Differentiating multiple-system atrophy from Parkinson’s disease

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The purpose of this review is to illustrate the differentiating features of multiple-system atrophy from Parkinson’s disease at MRI. The various MRI sequences helpful in the differentiation will be discussed, including newer methods, such as diffusion tensor imaging, MR spectroscopy, and nuclear imaging.

Introduction

Parkinson’s disease (PD) and multiple system atrophy (MSA) are neurodegenerative disorders that frequently have overlapping symptoms, including Parkinsonism and autonomic dysfunction. In both disorders, patients typically present with motor symptoms and signs such as slowness of movements (bradykinesia), rigidity, tremulousness, and gait difficulty. In MSA, “axial” motor features, such as dysarthria, dysphagia, and postural instability, tend to be prominent, as are urinary dysfunction (retention or incontinence) and orthostatic hypotension, which can result in syncopal episodes and falls. However, the above features can also be seen in PD patients, and currently, it is often difficult to distinguish these entities solely by clinical assessment, especially in the earlier stages of disease. In fact, clinicopathological studies at post-mortem show that MSA is the commonest reason for a misdiagnosis of PD. Accurate diagnosis is important as this has implications for prognosis, treatment, and research.

Over recent years, there has been increasing interest in neuroimaging as a means to differentiate these conditions. Several advanced MRI techniques have been studied in these disorders, including proton density-weighted spin-echo images, short inversion time inversion recovery imaging, multishot diffusion-weighted imaging, and diffusion tensor imaging. These studies have focused on the basal ganglia (putamen and substantia nigra), cerebellum, and pons. Recently, a decision tree based on MRI with linear and diffusion tensor parameters was shown to differentiate between MSA and PD with a fairly high degree of sensitivity and specificity. This study highlighted the usefulness of combining various MRI sequences in the diagnostic process.

In this review, we highlight the ultrasound, CT, MRI, and nuclear medicine imaging features that help to differentiate MSA from PD. The aim is to provide a useful framework for the radiologist and neurologist in clinical practice. This study was approved by institutional research ethics committee.
**Anatomical considerations**

In PD, the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) resulting in loss of dopamine in the striatum is the pathological hallmark of the disease. The subthalamic nucleus as well as the corpus striatum containing the caudate and putamen are also affected. In MSA, besides the striatum and the substantia nigra, there is often also significant involvement of the pons, cerebellum, and middle cerebellar peduncle (MCP). There is progressive neuronal cell loss and gliosis in the putamen, posterior aspect of the substantia nigra, locus ceruleus, inferior olives, pontine nuclei, cerebellar Purkinje cells, and intermediolateral cell columns of the spinal cord. Other less affected areas are the thalamus, subthalamic nucleus, caudate nucleus, globus pallidus, dentate nucleus, vestibular nuclei, anterior horn cells, and pyramidal tracts. These pathological changes may not necessarily translate into distinguishable changes that can be seen on imaging; however, they provide anatomical landmarks for areas of interest in most imaging studies.

**Iron deposition in regions of interest**

MRI has the ability to assess iron deposition in the brain. The MRI sequences used to assess iron deposition are T2-weighted (T2W), T2*-weighted gradient-echo (GRE), and susceptibility-weighted sequences. Different patterns of iron deposition in the brain have been reported in these neurodegenerative diseases. In the substantia nigra, caudate nucleus, globus pallidus, and thalamus iron deposition can be seen in PD, MSA, and normal patients. The differentiating regions are the posterior regions of the putamen and pulvinar thalamus in which there is a higher iron-deposition pattern observed in MSA. Increased nigral iron deposition is correlated with increasing severity of extrapyramidal motor symptoms in PD. Quantifiable measurements of iron deposition using SWI phase-shift values in the.
substantia nigra were found to have a positive correlation with the unified Parkinson’s disease rating scale motor score.\textsuperscript{12} Therefore, analysing the pattern of iron deposition in the posterior regions of the putamen and pulvinar thalamus using GRE or SWI sequences, which are sensitive for iron deposition, may improve diagnostic accuracy and differentiation between PD and MSA. The quantifiable measurements provided by SWI in the substantia nigra may also be related to disease severity of PD.

