Movement Disorders
CLINICAL PRACTICE
REVIEW

Role of Magnetic Resonance Imaging in the Diagnosis of Multiple System Atrophy

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Abstract: **Background:** Multiple system atrophy (MSA) is a rapidly progressing neurodegenerative disorder without effective disease-modifying therapies. Because of a lack of reliable diagnostic biomarkers, there has been increasing interest in using magnetic resonance imaging (MRI) to improve the diagnostic accuracy of MSA.
Methods: This review summarizes recent literatures on the role of MRI in the diagnosis of MSA.
Results: Several MRI abnormalities on conventional MRI already are included in the current diagnostic criteria for MSA. Other features on conventional MRI are also used to make a diagnosis of MSA or to rule out alternative diagnoses. On the other hand, some of the MRI findings that were previously considered suggestive of a diagnosis of MSA are now being challenged, because it turned out that they were not as specific to MSA as previously thought. More advanced MRI modalities, including susceptibility-weighted imaging, diffusion-weighted imaging, diffusion tensor imaging, voxel-based morphometry, and cortical thickness analysis, are now used to study the changes in the brains of patients with MSA. Furthermore, studies have produced promising results demonstrating the use of MRI as a tool for monitoring and assessing disease progression in MSA.
Conclusions: MRI is useful and indispensable in the diagnosis of MSA and also possibly for monitoring disease progression. In this regard, well-designed, long-term, prospective studies on large numbers of patients are needed.

Introduction

Multiple system atrophy (MSA) is an adult-onset, neurodegenerative disease characterized by progressive autonomic failure, parkinsonism, cerebellar dysfunction, and pyramidal features in various combinations.[1,2] MSA with predominant or sole parkinsonism is designated as MSA-P, and MSA with predominant or sole cerebellar dysfunction is designated as MSA-C. Because progression of MSA is relatively rapid and there still is no effective disease-modifying therapy, accurate diagnosis as early as possible is important not only for the management of patients but also for the development of new therapeutic strategies. Diagnosis of MSA can be readily made without difficulty in some patients, especially in advanced cases. However, in other patients, especially in early cases, it is hard to make a secure diagnosis of MSA due to a lack of reliable biomarkers and the fact that many conditions can be confused with MSA.[3] In this regard, to improve the clinical diagnosis of MSA, various ancillary investigations are used in clinical practice or are under development.[1,4,5]

With advances in magnetic resonance imaging (MRI) techniques in recent years, there has been increasing interest in using MRI to improve the diagnostic accuracy of MSA. Several MRI abnormalities on conventional MRI already are included in the current diagnostic criteria for MSA along with abnormalities of functional neuroimaging, including ^{18}F-flurodeoxyglucose positron-emission tomography (FDG-PET) and presynaptic dopaminergic imaging.[6] Other features on conventional MRI are also used to make a diagnosis of MSA or to

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rule out alternative diagnoses. More advanced MRI modalities, including susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), voxel-based morphometry (VBM), and cortical thickness analysis, are now used to study changes in the brains of patients with MSA; however, it is still too early to apply these modalities in clinical practice given the inconsistencies in the results reported.

Herein, we review MRI findings of MSA and present recent advances in various MRI modalities in the diagnosis and differential diagnosis of MSA. We also highlight the possible role of MRI in monitoring and assessing disease progression and the correlation of MRI findings with nonmotor symptoms (NMS) in MSA.

MRI Findings of MSA

Conventional Structural MRI

Atrophy on MRI of the putamen, middle cerebellar peduncle (MCP), pons, or cerebellum is included as an additional feature for the diagnosis of possible MSA in the current clinical diagnostic criteria.[6] Pathologically, putaminal atrophy on MRI in MSA reflects neuronal loss and gliosis,[7] whereas atrophy of the MCP, pons, and cerebellum on MRI reflects atrophy of the pontocerebellar fibers, transverse pontine fibers, pontine neurons, cerebellar white matter, and, to a lesser degree, cerebellar cortices.[8] In addition to these findings, many studies have reported that putaminal hypointensity, slit-like hyperintense putaminal rim, MCP hyperintensities, and hot-cross-bun sign (HCB) on T2-weighted images (T2WIs) can help in the diagnosis of MSA.[9–14] In agreement with pathology reports,[15] MRI studies have also shown brainstem and cerebellar involvement in MSA-P and striatal involvement in MSA-C. The presence of these features indicates the diagnosis of MSA when a diagnosis by clinical features alone is uncertain.

