Differentiation of Parkinsonism-Predominant Multiple System Atrophy from Idiopathic Parkinson Disease Using 3T Susceptibility-Weighted MR Imaging, Focusing on Putaminal Change and Lesion Asymmetry


AJNR Am J Neuroradiol 2015, 36 (12) 2227-2234
doi: https://doi.org/10.3174/ajnr.A4442
http://www.ajnr.org/content/36/12/2227
Differentiation of Parkinsonism-Predominant Multiple System Atrophy from Idiopathic Parkinson Disease Using 3T Susceptibility-Weighted MR Imaging, Focusing on Putaminal Change and Lesion Asymmetry


ABSTRACT

BACKGROUND AND PURPOSE: Asymmetric presentation of clinical feature in parkinsonism is common, but correlatable radiologic feature is not clearly defined. Our aim was to evaluate 3T susceptibility-weighted imaging findings for differentiating parkinsonism-predominant multiple system atrophy from idiopathic Parkinson disease, focusing on putaminal changes and lesion asymmetry.

MATERIALS AND METHODS: This retrospective cohort study included 27 patients with parkinsonism-predominant multiple system atrophy and 50 patients with idiopathic Parkinson disease diagnosed clinically. Twenty-seven age-matched subjects without evidence of movement disorders who underwent SWI were included as the control group. A consensus was reached by 2 radiologists who visually assessed SWI for the presence of putaminal atrophy and marked signal hypointensity on each side of the posterolateral putamen. We also quantitatively measured putaminal width and phase-shift values.

RESULTS: The mean disease duration was 4.7 years for the patients with parkinsonism-predominant multiple system atrophy and 7.8 years for the patients with idiopathic Parkinson disease. In the patients with parkinsonism-predominant multiple system atrophy, putaminal atrophy was frequently observed (14/27, 51.9%) and was most commonly found in the unilateral putamen (13/14). Marked signal hypointensity was observed in 12 patients with parkinsonism-predominant multiple system atrophy (44.4%). No patients with idiopathic Parkinson disease or healthy controls showed putaminal atrophy or marked signal hypointensity. Quantitatively measured putaminal width, phase-shift values, and the ratio of mean phase-shift values for the dominant and nondominant sides were significantly different between the parkinsonism-predominant multiple system atrophy group and the idiopathic Parkinson disease and healthy control groups (P < .001).

CONCLUSIONS: 3T SWI can visualize putaminal atrophy and marked signal hypointensity in patients with parkinsonism-predominant multiple system atrophy with high specificity. Furthermore, it clearly demonstrates the dominant side of putaminal changes, which correlate with the contralateral symptomatic side of patients.

ABBREVIATIONS: IPD = idiopathic Parkinson disease; MSA-p = parkinsonism-predominant multiple system atrophy; MSA-c = cerebellar dysfunction type multiple system atrophy; ROC = receiver operating characteristic

Parkinsonism-predominant multiple system atrophy (MSA-p) is one of the Parkinson-plus syndromes that has a clinical manifestation similar to that of idiopathic Parkinson disease (IPD) and is often challenging to diagnose in its early stage. MR imaging plays a role in differentiating MSA-p from IPD and is included as an additional feature for the diagnosis of possible multiple system atrophy. Various conventional and functional MR imaging findings regarding the putamen in MSA-p have been reported. However, these findings had limited sensitivity and specificity. An asymmetric presentation of clinical features is common for IPD in its early stage, while symmetric symptoms are more common in MSA-p than in IPD. However, the clinical manifestation of parkinsonism develops asymmetrically in many patients with MSA-p, and it has been reported that approximately 40%–50% of patients with MSA-p present with initial asymmetric symptoms. This presentation increases the difficulty of clinically differentiating IPD from MSA-p in the early stage of disease. However, to our knowledge, there are few previous reports that used imaging to examine the asymmetry of putaminal abnormalities in MSA-p.