Another method of analysing iron deposition that has been employed with variable success in the midbrain is transcranial ultrasound. The finding of a hyperechogenic substantia nigra is more sensitive and specific for PD, whereas a hyperechogenic lentiform nucleus is more commonly seen in MSA.\textsuperscript{16} However, a recent study, which prospectively evaluated the sensitivity and specificity of this test on patients with new-onset clinically unclear Parkinsonian features, concluded that transcranial ultrasound failed to show satisfactory clinical use in confirming the diagnosis.\textsuperscript{17}

Hyperintense putaminal rim sign

Hyperintense putaminal rim sign (HPR) on T2W sequences is visualized along the outer margin of the putamen, which would normally be hypointense due to iron deposition. The sign, which may be the result of tissue degeneration and gliosis, was reported as having 100% specificity and positive predictive value in MSA-putaminal type versus PD and controls using 1.5 T.\textsuperscript{18} PET imaging studies correlated this finding with reduced putaminal glucose metabolism and postsynaptic dopamine receptor density in MSA.\textsuperscript{19,20} However, other studies have reported the presence of this sign in PD patients as well.\textsuperscript{21,22} HPR has also been observed in healthy subjects using higher magnetic fields (3 T).\textsuperscript{23} This study also found that HPR was more obvious on 3 T compared to images obtained from a 1.5 T system, postulated to be due to chemical shift and truncation artefacts. Several studies have thus suggested that the HPR sign is more specific for MSA when seen using FLAIR sequences and in conjunction with putaminal atrophy.\textsuperscript{20,24}

Fig 2 shows a comparison between MSA, PD, and normal subjects whereby the dorsoputaminal hyperintense sign is seen in MSA along with mild putaminal atrophy. Other imaging methods are not beneficial in eliciting this sign or to assess putaminal atrophy.

“Hot cross bun” sign

The pontine cruciform hyperintensity seen on T2W MRI is described as the “hot cross bun” (HCB) sign. It is postulated to be due to selective loss of myelinated transverse pontocerebellar fibres in the pontine raphe with selective preservation of the corticospinal tracts.\textsuperscript{18} It is one of the most specific signs for MSA with 100% specificity in the present authors’ cohort of patients, when compared with PD patients (Fig 3). However, it can also be seen in other cerebellar degenerations (such as the spinocerebellar ataxias) and the sensitivity in MSA is only 35.7%.\textsuperscript{25} The HCB sign has been reported in Parkinsonism secondary to presumed spinocerebellar ataxia, vasculitis, and in variant Creutzfeldt–Jacob disease.\textsuperscript{26–28} The latter two diseases, however, are clinically distinguishable from either PD or MSA.

![Figure 2](image-url) (a) Hyperintense putaminal rim sign (black arrows) with mild putaminal atrophy in both putamina (asterisk) in patient with MSA. This sign was not seen in (b) PD.
Volumetry

Volumetry is regarded as useful in conditions that show volume loss as part of the disease process. With multiplanar images and thin sections on MRI, volume measurement can be performed in three planes to measure gross atrophy and, more importantly, assess the pattern differentiating the disease (Figs 4–6). There are various MRI acquisition parameters for volumetric analysis. It is important to utilize high spatial resolution, which can be reformatted into three dimensions (axial, sagittal, and coronal). This requires the smallest isotropic voxels dimension possible utilizing a commercially available sequence, such as 3D MPRAGE (Siemens) and 3D FSPGR (General Electric). For post-

Figure 3 Axial T2W image at the level of the pons depicting (a) the HCB sign in MSA, but is not seen in (b) PD.

Figure 4 Three-dimensional volumetric sequence of the putamen showing the ROI in axial plane depicting volume loss in MSA (a–c) in comparison to PD (d–f).
processing analysis, semi-automated measurements are generally reproducible; however, this assessment technique may be time-consuming and impractical in some busy centres. With advances in technology, automated volume measurement software programs, such as fully-automated segmentation software (FreeSurfer), can be designed to overcome the limitations.

In MSA, the volume of the cerebellum, the thalamus, the putamen, and the brainstem were significantly reduced compared to patients with PD and control subjects. In clinical practice it is useful to recognize the structures affected to assist in differentiating MSA and PD. However, absolute quantifiable measurements for individuals with a cut-off point will be difficult to implement due to the different methods employed in various studies.

