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REVIEW

Can Autonomic Testing and Imaging Contribute to the Early Diagnosis of Multiple System Atrophy? A Systematic Review and Recommendations by the Movement Disorder Society Multiple System Atrophy Study Group

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ABSTRACT: Background: In the current consensus diagnostic criteria, the diagnosis of probable multiple system atrophy (MSA) is based solely on clinical findings, whereas neuroimaging findings are listed as aid for the diagnosis of possible MSA. There are overlapping phenotypes between MSA-parkinsonian type and Parkinson's disease, progressive supranuclear palsy, and dementia with Lewy bodies, and between MSA-cerebellar type and sporadic adult-onset ataxia resulting in a significant diagnostic delay and misdiagnosis of MSA during life.
Objectives: In light of an ongoing effort to revise the current consensus criteria for MSA, the Movement Disorders Society Multiple System Atrophy Study Group performed a systematic review of original articles published before August 2019.
Methods: We included articles that studied at least 10 patients with MSA as well as participants with another disorder or control group for comparison purposes. MSA was defined by neuropathological confirmation, or as clinically probable, or clinically probable plus possible according to consensus diagnostic criteria.
Results: We discuss the pitfalls and benefits of each diagnostic test and provide specific recommendations on how to evaluate patients in whom MSA is suspected.
Conclusions: This systematic review of relevant studies indicates that imaging and autonomic function tests significantly contribute to increasing the accuracy of a diagnosis of MSA.

Introduction

Multiple system atrophy (MSA) is an adult-onset, relentlessly progressive neurodegenerative disorder clinically characterized by autonomic failure, parkinsonism, and cerebellar and pyramidal features in various combinations.[1] Despite the recent advances in imaging and genetics, the diagnosis of MSA remains primarily a clinical exercise and is based on widely accepted consensus

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criteria.[2] According to these, the diagnosis of probable MSA is based solely on clinical findings, whereas neuroimaging findings are allowed to contribute to a diagnosis of possible MSA.[2] The overlapping phenotypes of MSA-parkinsonian type (MSA-P) with Parkinson's disease (PD), progressive supranuclear palsy (PSP), and dementia with Lewy bodies (DLB) and of MSA-cerebellar type (MSA-C) with sporadic adult-onset ataxia (SAOA) can lead to a high proportion of misdiagnosed MSA cases. Only 25% of patients with MSA are correctly diagnosed at the first visit by primary neurologists,[3] and 20% to 38% of patients clinically diagnosed as MSA during life turn out to have another disease on autopsy, the largest confounds being DLB followed by PSP and PD.[4,5]

Given these diagnostic challenges, defining whether specific neuroimaging or automomic biomarkers can improve and accelerate the diagnosis of MSA is an important research question. In light of an ongoing effort to revise the current consensus criteria for MSA, the Movement Disorder Society Multiple System Atrophy Study Group identified a need to review the usefulness of imaging and autonomic function tests and define specific findings that can reliably assist in the early diagnosis of patients with MSA who present with an autonomic, parkinsonian, or cerebellar dysfunction.

Methods

We performed a systematic review of the literature. Original reports published between 1989 and August 1, 2019, were identified by applying the predefined search terms in PubMed (MEDLINE). Inclusion criteria were publications in the English language; publications including at least 10 patients with MSA per study defined by postmortem verification, clinically probable, or clinically probable plus possible MSA according to the consensus criteria,[1,6,7] and at least 1 reference group of MSA-related disorders, such as pure autonomic failure (PAF), PD, PSP, DLB, and SAOA, or healthy controls for comparison purposes. The following search terms were used (phrases are enclosed by quotation marks, and parentheses are used to "nest" concepts that should be processed as a unit):

1. Autonomic function tests: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (autonomic OR dysautonomia OR "orthostatic hypotension" OR OH OR incontinence OR retention OR "residual volume" OR genital OR "erectile dysfunction" OR impotence)
2. Neuroimaging: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (imaging OR neuroimaging OR "magnetic resonance imaging" OR MRI OR "single photon emission tomography" OR SPECT OR "positron emission tomography" OR PET OR TCS OR "transcranial parenchymal sonography" OR "transcranial sonography")
3. Cardiac imaging: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (imaging OR metaiodobenzylguanidine OR MIBG OR iobenguane) *

Data including the number of patients and the probability level of MSA diagnosis (definite, probable, or probable plus possible)[1,6,7] were compiled in tables (Tables S1 and S2). Experts from the Movement Disorder Society Multiple System Atrophy Study Group selected and critically analyzed the relevant studies and defined specific findings that can reliably assist in the early diagnosis of MSA with an autonomic, parkinsonian, or cerebellar presentation at onset.