Susceptibility-weighted imaging (SWI), which was recently...
introduced and is now widely used in clinical brain imaging, reflects the physical magnetic properties of tissues because susceptibility changes in tissues, such as iron deposition, are very sensitive. In addition to the sensitivity of SWI to paramagnetic material, corrected phase images that are calculated to form final SWI can provide quantitative phase-shift values that reflect tissue iron content. Recently published studies attempted to use SWI to differentiate movement disorders, including MSA-p, and demonstrated different iron-deposition patterns between MSA-p and IPD by measuring phase-shift values by using corrected phase images of SWI sequences. However, most previous studies regarding SWI were performed on 1.5T or weaker main magnetic field MR imaging machines. When main magnetic field is increased to 3T, spins process at a higher frequency, which may result in phase shifts caused by susceptibility changes being more exaggerated on SWI.

Thus, the purpose of the present study was to evaluate the imaging findings of 3T SWI for differentiating MSA-p from IPD, focusing on putaminal changes and lesion asymmetry.

**MATERIALS AND METHODS**

**Study Population**

This retrospective cohort study was approved by the institutional review board of our hospital, and the requirement for informed consent was waived. The investigators searched all patients who were referred from the Movement Disorder Center to undergo brain MR imaging, including SWI, for further evaluation of parkinsonism between April 2010 and May 2012 (n = 207). Among those patients, we enrolled subjects who had been initially, clinically diagnosed with either MSA-p (n = 33) or IPD (n = 50). All routine brain MR imaging protocols performed during the study period for the evaluation of movement disorders included SWI, except in 1 patient. Neurologists experienced with movement disorders (H.-J.K. and B.S.J.) made the final clinical diagnosis by reviewing the initial and follow-up clinical data in December 2013. MSA-p was diagnosed according to the "Second Consensus Statement on the Diagnosis of Multiple System Atrophy” and was categorized as probable or possible. IPD was diagnosed on the basis of the UK Parkinson’s Disease Society Brain Bank criteria.

Five initial patients with MSA-p were excluded for the following reasons: an old intracerebral hemorrhage involved the basal ganglia (n = 1), diagnoses were changed to cerebellar dysfunction type multiple system atrophy (MSA-c) (n = 3), and final diagnosis found no movement disorder (n = 1). One initial patient with IPD was excluded due to lack of SWI by a technical error. One initial patient with MSA-p had the final diagnosis changed to IPD. Finally, there were 27 patients with MSA-p and 50 patients with IPD. Twenty-seven age-matched subjects who met the following criteria were enrolled as the control group: 1) They underwent brain MR imaging with SWI between September 2012 and November 2012, 2) had no definite focal lesions in the brain parenchyma, and 3) had no clinical evidence of neurodegenerative diseases or movement disorders. The control group subjects were age-matched 1:1 with the subjects with MSA-p. Finally, our study included 27 patients with MSA-p (17 probable and 10 possible), 50 patients with IPD, and 27 healthy control subjects.

**MR Imaging Protocol**

All subjects underwent brain MR imaging by using a 3T scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 32-channel head coil. A set of images was acquired by using a 3D fully flow-compensated gradient-echo SWI sequence along the transverse plane parallel to the anterior/posterior commissure lines. The imaging parameters were as follows: TR = 28 ms, TE = 20 ms, flip angle = 15°, section thickness = 2 mm, FOV = 178 × 220 mm, matrix size = 364 × 448, and number of excitations = 1. Therefore, the voxel size was 0.49 × 0.49 × 2.0 mm. The magnitude and phase images were processed to create final SWI on the MR imaging console workstation (syngo MR B17; Siemens). The corrected phase images and final processed SWI were used for further analyses.

**Image Interpretation**

Two radiologists (I.H. and C.-H.S., with 4 and 17 years of experience in neuroradiology, respectively), who reached a consensus, reviewed the processed SWI. The investigators qualitatively evaluated the imaging findings for putaminal atrophy and signal intensity of the posterolateral putamen compared with adjacent structures in the basal ganglia (eg, globus pallidus). In particular, loss of lateral convexity of the posterolateral putaminal border was also indicative of putaminal atrophy. In addition to the SWI findings, cerebellar and brain stem findings were also reviewed with T2-weighted axial images for the following: 1) hot-cross bun sign of the pons, 2) high signal intensity in the middle cerebellar peduncle, and 3) cerebellar atrophy. The putaminal signal intensity was graded by using a relative 4-step scale introduced by Kraft et al., in which the signal of the putamen was rated as higher = 0, equal = 1, hypointense = 2, or markedly hypointense = 3. Other image findings were rated as negative = 0, suspicious = 1, or definitely positive = 2. Laterality was also recorded if a finding of putaminal atrophy was rated as suspicious or definitely positive or the signal intensity was rated as marked hypointensity. During the interpretation, images were presented randomly and investigators were blinded to the patients’ diagnoses.