Putaminal atrophy is 1 of the most commonly reported MRI findings of MSA (both MSA-P and MSA-C) and is thought to be characteristic of MSA.[14,16] However, caution should be exercised, because putaminal atrophy on MRI can be observed in other conditions, including progressive supranuclear palsy (PSP); and 1 study actually reported that the frequency of putaminal atrophy on MRI was higher in PSP than in MSA.[13,17] In patients with adult-onset, progressive cerebellar ataxias, differentiation of MSA-C from idiopathic late-onset cerebellar ataxia is a diagnostic challenge.[3] Several studies have shown that atrophy of the brainstem and MCP could distinguish MSA-C from idiopathic late-onset cerebellar ataxia.[18,19]

Although it can be regarded as an advantage rather than a disadvantage from a different perspective, 1 of the practical problems with using these MRI findings in clinical diagnoses is the lack of objective measurement criteria, which leads to subjective assessment of MRI findings. Although studies have shown that interrater agreement for the diagnosis of MSA based on MRI findings is substantial and radiologic diagnosis of MSA by experts can outperform clinical diagnosis,[13] in some cases with equivocal MRI findings, subjective assessments may lead to disagreement in clinical diagnosis. According to the current diagnostic criteria, presence or absence of the aforementioned MRI abnormalities is critical for a diagnosis of possible MSA. For example, if a patient who presents with parkinsonism or cerebellar ataxia has autonomic dysfunction not severe enough to meet the diagnostic criteria for probable MSA, then a diagnosis of possible MSA will depend on the interpretation of the MRI findings. In addressing this issue, some studies have manually measured the width, length, or area of several subcortical and infratentorial structures and demonstrated that these relatively objective methods, which can easily be used in clinical practice without specialized techniques, provide good discrimination of MSA from other conditions on an individual basis.[20–23] These measures include the MCP width, anteroposterior diameter of the pons, the pons area, and the putamen/caudate volume ratio. However, these studies are limited by small sample sizes, heterogeneity in methodology, and the lack of pathologic confirmation in most studies.

Slit-like hyperintense putaminal rim has been reported as an MRI finding specific to MSA that is related to the enlargement of the intertissue space between the putamen and the external capsule and the tissue rarefaction associated with neuronal loss and gliosis.[7] However, several studies have shown that the slit-like hyperintense putaminal rim is present in normal individuals on 3-Tesla (3T) MRI[12,16,24] and even on 1.5T MRI[25] and is thought to be a truncation artifact or an age-related disproportionate ferritin deposit between the lateral margin area and the remainder of the putamen. Furthermore, in a study using 0.35T, 1.5T, and 3T MRI in patients who had MSA and Parkinson's disease (PD), it was demonstrated that, with increasing field strength, the occurrence of a hyperintense putaminal rim decreased, whereas the occurrence of hypointensity at the dorsolateral putaminal margin increased in those with MSA.[26] One recent study reported that the sensitivity and specificity of the slit-like hyperintense putaminal rim on 3T MRI for the diagnosis of MSA-P were 33% and 51%, respectively.[27] Thus, it has been suggested that the discontinuity or irregular disruption of the rim is a more reliable marker for MSA rather than the rim itself.[12,25]

HCB, a cruciform hyperintensity within the pons that results from atrophy of the pontine neurons and pontine fibers with preservation of the pyramidal tract and pontine tegmentum,[28] has been reported as a specific sign for MSA, especially MSA-C.[29] However, this finding is not specific to MSA and can be observed in other diseases with pontocerebellar degeneration, including spinocerebellar ataxias, variant Creutzfeldt-Jakob disease, vasculitis-associated parkinsonism, and even after bilateral pontine infarction.[30,31] Interestingly, a recent study demonstrated that observed T2 (T2*) imaging was superior to conventional T2WI in detecting HCB, and HCB on a T2* image may improve the diagnosis of MSA, in that HCB preceded the appearance of putaminal signal changes on the T2* image in some patients with MSA-P.[32]