Results

A total of 173 articles on imaging and autonomic function diagnostic tests in MSA fulfilled the inclusion criteria and were analyzed. Details on each study are specified in Tables S1 and S2.

Section 1: Imaging

Magnetic Resonance Imaging (MRI)

Conventional MRI Sequences. The best described imaging features in MSA include putaminal atrophy, putaminal hypointensity with hyperintense lateral putaminal rim on T2-weighted sequences (at 1.5 Tesla magnet strength), and a number of infratentorial abnormalities, including atrophy of the pons, middle cerebellar peduncle (MCP), medulla oblongata, inferior olives, and cerebellum as well as T2 hyperintensities in the pons ("hot cross bun sign"), MCP, and cerebellum.[8] Signal abnormalities depend on the strength of the applied magnetic field, in particular the putaminal rim sign, and T2 signal hyperintense changes are possibly unreliable at 3-Tesla MRI.[9] These MRI abnormalities demonstrate an excellent specificity for distinguishing MSA from PD and PSP, but suboptimal sensitivity particularly at early stages.[10] However, in studies including patients with autopsy-proven MSA, the overall sensitivity of the MRI-based diagnosis was 77%, with MCP hyperintensities and hot cross bun sign with 100% specificity for MSA versus PD. In 30% of patients with a clinical suspicion of MSA-P, conventional MRI biomarkers (in particular, putaminal atrophy, putaminal hypointensity, and putaminal rim) may contribute to an early diagnosis, preceding the diagnosis of possible or probable MSA-P according to current criteria.[11] There is a lack of data on conventional MRI in patients with a clinical suspicion of MSA with a cerebellar or autonomic presentation.

The specificity of putaminal abnormalities is insufficient to distinguish MSA from PSP, although the combination of putaminal hypointensity with putaminal atrophy seems to be specific for MSA-P compared with PSP.[12–14] The hot cross bun sign may also be observed in genetically determined spinocerebellar ataxias[10] and rare cases of nondegenerative

parkinsonism,[15] thus reducing its diagnostic accuracy. In terms of infratentorial atrophy, MSA is often associated with relatively greater pontine and MCP atrophy compared with PSP and PD.[10,14] There are no studies comparing conventional magnetic resonance (MR) sequences to distinguish MSA-C from SAOA.

Diffusion-Weighted Imaging. Putaminal diffusivity changes in MSA-P seem to correspond to prominent neuronal loss in the putamen in this disorder. Differences in putaminal diffusivity are highly accurate for distinguishing patients with MSA-P versus PD (sensitivity, 90%; specificity, 93%).[16] However, putaminal diffusivity values were found to overlap in MSA-P and PSP patients.[17] There is conflicting data on the sensitivity of MCP diffusivity changes for the diagnosis of MSA-P.[13,18] There is a lack of studies on the differential diagnosis of MSA-C versus SAOA. Cut-off values for mean diffusivity depend on the scanner model and sequence properties. Diffusion-weighted imaging is increasingly included in routine brain MRI protocols; however, harmonized diffusion-weighted imaging sequences and regions of interest are needed to increase the interscanner and intersite comparability and reduce heterogeneity among studies using MRI diffusion measures.[16]