**Quantitative Image Analysis**

We quantitatively measured the putaminal width and phase-shift values in corrected phase images. Image analyses were also performed by 2 radiologists who performed qualitative image interpretation and reached a consensus. The most representative section demonstrating the largest width and most well-demarcated border of the posterior putamen was selected for further analysis. The images were analyzed by using ImageJ 1.46r software (National Institutes of Health, Bethesda, Maryland) with 400% magnification to more easily determine the boundaries of the basal ganglia structures. Investigators drew 3 straight lines with widths of 3 pixels crossing the midportion, posterior half, and far posterior portion of the putamen in the right-to-left direction, as shown in Fig 1A. Using the Plot Profile function in ImageJ, we plotted phase-shift values along the straight line, and putaminal positive phase-shift values were easily recognized (Fig 1A). The width and the mean phase-shift value on each side of the putamen were recorded by using the 3 lines. The phase-shift value was recorded in Siemens Phase Units, which range from 0 to 4096
corresponding to $-\pi$ to $+\pi$ radian. To normalize the putamen width by brain size, we also measured the largest biparietal diameter of the brain parenchyma on the same image plane. The normalized putaminal width (putaminal width/biparietal diameter mean of biparietal diameter of all subjects) was calculated and used for the statistical analysis. Dominant-side values (shorter putamen width or higher mean phase-shift value) and the mean of the values of both sides were calculated and used for the statistical analysis. Finally, to evaluate the asymmetry of the measured values, we also calculated the dominant/nondominant side ratios of the measured values. All analyses were performed for each straight line drawn at the mid-, posterior half, and far posterior portion of the putamen; then, the level that showed the most differentiation was selected and further analyzed.

**Neurologic Assessment**

Experienced neurologists (H.-J.K. and B.S.J.) assessed the final clinical diagnoses of IPD or MSA-p by reviewing the initial and follow-up clinical data. Those neurologists also assessed initial modified Hoehn and Yahr scale scores. In addition, the clinical-onset side of resting tremors or bradykinesia was recorded if the patient presented with asymmetric symptoms at the time of disease onset. If the symptom onset was not asymmetric or information regarding the side of onset was unclear, the more severe symptomatic side was recorded.

**Statistical Analyses**

All statistical analyses were performed by using MedCalc for Windows, Version 14.10.2 (MedCalc Software, Mariakerke, Belgium). For all statistical analyses, a $P$ value $<.05$ was considered a statistically significant difference. For the qualitative assessment, the prevalence of each finding was calculated. In addition, the sensitivity and specificity for differentiating MSA-P from IPD were also investigated. To assess interrater agreement, we calculated the weighed $k$ coefficient for 2 major qualitative imaging findings (putaminal atrophy and signal intensity of the posterolateral putamen) on the basis of the initial review data before the 2 reviewers arrived at a consensus. A $\chi^2$ test, Mann-Whitney $U$ test, 1-way analysis of variance test, and Kruskal-Wallis test were used to compare the clinicopathologic characteristics and quantitatively measured values for the MSA-p, IPD, and control subjects, as appropriate. A pair-wise comparison was used for the post hoc analysis. Furthermore, a receiver operating characteristic (ROC) curve was drawn for the variables that were significantly different by the Kruskal-Wallis test for differentiating MSA-p from IPD. The area under the ROC curve was calculated to evaluate the diagnostic performance of those variables.

**RESULTS**

**Demographic and Clinical Characteristics**

The demographic and clinical characteristics of each group are described in Table 1. The mean disease duration at the time of MR imaging was significantly longer for the IPD group than the MSA-p group.