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Iron-Sensitive MRIs

In addition to iron deposition in the brain accompanying normal aging, pathologic changes in some neurodegenerative disorders include iron deposition in several brain structures.[33] Each disorder exhibits its characteristic pattern of iron deposition, and this pattern can be visualized by using iron-sensitive MRI in the diagnosis and differential diagnosis. Iron-sensitive MRIs are becoming more widely used in clinical practice, and quantitative values obtained on R2* and SWI images have shown correlations with postmortem iron concentrations.[34,35] Many studies have indicated that iron-sensitive MRIs can differentiate MSA from other disorders.

Commonly reported findings on iron-sensitive MRIs from patients with MSA include iron deposition in subcortical structures, including the putamen (especially the posterior putamen), globus pallidus, caudate nucleus, substantia nigra, and thalamus, observed as hypointensity on T2* and SWI images. Although previous studies have indicated that hypointensity of the posterior putamen in MSA can be observed even on conventional T2WIs,[26,36] it has been reported that putaminal hypointensity on conventional MRI had no discriminating power between MSA-P, PSP, and healthy controls.[16] T2* imaging, which is more sensitive to the susceptibility effect of mineral deposition than conventional T2WI, is superior to T2WI in this regard. It has been demonstrated that hypointensity of the putamen was observed more often in MSA than in PD on T2* imaging but not on T2WI.[37]

SWI, which was recently introduced and is now widely used in clinical practice, uses both magnitude and phase information to generate contrast and thus is superior in detecting brain susceptibility changes compared with T2* imaging.[38] Although studies using 1.5T SWI in patients with MSA showed conflicting results,[39,40] recent studies using 3T SWI demonstrated that MSA-P could be discriminated from other conditions, including PD, PSP, and dementia with Lewy bodies, as well as from healthy controls by putaminal hypointensity and putaminal atrophy.[41–43] Actually, at 3T, putaminal hypointensity on T2WI and T2* imaging as well as SWI could distinguish MSA-P from other conditions,[12] and 1 study using 3T MRI reported a correlation between the putaminal R2* value and putaminal atrophy.[44]

Recently, it has been claimed that dorsolateral nigral hyperintensity on 7T MRI or iron-sensitive MRI at 3T, the so-called "swallow-tail sign," which is normally seen in healthy controls, is lost in almost all patients with PD.[45] The diagnostic value of this finding was evaluated in patients with MSA-P using 3T SWI, and a unilateral absence of this finding was observed in all patients with MSA. However, because the absence of this finding also was observed in all patients with PSP and in 83 of 90 patients with PD, its clinical usefulness in differentiating between different causes of neurodegenerative parkinsonism is questionable, although it seems to be specific for neurodegenerative parkinsonism.[46] Another recent study also showed that the loss of dorsolateral nigral hyperintensity is observed in patients with neurodegenerative parkinsonism, including MSA; furthermore, it corresponds to presynaptic dopaminergic imaging with a concordance rate of 86.2%.[47]

Automated Volumetric and Cortical Thickness Analyses

Volumetric MRI analysis using automated methods reveals atrophy of many subcortical and infratentorial structures in patients with MSA that were reported in previous studies using visual analysis or analyses of manually drawn regions of interest.[48–52] In addition to the atrophy of subcortical and infratentorial regions, cerebral and cortical involvement has repeatedly been reported in radiologic and pathologic studies of patients with MSA.[53,54] VBM allows the detection of those cortical changes without the need to select regions of interest. In MSA-P, studies using VBM demonstrated volume loss in several cortical areas, including the frontal, temporal, parietal, and insular cortices, in addition to the putamen, pallidum, midbrain, and cerebellum.[49,51,55,56] Studies in patients with MSA-C reported volume loss in the frontal, temporal, and insular cortices in addition to the cerebellum, brainstem, and basal ganglia.[48,51] However, those studies were heterogeneous regarding the area of volume loss, and 1 study reported no cerebral cortical involvement in patients with MSA-C.[57]