Volumetry and Morphometry Studies. Other well-studied MR-imaging features of MSA include putaminal atrophy, atrophy of the pons, MCP, medulla oblongata, inferior olives, and cerebellum.[8] Measures of MR volumetry using semiautomatic segmentation techniques and region of interest–based approaches have shown atrophy of these supratentorial and infratentorial brain structures in patients with atypical parkinsonian disorders. However, accurate diagnosis exploiting volumetric techniques is limited by difficulties in normalizing individual brain atrophy.[8] With respect to voxel-based morphometry, a meta-analysis showed that patients with MSA-P with disease duration of up to 5 years had decreased gray matter volume in the bilateral putamen and claustrum compared with PD. However, this difference could not be observed within 3 years from onset, suggesting insensitivity of voxel-based morphometry for discriminating MSA-P from PD in the early stages of the disease.[19] Another meta-analysis identified distinctive patterns of gray matter volume loss across atypical parkinsonian disorders relative to PD, with putaminal atrophy being particularly suggestive of MSA-P.[20] Bilateral reduction of gray matter volume in cerebellar hemispheres and vermis have been reported in patients with SAOA.[21] However, given that voxel-based morphometry is based on group-wise comparisons, it may not be used for diagnostic purposes in individual patients.[22] Conversely, automated brain segmentation techniques have allowed high diagnostic accuracy at the level of single cases.[23] Automated segmentation of subcortical structures obtained from volumetric T1-weighted MRI yielded a pattern of volume loss in the putamen and cerebellar gray matter without involvement of the midbrain. This allowed for the correct diagnosis of MSA-P versus PD or PSP at the first neurological visit in 100% of patients, substantially improving the clinical diagnostic accuracy of 63%.[23] The combination of automated subcortical and supra- and infratentorial segmentation that included the volumetric measure of the MCP confirmed the high diagnostic accuracy of this approach in separating both MSA-P and MSA-C from PD.[24] There is yet no comparative data from volumetric studies addressing MSA-C versus SAOA.

Magnetization Transfer Ratio. Reductions in the magnetization transfer ratio have been reported in the putamen of patients with MSA compared with patients with PD and in the substantia nigra of patients with MSA, PSP, and PD, allowing discrimination of these disorders.[25] Decreased magnetization transfer ratio values in the putamen of patients with MSA-P on 3T MRI were reported in another study, but parkinsonian disorders could not be differentiated on this basis.[26]

Iron-Sensitive Imaging. Patients with MSA often show putaminal changes on iron-sensitive MRI sequences, but the results varied considerably across different studies and larger confirmatory studies are warranted.[8] The combination of putaminal atrophy with abnormal putaminal iron accumulation, however, seems to be specific for MSA.[14] Bilaterally increased putaminal R2* signal reliably distinguished MSA-P from PD.[26] In particular, iron accumulation in the posterior inner region of the putamen is specific for MSA.[27] A visual rating scale for putaminal hypointensities can be useful for evaluation of patients with MSA-P as it correlates with R2*, volume loss, and motor scores.[28]

Neuromelanin Imaging. Results from studies using neuromelanin-sensitive MRI to differentiate patients with MSA from those with other degenerative parkinsonian disorders have been variable, and no overall conclusion can be drawn to date. One study in patients in early disease stages showed that neuromelanin–MRI signal intensities in the substantia nigra pars compacta and locus coeruleus distinguished between MSA-P and PD with a sensitivity of 60% and specificity of 90% and between MSA-P and PSP with a sensitivity of 80% and specificity of 85%.[29] There is currently insufficient evidence to support or reject the use of neuromelanin imaging in the differential diagnosis of MSA.

Multimodal Imaging. Multimodal imaging of nigrostriatal changes including measurements of volume, T2* relaxation rates, and mean diffusivity has been recently used to distinguish MSA-P from PD.[30] A discriminant analysis showed that using T2* relaxation rates and mean diffusivity in the putamen distinguished patients with MSA-P from those with PD with 96% accuracy.[30] Multimodal imaging approaches seem to be useful for the differential diagnosis,[31] but are currently restricted to specialized research centers. There is limited evidence concerning the use of multimodal imaging to distinguish MSA versus PSP and a lack of studies to distinguish MSA versus SAOA. We recommend multimodal imaging approaches for future diagnostic studies.

Radio-Tracer Imaging

[18F]Fluorodeoxyglucose (FDG)–Positron Emission Tomography (PET) Imaging. Most [18F]FDG-PET studies involved small numbers of patients with MSA, and neuropathological confirmation was usually lacking. Hence, the true diagnostic accuracy is difficult to estimate. Cerebellar, brainstem, and putaminal glucose hypometabolism is frequent in patients with MSA and represents a feature of possible MSA in the current consensus criteria.[2] The specificity of [18F]FDG-PET for diagnosing MSA was >90%, however, the sensitivity was more variable although still >75%.[32] In a recent meta-analysis of 15 studies, visual analysis of [18F]FDG brain uptake patterns discriminated MSA from PD with a sensitivity of 87% and a specificity of 93%.[33] In patients with clinically suspected atypical parkinsonism, fulfilling clinical diagnoses after a median follow-up time of 12 months, visual assessment of disease-specific patterns discriminated MSA from DLB with a sensitivity of 77% and a specificity of 97%.[34]

Compared with visual analysis, automated image-based classification exploiting pattern recognition identified MSA more accurately and differentiated it from PD/PSP with a sensitivity of 85% and a specificity of 96%.[35] However, the diagnostic accuracy of this approach varies depending on the algorithm used and an expert review might be required. There is limited evidence for the use of [18F]FDG-PET to distinguish MSA from SAOA.