**Qualitative Image Interpretation**

Table 2 shows the prevalence of putaminal atrophy and marked signal hypointensity. No subject showed suspicious or definite

---

**Table 1: Demographic and clinical characteristics of the study groups**

<table>
<thead>
<tr>
<th></th>
<th>MSA-p</th>
<th>IPD</th>
<th>Healthy Control</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>27</td>
<td>50</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>64.8 ± 8.6 (47–77)</td>
<td>66.5 ± 6.7 (54–81)</td>
<td>64.7 ± 8.5 (47–77)</td>
<td>.521</td>
</tr>
<tr>
<td>Mean disease duration (yr)</td>
<td>4.7 ± 2.9</td>
<td>7.8 ± 5.0</td>
<td>NA</td>
<td>.010</td>
</tr>
<tr>
<td>H&amp;Y scale</td>
<td>2.85 ± 0.72</td>
<td>1.95 ± 0.57</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients with asymmetric presentation</td>
<td>17</td>
<td>10</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: — H&Y scale indicates modified Hoehn and Yahr scale. NA, not applicable.

*a Data are presented as mean ± SD, with ranges in the parentheses.

*b One-way analysis of variance test.

*c $\chi^2$ test.

*d Mann-Whitney $U$ test.

---

**Fig 1.** Measurement of putaminal width and mean phase-shift values from corrected phase images by using ImageJ software. A, Three lines crossing the mid-, posterior half, and far posterior putamen are drawn to allow measurements. B, The corresponding plot profile of the line crossing the far posterior portion of the putamen demonstrates increased phase-shift values in both putamina (arrows).
putaminal atrophy or marked signal hypointensity in the IPD or healthy control groups. Therefore, the specificity for each finding was 100%. The sensitivities of putaminal atrophy and marked signal hypointensity were 51.9% (14/27) and 44.4% (12/27), respectively (Fig 2). Most of these findings were unilateral rather than bilateral (Table 3).

Table 3 summarizes the correlation between the clinically symptomatic side and asymmetry in the imaging findings. Among 14 subjects with MSA-p with suspicious or definite putaminal atrophy, 9 subjects presented with a symptomatic side that was contralateral to the atrophy side determined by imaging. The relationship between the clinically symptomatic side and marked signal hypointensity was weaker: Six subjects demonstrated a contralateral correlation between the symptomatic side and the marked hypointense signal side.

Simultaneous putaminal atrophy with marked putaminal signal hypointensity was observed in 11 of 27 patients with MSA-p (40.7%). One patient with MSA-p had bilateral marked signal hypointensity without putaminal atrophy. Otherwise, all patients with MSA-p with marked signal hypointensity showed a loss of lateral convexity. Representative images from the patients with MSA-p and patients with IPD are shown in the Figs 3 and 4.

The weighted $k$ coefficients for 2 major qualitative imaging findings—putaminal atrophy and signal intensity of the postero-lateral putamen—were 0.728 (95% CI, 0.561–0.894) and 0.636 (95% CI, 0.461–0.812), respectively.

**Comparison of Measured Putaminal Width and Phase-Shift Values**

The On-line Table summarizes the measured values and the dominant/nondominant side ratios of the measured values at
the midportion, posterior half, and far posterior portion of the putamen. The measured values at the far posterior putamen showed the most significant differences between the MSA-p and IPD and control groups. Table 4 demonstrates the values of the far posterior putamen, and further analyses were based on the values measured at the far posterior putamen. The dominant-side (shorter) putaminal width and the mean of both putaminal widths were smaller in the MSA-p group compared with IPD and healthy control groups. The dominant-side mean phase-shift values and the mean phase-shift values of both putamina were also significantly different in the MSA-p group compared with the IPD and healthy control groups. The MSA-p group showed the highest phase-shift values among all groups.

**ROC Curve Analysis for Values Measured to Differentiate MSA-p from IPD**

An ROC curve analysis was performed for the values that were quantitatively measured at the far posterior portion of the putamen to differentiate MSA-p from IPD. The area under the ROC curve was highest for the phase-shift value of both putamina (0.803; 95% CI, 0.697–0.885), followed by the phase-shift value of the dominant side (0.793; 95% CI, 0.685–0.877), the putaminal width of the dominant side (0.761; 95% CI, 0.650–0.851), the mean putaminal width of both sides (0.754; 95% CI, 0.643–0.845), and the dominant-to-nondominant side ratio of the phase-shift value (0.752; 95% CI, 0.640–0.843). Figure 5 demonstrates the ROC curve of the measured values. The optimal cutoff point of the phase-shift value of both putamina was 2121.6 Siemens Phase Units.
mens Phase Units, and the diagnostic performance was defined by 77.8% sensitivity and 76.0% specificity.