### Linear parameters

Linear parameter measurements are easily applied in clinical practice. Identification and measurement of the substantia nigra width, middle cerebellar peduncles (MCP) width, and anteroposterior (AP) diameter of the pons are easily performed using axial T2W MRI (Fig 7). The parameter values have been shown to correlate with the specific disorders. In MSA, the presence of significant atrophy in the pontocerebellar region, resulted in lower MCP width and AP diameter of the pons as compared to PD. An MCP width of <14.6 mm has been shown to be 100% specific for MSA. Routine MRI has modest ability to differentiate PD from controls. This is due to the fact that only 20% of PD patients demonstrate MRI abnormalities. In advanced PD, significant reduction of the substantia nigra pars compacta width, which is hyperintense on T2W sequences, has been reported widely between PD and age-match controls. However, the application of this parameter to differentiate PD in clinical practice is difficult, due to the fact that the mean differences between them are fairly slight at approximately 1 mm only.

As MSA progresses rapidly compared to PD, changes in the MRI can be detected in MSA patients as early as in the first 3 years of the disease in longitudinal studies. From the literature review, the width of the MCP and AP diameter of the pons are the most reliable linear parameters, which show consistent trends and may be advocated as early markers for a more accurate diagnosis of MSA.

### Myelination parameters

Methods of assessing myelin integrity with MRI could be performed using diffusion tensor imaging (DTI). Using DTI, disruption and loss of neuronal fibres can be quantified. The parameters that can be obtained are fractional anisotropy (FA) and mean diffusivity (MD). Generally, FA is reduced when the neuronal fibres are disrupted by degenerative processes causing water diffusion to occur in all directions resulting in a lower anisotropy value, whereas MD will show higher values. Most studies utilize comparison values. When comparison was made between PD and normal

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**Figure 5** Three-dimensional volumetric sequence of the pons showing the ROI in sagittal plane depicting severe volume loss in MSA (a–b) in comparison to PD (c–d).
subjects, FA values of PD patients was significantly reduced in the substantia nigra in several studies.\textsuperscript{38,39} Other areas that demonstrate reduced FA values in PD were the putamen and caudate.\textsuperscript{40} To differentiate MSA and PD, manual regions of interest (ROIs) drawn at the level of the putamen with ADC values of $>0.79 \times 10^{-3}$ mm$^2$/s have been found to have sensitivity of 85% and specificity of 89%.\textsuperscript{41} A trend of reduced FA and increased MD values in MSA compared to

**Figure 6** Three-dimensional volumetric sequence of the cerebellum showing the ROI in coronal plane depicting volume loss in MSA (a–b) in comparison to PD (c–d).

**Figure 7** T2W image in the axial plane at the level of the fourth ventricle showing linear measurements of width of the middle cerebellar peduncles of (a) 58-year-old patient with MSA and (b) a 60-year-old patient with PD.
PD in the substantia nigra (Fig 8), putamen, and pons (Fig 9) was observed in our study, although significance is fairly small and negative findings in the meta-analysis limits the usefulness of the FA/MD values as a biomarker of PD.

Comparison between PD from MSA using DTI, has its usefulness. The cerebellum, globus pallidus, and in particular, MCP regions of MSA patients have been found to be most likely to have reduced FA or regional apparent

![Figure 8](image1)

**Figure 8** Fixed circular ROIs drawn on colour map tensor images for measurements of FA and MD in the rostral, mid, and caudal of bilateral substantia nigra with corresponding median and interquartile range of FA and MD values in MSA and PD.

<table>
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<th>Median (IQR) MD ($10^{-4}$mm$^2$/s)</th>
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<td>PD</td>
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<th>Region</th>
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<th>Median (IQR) MD ($10^{-4}$mm$^2$/s)</th>
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![Figure 9](image2)

**Figure 9** Closed curved ROIs drawn on colour map tensor images for measurements of FA and MD in the (a) bilateral putamen and (b) pons with corresponding median and interquartile range of FA and MD values in MSA and PD.
diffusion coefficient (ADC) values. MD values are reported to be higher in the cerebellum and MCP of MSA patients compared to PD patients, which reflects the two primary areas involved in the pathological process of MSA (Fig 10). DTI study of the HCB sign also shows more extensive changes in MSA than seen on T2W sequences, with a marked decrease in FA and increase in MD, observed in not only the transverse pontocerebellar fibres but the corticospinal tracts, pons, and cerebellum as well. These findings are in keeping with neuropathological studies.

