. Seven patients with MSA-P had brainstem atrophy (Figure 3). Five patients had atrophy affecting the midbrain (rated mild in 4 and moderate in 1), 6 patients had atrophy affecting the pons (rated mild in 5 and moderate in 1), and 6 patients had atrophy affecting the medulla (rated mild in 4 and moderate in 2). Cruciform hyperintensity of the pons, the “hot-cross bun” sign (Figure 4), was present in 1 patient.

Brainstem atrophy was seen in 3 patients with MSA-C. Two patients had moderate atrophy in all brainstem areas. The hot-cross bun sign was present in 2.

**Cerebellar Findings**

Six patients with PD had some cerebellar abnormality, all rated mild. All 6 of these patients had atrophy of the vermis and 3 had atrophy of the cerebellar hemispheres. One patient had mild signal abnormality in the middle cerebellar peduncle (Figure 5). Eleven patients with
MSA-P had cerebellar abnormalities ($P = .006$ vs PD), 7 had atrophy of the cerebellar vermis, 5 mild and 2 moderate; 6 had atrophy of the cerebellar hemispheres, 5 mild and 1 moderate; and 3 had abnormal signal in the middle cerebellar peduncle, 1 mild, 1 moderate, and 1 severe.

All patients with MSA-C had cerebellar abnormalities; all had atrophy of the vermis, 1 mild, 2 moderate, and 2 severe; 3 had atrophy of the cerebellar hemispheres, 1 mild, 1 moderate, and 1 severe; and 2 had abnormal signal in the middle cerebellar peduncles, 1 mild and 1 moderate. The combination of infratentorial and putaminal abnormalities was present in 6 patients with PD, 10 with MSA-P ($P = .02$ vs PD), and all patients with MSA-C.

**CONCORDANCE BETWEEN RADIOLOGICAL AND CLINICAL DIAGNOSIS**

The neuroradiologists “erroneously” diagnosed 5 patients with a clinical diagnosis of MSA-P as having PD (Table 2). Of these, mild atrophy of the putamen was present in 1, 3 had mild hypointensity of its body, and 4 had mild hyperintensity of its posterolateral margin. Two
of these patients had brainstorm atrophy and 2 had mild cerebellar atrophy. Patients with MSA-P “wrongly” diagnosed radiologically as having PD had significantly shorter disease duration (4 ± 1 vs 6 ± 3 years; P = .05), although they were of similar age in comparison with patients with MSA-P “correctly” diagnosed by the neuroradiologists. The neuroradiologists “erroneously” diagnosed 2 patients with a clinical diagnosis of PD as having MSA-P. One patient had mild signal abnormality in the middle cerebellar peduncle and the other had mild putaminal and cerebellar abnormalities.

The 1 patient with MSA-C “erroneously” diagnosed by the neuroradiologists as having PD had only mild changes in the putamen, brainstorm, and cerebellum.

Table 2. Brain MR Imaging Findings in Patients With MSA-P With Concordant Radiological Diagnosis of MSA-P and Nonconcordant Radiological Diagnosis of PD*

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis of MSA-P (n = 9)</th>
<th>Diagnosis of PD (n = 5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>61 ± 12</td>
<td>57 ± 10 s</td>
<td>.25</td>
</tr>
<tr>
<td>Disease duration, y (mean ± SD)</td>
<td>6 ± 3</td>
<td>4 ± 1</td>
<td>.05</td>
</tr>
<tr>
<td>Putamen, No. (%)</td>
<td>5 (56)</td>
<td>1 (20)</td>
<td>.30</td>
</tr>
<tr>
<td>Lateral slitlike hypointensity</td>
<td>7 (78)</td>
<td>4 (80)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Lateral slitlike hypointensity &gt;1</td>
<td>5 (71)</td>
<td>0</td>
<td>.09</td>
</tr>
<tr>
<td>Low signal (body)</td>
<td>8 (89)</td>
<td>3 (60)</td>
<td>.51</td>
</tr>
<tr>
<td>Low signal &gt;1 (body)</td>
<td>6 (75)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Atrophy</td>
<td>5 (56)</td>
<td>1 (20)</td>
<td>.30</td>
</tr>
<tr>
<td>Atrophy &gt;1</td>
<td>2 (40)</td>
<td>0</td>
<td>.51</td>
</tr>
</tbody>
</table>

*MR indicates magnetic resonance; MSA-P, multiple-system atrophy with predominant parkinsonism; and PD, Parkinson disease. Rating scale for MR imaging abnormalities is as follows: 0, normal; 1, mild abnormality; 2, moderate abnormality; and 3, severe abnormality.

We found that several features on brain MR images of patients with parkinsonism are diagnostic of MSA-P, as they are never seen in patients with PD. These included putaminal and brainstorm atrophy and abnormal signal in the middle cerebellar peduncles. Other abnormalities were found in both patients with MSA-P and those with PD, but they varied in severity. These included hypointensity of the putaminal body, slitlike hyperintensity of the lateral putaminal border, and atrophy of the cerebellar vermis or hemispheres. When the severity of these abnormalities was graded, it was always mild in patients with PD. All patients with MSA-P and two thirds of patients with PD had some abnormality on brain MR imaging.

Two patients with PD were assigned a diagnosis of MSA-P by the neuroradiologists. One was a 38-year-old woman with onset of PD at age 18 years. On MR imaging she had mild signal change in the middle cerebellar peduncle. We speculate that patients with juvenile-onset PD may have different MR imaging characteristics than those in patients with adult-onset PD. The other patient was a 68-year-old man with disease duration of 4 years, asymmetric onset of tremor, excellent levodopa responsiveness, and dyskinesias, making a diagnosis of MSA-P unlikely. On brain MR imaging, he had mild hypointensity of the body of the putamen, mild hyperintensity of its lateral rim, and mild atrophy of the cerebellar vermis and hemispheres.