Recently introduced cortical thickness analysis has been claimed to be superior to VBM in detecting cerebral cortical changes, especially in highly convoluted areas, although these 2 methods have not been compared with a "gold standard" based on histopathologic findings in MSA. Indeed, it is difficult to compare VBM performed with statistical parametric mapping with cortical thickness measures, because these 2 methods are based on a completely different statistical background. Cortical thickness analysis in MSA-C showed cortical thinning in the frontal, temporal, parietal, parahippocampal, and lingual cortices.[58,59] Intriguingly, cortical thinning in the left prefrontal cortex and the right parahippocampal cortex correlated with the severity of dysarthria. In MSA-P, cortical thinning was reported in the frontal motor cortex and the premotor cortex.[58,60] Cortical thinning in widespread cerebral cortical areas in patients with mixed MSA was associated with the severity of motor symptoms in 1 study.[61] However, some studies reported no cerebral cortical thinning in MSA.[55,62]

The causes for these inconsistencies between studies, even when using the same computational anatomy methodology, are unclear. Differences in the patients, including age, disease duration, and clinical features, and in the details of the methods used may be responsible for the inconsistencies. In addition, it was recently suggested that microstructural tissue changes could lead to the detection of spurious morphologic changes in computational anatomy studies.[63]

DWI/DTI

DWI allows the identification of microstructural damage in the brain that cannot be detected on conventional MRI by

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quantifying the motion of the water molecules, which is normally constrained by microstructural barriers. Averaged diffusion, which is called "averaged apparent diffusion coefficient" or "mean diffusivity" in DWI or "trace" in DTI, is calculated by averaging the diffusion in 3 orthogonal directions, and an increased value indicates increased microstructural damage. Fractional anisotropy (FA) is calculated using the directional information of the diffusion of water molecules on DTI. FA values represent the microstructural integrity of white matter tracts; thus, the value is low in damaged white matter tracts, because water molecules diffuse in all directions rather than along the tract.

Many studies have shown that DWI could differentiate MSA from PD and PSP as well as healthy controls. Furthermore, some studies have demonstrated that DWI abnormalities correlated with the duration or severity of disease in patients with MSA.[64–67] Increased diffusivity in the putamen, especially in the posterior putamen, is the most consistently reported DWI abnormality in MSA.[66,68–74] It correlates with putaminal hypometabolism on FDG-PET[75] and may improve the diagnostic accuracy of MSA-P compared with conventional MRI alone.[27] It is noteworthy that the studies reporting increased diffusivity in the putamen in MSA used conventional echo-planar imaging–based DTI, whereas a study using STEAM (statistical template estimation for abnormality mapping)-based DTI could not differentiate MSA-P from PD based on the putaminal diffusivity, mainly because of a lower signal intensity-to-noise ratio compared with echo-planar imaging–based DTI.[76] Increased diffusivity and reduced FA in MCP is another common finding in MSA and is observed not only in MSA-C but also in MSA-P,[20,70,73,77–79] although no change in MCP FA values has been reported in patients with MSA-P.[66] In addition to the putamen and MCP, DWI abnormalities in the pons and cerebellum have been reported in both MSA-P and MSA-C.[64,68,70,73,77,79] One recent study showed that mean diffusivity of the cerebellar hemispheres completely discriminated MSA-P and MSA-C from PD, PSP, and healthy controls.[80] Abnormalities in the corticospinal tract[65,81,82] and pontine fibers[83,84] have been reported in studies using tract-based analysis.