Another method to measure the degree of myelination and axonal density is magnetization transfer imaging (MTR). Similar to DTI, this method allows brain structure segmentation and MTR calculation of the specific ROI. Using 1.5 T MRI, a significant decrease in MTR of the globus pallidus, putamen, and substantia nigra is reported in MSA compared to PD. This study utilized quantifiable reduction methods, which are claimed to be slightly superior to ratio methods. Several studies on PD and MSA have reported a reduction in NAA in both disorders but a trend for normal values in the basal ganglia in PD.

MR spectroscopy

There is limited evidence in literature on the usefulness of MR spectroscopy in differentiating PD from MSA. In particular, ratio-based methods have been found to yield mixed results with regards to N-acetyl aspartate/choline (NAA/Cho) ratio and NAA/creatine (Cr) ratios. Significant NAA reduction has been reported in the pallidum, putamen, and lentiform nucleus of MSA patients compared with PD. This study utilized quantifiable reduction methods, which are claimed to be slightly superior to ratio methods. Several studies on PD and MSA have reported a reduction in NAA in both disorders but a trend for normal values in the basal ganglia in PD.

Single-photon emission CT (SPECT) imaging

Advancement in imaging techniques has made it possible to assess function of the pre-synaptic dopamine transporters and quantify the loss of these terminals. SPECT imaging using dopamine transporters (DAT) such as 123I-β-carbomethoxy-3β-(4-iodophenyl) tropane (123I-β-CIT), has been reported to be able to distinguish PD from MSA based on the symmetry of the tracer distribution. Studies based on the clinical diagnosis of PD and MSA show a greater symmetry and more diffuse striatal DAT binding reduction in MSA compared with PD. However, another study based on histopathological diagnosis of PD and MSA found the opposite, where greater asymmetry of striatal DAT binding was found in MSA compared with PD. Yet another study with clinically probable MSA patients and PD patients found no significant differences in DAT binding. From the inconsistency of the findings, it can be concluded in all these studies that DAT SPECT is not a reliable method with which to differentiate PD from MSA.

The lack of a clear definitive feature with which to differentiate PD and MSA, along with other factors such as high cost of imaging, low availability of dopamine traces, high radiation dose, and high technicality required, make the application of this imaging method impractical.
Positron-emission tomography (PET)

PET, similar to SPECT imaging, is used to perform functional imaging. The European Association of Nuclear Medicine Neuroimaging Committee has recommended resting-state cerebral 2-18F-fluoro-2-deoxy-o-glucose (FDG) to differentiate PD and atypical Parkinson syndromes. FDG has the advantage of evaluating neuronal activity by imaging regional cerebral glucose metabolism using PET. The patterns of abnormal metabolic networks involved in differentiating PD from MSA consist of excess network (where FDG uptake is relatively increased in PD compared with MSA) in the cerebellum (both vermis and cerebellar hemispheres), medial thalami, posterior putamen, caudate nuclei, the hypothalamic region, limbic areas (anterior and middle cingulate regions and insula cortices), and caudal and lateral aspects of the frontal lobes. The deficit network mainly involved the lateral thalamic areas and posterior associative cortices and inferior frontal lobes.

Conclusion

Clinical accuracy in differentiating MSA and PD can be further improved when done in conjunction with MRI. MRI abnormalities in PD are subtle, whereas MSA generally will have more obvious imaging abnormalities such as the HCB sign, putaminal hypointensity, atrophy of the pons, cerebellum, and globus pallidus. These abnormalities, in turn, affect linear, volumetric, or DTI/MTR parameters, as highlighted throughout this article. As no single feature is completely sensitive and specific, an overall compilation of findings, such as that used in decision trees, can further improve diagnostic accuracy.

Acknowledgements

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References