The 5 patients with MSA-P, assigned an MR imaging diagnosis of PD by the neuroradiologists, had, in general, mild putaminal and cerebellar abnormalities on brain MR images. Their mean disease duration was less than 5 years (range, 1-5 years), significantly shorter than that of patients with MSA-P assigned the “correct” MR imaging diagnosis. Brain MR imaging may be of limited value in patients with MSA-P early in their disease, as it may show only mild abnormalities. However, in these 5 patients there were abnormalities present, which were specific to MSA-P, 1 patient had mild atrophy of the putamen and 2 had brainstorm atrophy. The patient with MSA-C neuroradiologically diagnosed as having PD had only mild putaminal and cerebellar abnormalities but also mild brainstorm atrophy, an abnormality not found in patients with PD. In sum, nonconcordance between clinical and radiological diagnoses occurred in cases with mild putaminal hypointensity, mild hyperintensity of the lateral putaminal border, and mild cerebellar atrophy, which were abnormalities found in all 3 patient groups. Identifying abnormalities found only in MSA-P, such as atrophy of the putamen and brainstorm or abnormal signal change in the cerebellar peduncle, improves the accuracy of radiological diagnosis in MSA-P and PD.

We therefore propose a simple diagnostic algorithm for the diagnosis of PD and MSA-P using brain MR images (Figure 6). Atrophy of the putamen or brainstorm and abnormal signal in the middle cerebellar peduncle are diagnostic of MSA-P. Hypointensity of the body of the putamen, hyperintensity of its lateral rim, and atrophy of the cerebellar vermis and hemispheres are found in both MSA-P and PD and are diagnostic of MSA-P only when severity is rated as more than mild, ie, moderate or severe. Mild putaminal hypointensity, mild putaminal slitlike hyperintensity, and mild cerebellar atrophy could represent PD or early MSA-P of less than 5 years’ duration, and thus follow-up MR imaging is needed. If brain MR imaging is normal, the patient could have PD or MSA-P of less than 1 year’s duration, as, although MR imaging was abnormal in all patients with MSA-P, no patient had disease duration of less than 1 year.

With this algorithm, the 3 patients with MSA-P and the 1 patient with MSA-C “wrongly” diagnosed radiologically as having PD would not have been assigned a brain MR imaging diagnosis of MSA-P or MSA-C, as they had abnormalities never found in patients with PD. Therefore, the proposed algorithm increases the concordance between radiological and clinical diagnoses.

The major limitation of this algorithm is that it has not been validated by neuropathologic data and clinical diagnosis could be wrong. It is possible that patients with PD who had MR imaging abnormalities could have received an incorrect clinical diagnosis and actually had MSA-P, and that patients with MSA-P who had mild MR imaging abnormalities could have indeed had PD.
ever, several factors suggest that the clinical diagnosis was the right one. First, during an average of 7 years of follow-up, no patient with clinically diagnosed PD developed signs or symptoms suggestive of MSA-P, but this is not conclusive. Second, all patients with clinically diagnosed PD had asymmetric onset of symptoms and signs and were levodopa responsive, and almost all developed dyskinesias over time, features unusual in MSA-P but again nonconclusive. Similarly, several factors suggest that the clinical diagnosis was the correct one in MSA-P. All patients with MSA-P had early autonomic failure, had symmetric onset of parkinsonism, were poorly levodopa responsive or were levodopa unresponsive, and, within an average of 5 years of follow-up, did not develop dyskinesias.

Atrophy of the putamen and moderate or severe hypointensity of its body were found only in patients with MSA-P and not in patients with PD or MSA-C. This suggests that putaminal atrophy and hypointensity of the putaminal body, thought to be due to iron deposition in the putamen, are indicative of “end-organ” striatal damage, as they were not present or were mild in patients with PD or MSA-C with mild extrapyramidal signs but were present with increased severity in patients with MSA-P and severe extrapyramidal signs. This is in agreement with previous studies finding correlation between degree of putaminal atrophy and severity of extrapyramidal signs.

Slitlike hyperintensity of the posterolateral putaminal margin has not, to our knowledge, been reported in PD. We found definite but mild slitlike hyperintensity of the lateral putamen in 11 of 21 patients with a clinical diagnosis of PD. Mild putaminal rim hyperintensity is frequently seen on brain MR images in normal aging (B.D., unpublished data, 2000) and may represent age-related reactive gliosis. Interestingly, patients with PD who have this finding were significantly older than those without it. We found that all patients with MSA-P with pronounced putaminal rim hyperintensity had concomitant putaminal atrophy, suggesting that marked putaminal rim hyperintensity may be due to extracellular fluid accumulation in the putaminal capsule secondary to atrophy of the nucleus.

Although radiological abnormalities of the substantia nigra, including decreased width and smudging of its posterior border, have been reported in MSA-P, MSA-C, and PD, we found a low frequency, in only 2 of 21 patients with PD and no patients with MSA-P or MSA-C.
Therefore, substantia nigra abnormality was not included in the algorithm.

In conclusion, it is often difficult to distinguish clinically between patients with MSA-P and PD, and high-field-strength brain MR images may be useful, as patients with MSA-P show specific abnormalities that can distinguish them from patients with PD. Other abnormalities are found in both disorders, but, when the severity of the abnormality is graded, it is always mild in patients with PD. On the basis of these findings, we have designed a simple algorithm to help distinguish patients with MSA-P from patients with PD by means of brain MR imaging.

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REFERENCES