Recently, it was demonstrated that free-water imaging using a bi-tensor analysis model, which separated the diffusion properties of water in brain tissue from those of water in the extracellular space,[85] could discriminate MSA from PD and PSP.[86]

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) detects microstructural, functional, and biochemical alterations in the brain by estimating the concentrations of metabolites. A reduction in N-acetylaspartate (NAA) is related to neuronal and axonal damage, and an increase in myoinositol indicates increased gliosis. Choline and creatine are related to membrane turnover and energy metabolism, respectively.

A reduction in the NAA/creatine ratio in the putamen or lenticular nucleus has been described repeatedly in MSA, although with conflicting results.[87] In addition, MRS abnormalities in the pons, medulla, cerebellum, and frontal cortex have been reported.[88–91]

A recent study using phosphorus and proton MRS found no change in high-energy phosphate in the basal ganglia of patients with MSA-P, indicating that there was no change in the basal ganglia energy metabolism despite a reduction in NAA.[92]

Other New MRI Techniques

Default mode network (DMN) refers to a network that is active when a person is not involved in a task and not focused on the outside world and is deactivated when a person is engaged in cognitively complex tasks. The DMN includes the median prefrontal cortex, posterior cingulate cortex, precuneus, lateral parietal cortex, and medial temporal cortex. The DMN is disrupted in many neurological and psychological disorders, including Alzheimer's disease, PD, depression, and schizophrenia, and in normal aging. One recent study evaluated DMN activity in patients with MSA using resting-state functional MRI and found that they had reduced activity in the superior frontal sulcus and middle frontal gyrus DMN components and reduced interhemispheric and intrahemispheric frontoparietal and parietocingulate connectivity within the DMN nodes.[60] However, those authors concluded that these findings has no diagnostic value, because there were only minor differences compared with what was observed in patients with PD.

Neuromelanin-sensitive MRI at 3T visualizes neuromelanin-containing nuclei, such as the substantia nigra pars compacta (SNpc) and locus coeruleus (LC). In patients with PD, sensitivities and specificities in discriminating those with early PD from healthy controls were 73% and 87%, respectively, in the SNpc and 82% and 90%, respectively, in the LC.[93] The diagnostic utility of neuromelanin-sensitive MRI in MSA has been tested in 2 recent studies. One study demonstrated greater signal attenuation of the lateral SNpc in patients with PD and MSA-P than in patients with PSP and healthy controls.[94] Although the other study also reported signal attenuation of the SNpc and LC in patients with MSA and PD, the most prominent signal attenuation was observed in the LC of patients with MSA.[95] The discrepancy between the 2 studies might be due to the inclusion of patients with MSA-C in the latter study.

Very recently, a new MRI technique, dynamic cerebrospinal fluid flow imaging, was tried in patients with MSA-C and cortical cerebellar atrophy.[96] The results showed that the velocity of the prepontine cerebrospinal fluid flow was reduced in patients with MSA-C compared with those who had cortical cerebellar atrophy.

Magnetization transfer imaging (MTI), a measure that correlates with myelination and axonal density, has shown good discrimination between PD, MSA, and PSP.[97] Although a relatively long scanning time at 1.5T has limited the use of MTI, the scanning time becomes much shorter with higher field strengths, enabling more frequent use of MTI in future studies.[76]

Considering the abnormalities seen in various MRI modalities, a combination of multiple MRI modalities could provide

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better discrimination of MSA. Using a multimodal MRI analysis combining volumetry, R2*, and DWI, a recent study showed a different pattern of nigrostriatal involvement in patients with PD that that in patients with MSA.[98]

Early Diagnosis of MSA

Because patients who have atypical parkinsonism, including MSA, exhibit different clinical courses and different responses to treatment compared with patients who have PD despite similar clinical features in early disease stages, improving the diagnostic accuracy of MSA in the early course of the disease is of utmost importance. Although many studies have reported MRI abnormalities on conventional MRI or other advanced MRI modalities in patients diagnosed with early MSA, relatively few studies have evaluated the role of MRI in the early diagnosis of MSA in patients whose clinical features do not meet the clinical diagnostic criteria[6] and thus have an uncertain clinical diagnosis.