DISCUSSION
We investigated the 2 imaging findings of the putamen, putaminal atrophy and marked signal hypointensity, as a result of iron deposition on 3T SWI. Our results suggest that these image findings are very specific for patients with MSA-p (100% specificity) and appear asymmetrically in those patients. The sensitivity of previously reported imaging findings for MSA-p ranged from approximately 50% to 85%. Previous studies were most commonly performed by using an MR imaging system with a main magnetic

Table 4: Quantitatively measured putaminal width and phase-shift values: the ratios of dominant-to-nondominant-side values in the far posterior portion of putamen

<table>
<thead>
<tr>
<th>Measured values: dominant side</th>
<th>MSA-p</th>
<th>IPD</th>
<th>Healthy Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen width&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.17 ± 0.65</td>
<td>3.81 ± 0.53</td>
<td>3.87 ± 0.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Phase-shift value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2322.2 ± 236.9</td>
<td>2123.5 ± 44.4</td>
<td>2136.7 ± 45.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Measured values: mean of both sides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen width&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.42 ± 0.57</td>
<td>3.98 ± 0.52</td>
<td>4.05 ± 0.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Phase-shift value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2258.4 ± 180.1</td>
<td>2108.1 ± 39.8</td>
<td>2122.5 ± 37.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ratio of dominant/nondominant side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen width (shorter/longer side)</td>
<td>0.866 ± 0.123</td>
<td>0.921 ± 0.070</td>
<td>0.912 ± 0.048</td>
<td>.095</td>
</tr>
<tr>
<td>Phase-shift value&lt;sup&gt;b&lt;/sup&gt; (higher/lower side)</td>
<td>1.057 ± 0.065</td>
<td>1.013 ± 0.011</td>
<td>1.013 ± 0.011</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are presented as means.

<sup>b</sup>MSA-p was significantly different (P < .05) from IPD and healthy controls by post hoc analysis.
raphy. As mentioned earlier, the clinical manifestation of the disease usually occurs asymmetrically, which may not be discovered by support vector machine analysis, and our results were consistent with those of previous studies. Second, the longer disease duration in the IPD group may have decreased the proportion of unilateral disease manifestation. In the early disease stage, IPD frequently shows asymmetric symptoms, but in later stages, IPD has a more symmetric presentation. However, it is well-known that IPD shows no substantial putaminal changes by imaging studies, and our results were consistent with those of previous studies. Third, the diagnosis at the time of MR imaging did not discriminate between probable and possible MSA-p. Unfortunately, the data for probable and possible diagnosis for MSA-p were not available in all patients due to retrospective study design. The final diagnosis was made by reviewing the initial and follow-up clinical data in December 2013, while the imaging study had been done before May 2012. The direct comparison of imaging findings between final probable and possible MSA-p groups might lead to misclassification.
tion bias. Thus, imaging differences between patients with probable and possible MSA-p could not be analyzed.

CONCLUSIONS
3T SWI can visualize putaminal atrophy and marked signal hypointensity in patients with MSA-p with high specificity. Furthermore, it clearly demonstrates the dominant side of putaminal changes, which correlate with the contralateral symptomatic side of patients. We suggest that 3T SWI is a practical method for the evaluation of putaminal atrophy and iron deposition; thus, it could be helpful for differentiating MSA-p from IPD in clinical practice.

REFERENCES
2. Ito S, Shirai W, Hattori T. Evaluating posterolateral linearization of the putaminal margin with magnetic resonance imaging to diagnose the Parkinson variant of multiple system atrophy. Mov Disord 2007;22:578–81 CrossRef Medline
9. Wüllner U, Schmitz-Hubsch T, Abele M, et al. Features of probable multiple system atrophy patients identified among 8770 patients with parkinsonism enrolled in the multicentre registry of the German Com-