One study reported that, when patients with possible MSA or atypical parkinsonism who did not meet the specific diagnostic criteria showed putaminal abnormalities on 3T MRI with T2*, the diagnosis of MSA-P became more certain after a follow-up of more than 3 years in 86% of patients.[12] However, the sensitivity in that study was low, and 20% of patients who had a final diagnosis of MSA-P had no abnormalities on their initial MRI. In another study, 113 patients who had parkinsonism without a definite diagnosis underwent routine 1T or 1.5T MRI, and the clinical diagnosis was made after 3 years.[14] For the whole group, MRI at baseline contributed little above and over the clinically based diagnosis in the differentiation between PD and atypical parkinsonism. However, in patients whose clinical diagnosis was uncertain at baseline, cerebellar and putaminal atrophy on the MRI improved the differentiation. Recently, in separate studies, the same group of researchers demonstrated that both SWI and DTI improved the diagnostic accuracy of routine 3T MRI in the diagnosis of MSA-P when these MRIs were done in patients who had early parkinsonism with an uncertain diagnosis.[27,42] Another recent retrospective analysis showed that MRI signs supportive of a diagnosis of MSA predated its clinical diagnosis in 30% of patients with MSA-P.[99] A study using automated subcortical volume segmentation and subsequent generation of a decision tree showed accurate discrimination of early to moderately advanced stage parkinsonism including PD, MSA, and PSP at the individual patient level. Of 14 patients who had probable MSA at follow-up, all patients were correctly classified according to the MRI scan at baseline compared with an accuracy of 65% for the clinical diagnosis.[52]

Longitudinal MRI Changes in MSA

Identifying MRI biomarkers for the progression of MSA is as important as identifying MRI biomarkers for the diagnosis of MSA both for patient management and for understanding the pathophysiology. Many cross-sectional studies have shown the relation between MRI findings and the severity or duration of the disease in patients with MSA.[51,66,67,89,100] However, considering the interindividual variability in clinical features and the rate of progression, more reliable information on the change in MRI findings correlating with the progression of disease can be obtained from longitudinal follow-up studies.

In a study that used conventional MRI, the cerebral atrophy rate per year was 3.0% in patients with MSA-P and 1.9% in those with MSA-C.[53] MRI studies obtained a mean of 7.2 years apart in 9 patients who had MSA revealed significant atrophy in the cerebrum and the frontal and temporal lobes, with a cerebral atrophy rate per year of 1.7%.[101] Although VBM is applied to groups of scans rather than individual scan pairs, highlighting atrophy patterns shared across patients over time, methods using registration of serial imaging and boundary shift integral (BSI) measures are applied to individual scan pairs with accurate registration of follow-up and baseline scans, thus determining the rates of atrophy rather than the atrophy patterns.[102] A study using semiautomated segmentation by BSI reported annual atrophy rates of 1.0%, 4.5%, and 3.2% in the whole brain, pons, and cerebellum, respectively, in patients with MSA-P, and the atrophy rates of the cerebellum and pons were correlated with Unified Parkinson's Disease Rating Scale (UPDRS) motor scores.[103] In contrast, a study using VBM found no correlation between UPDRS motor scores and the atrophy rate of any brain region, including the striatum, mesencephalon, cerebellum, and cortical regions in patients with MSA-P,[104] whereas the atrophy rate of several cortical regions and the cerebellum correlated with disease duration. Interestingly, a short disease duration was correlated with progression of atrophy in the striatum, and a longer disease duration was correlated with increasing atrophy in cortical areas, suggesting that early basal ganglia atrophy drives late-onset cortical atrophy in patients with MSA-P. In MSA-C, an increased atrophy rate in the putamen and cerebellum compared with healthy controls has been reported.[105] Another study using VBM showed the progression of atrophy in the corpus callosum and the MCP in patients with MSA.[106]

A DWI study on10 patients with MSA-P reported increasing putaminal diffusivity at follow-up and its correlation with UPDRS motor scores,[107] whereas another DWI study found no correlation with the UPDRS activities of daily living and motor subscales despite the progression in diffusivity in the putamen, pons, and cerebellum.[108] An association of the change in MCP diffusivity with UPDRS motor scores was demonstrated in a recent study.[109]

By calculating the volume of several subcortical structures and their R2* values, 1 recent study showed that the atrophy rate of the putamen and caudate nucleus was greater in MSA-P than in MSA-C, and the progression of putaminal iron deposition occurred only in MSA-P but not in MSA-C.[110]

Knowledge from these longitudinal studies can be used in studies assessing the progression of a disease or the efficacy of a treatment. Interestingly, some authors have proposed MRI-based power calculations of clinical trials as a useful tool for evaluating the efficacy of disease-modifying treatments in

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patients with MSA-P.[108,111,112] Actually, MRI parameters like gray matter density and putaminal diffusivity have been used as outcomes in recent clinical trials on MSA.[113,114]

MRI and NMS in MSA

Many studies have demonstrated the association of MRI findings with the severity of motor symptoms, including parkinsonism and cerebellar dysfunction, as described above. In addition to those motor symptoms, autonomic dysfunction is a key feature of MSA. Furthermore, patients with MSA experience other NMS, including respiratory dysfunction, sleep disturbances, gastrointestinal dysfunction, and cognitive and neuropsychiatric dysfunctions.[1] However, only a few studies have investigated MRI abnormalities related to autonomic dysfunction and other NMS in MSA.

MRI studies relating to cognitive dysfunction in MSA have yielded heterogeneous results. One study on 23 patients with MSA showed a correlation of memory scores with prefrontal atrophy.[115] Another study using VBM on 15 nondemented patients with MSA-P reported an association of the basal ganglia, cerebellum, and temporal and frontal cortices with cognitive dysfunction.[55] On the other hand, 1 volumetric study using BSI measures demonstrated a correlation between cognitive function and the atrophy rate in the pons, midbrain, and cerebellum.[103] The frontal atrophy rate was associated with Beck Anxiety Inventory scores in that study.

Manual MRI morphometric analysis in 13 patients who had MSA with sleep disturbances revealed no abnormalities in the brainstem.[116] The severity of orthostatic hypotension was related to the mean diffusivity of the pontine tegmentum in patients with MSA-C, suggesting the contribution of the pontine tegmentum lesion in orthostatic hypotension.[67] Two independent studies have shown an the association of white matter hyperintensities with supine systolic blood pressure and a drop in orthostatic blood pressure. Those authors suggested that white matter hyperintensities in patients with MSA are a result of target-organ damage by fluctuations in blood pressure.[117,118]

Conclusions

The MRI findings reviewed here can help with the diagnosis of MSA, and some of them already are widely used in clinical practice. Furthermore, new MRI biomarkers are being developed with advances in MRI techniques. On the other hand, some of the MRI findings, such as the slit-like hyperintense putaminal rim and HCB signs, which were previously considered suggestive of a diagnosis of MSA, are now being challenged, because it turned out that they were not as specific to MSA as previously thought.

Several aspects should be considered before MRI findings, especially those from advanced MRI modalities, are used in the diagnostic process of MSA. First, although the MRI abnormalities of MSA have high specificity, their sensitivity generally is low. Second, the degree to which MRI findings improve the clinical diagnosis is still not clear. Third, there are considerable discrepancies among studies that originate from the small sample sizes in most studies; the heterogeneity in patients regarding age, duration, and disease severity; and the ratio of MSA-P to MSA-C as well as differences in study methodologies, including image acquisition and analysis. For these reasons, well-designed, long-term, prospective studies on large numbers of patients are needed.

Nevertheless, MRI is a useful and indispensable tool in the diagnosis of MSA, and studies using advanced MRI modalities have produced promising results for using them as tools for diagnosing and monitoring disease progression. In this regard, when revising the current diagnostic criteria,[6] MRI biomarkers could be incorporated more fully, or a new diagnostic category for the neuroimaging-supported diagnosis of MSA could be considered.[99]

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

H.J.K.: 1A, 3A
B.J.: 1A, 1B, 3B
V.S.C.F.: 1A, 1B, 3B

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