Presynaptic Dopaminergic Imaging. Similarly to patients with PD, patients with MSA-P have functional impairment of the presynaptic dopaminergic systems.[36] Although the caudate–putamen index [reflecting differences in 18F-fluoro-dihydroxyphenylalanine (F-DOPA) uptake] has been reported as helpful in distinguishing MSA from PD, a large amount of evidence suggests that imaging of presynaptic dopaminergic function is unable to reliably discriminate between MSA-P and PD. In contrast, presynaptic nigrostriatal denervation may assist in the early diagnosis of MSA-C and SAOA, as the latter tend to have normal presynaptic dopaminergic binding.[37] In a recent retrospective study, DaTscan (Ioflupane 123I), a dopamine transporter (DAT) single-photon emission computerized tomography (SPECT) imaging technique, contributed significantly to the diagnosis of possible MSA-C in 6 of 14 patients (43%) not yet fulfilling the diagnostic criteria for MSA at the time of imaging.[38]

There is no evidence about the utility of DAT SPECT in predicting the development of MSA in cases with pure autonomic failure (PAF), and ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy appears to be superior to DAT SPECT for the identification of premotor PD/DLB in patients presenting with PAF.[39]

Postsynaptic Dopaminergic Imaging. In untreated PD, D2 dopamine receptor binding shows a transient increase, but as the disease advances and patients are exposed to dopaminergic agents, D2 binding becomes normal. In contrast, in atypical parkinsonian syndromes, ^{11}C-raclopride PET and ^{123}I- Iodobenzamide SPECT imaging suggest that D_2 receptor density is already reduced at the onset of clinical symptoms. However, because of its suboptimal sensitivity, one could not reliably exclude MSA when ^{123}I- Iodobenzamide SPECT findings are normal.[40] Desmethoxyfallypride PET labeling of postsynaptic D_2 receptors has also been studied for the differential diagnosis of PD and atypical parkinsonian disorders.[41,42] One study assessing caudate 18F-Desmethoxyfallypride (18F-DMFP) binding yielded excellent specificity and sensitivity and overall accuracy of 100%, 74%, and 86%, respectively.[41] A second study confirmed these results (sensitivity, 87%; specificity, 96%; and accuracy, 91%).[42] However, it appears unlikely that the different atypical parkinsonian disorders can be distinguished by DMFP PET imaging. Overall, D_2 receptor imaging is possibly helpful to discriminate MSA-P from PD, but is not helpful to discriminate MSA from other atypical parkinsonian disorders. There is insufficient evidence for the use of postsynaptic dopaminergic imaging to distinguish MSA-C versus SAOA.

Other Radiotracer Imaging Approaches. With regard to the use of technetium-99 m-ethyl cysteinate dimer SPECT to measure blood flow, only putamen perfusion distinguished MSA and PD, with a sensitivity of 73.3%, a specificity of 84%, and an overall accuracy of 83.6%.[43] Applying voxel level exploratory statistical parametric mapping approach, areas of significantly reduced perfusion in the striatum, brainstem, and cerebellum were localized in patients with MSA compared with patients with PD and healthy subjects.[44] However, statistical parametric mapping analysis cannot be used for diagnosis in individual patients.

^{11}C-PK11195 PET is an in vivo marker of microglial activation. It has been used to study neuroinflammatory changes in MSA, identifying widespread subcortical increases in ^{11}C-PK11195 uptake in the substantia nigra, putamen, pallidum, thalamus, and brainstem and cortical areas.[45] However, similar changes are also present in patients with PD, although to a lesser extent.[46]

Transcranial Sonography

Normal echogenicity of the substantia nigra indicates MSA-P rather than PD [sensitivity, 90%; specificity, 98%; positive predictive value (PPV), 86%], whereas third-ventricle dilatation of more than 10 mm in combination with lenticular nucleus hyperechogenicity is characteristic of PSP rather than PD (sensitivity, 84%; specificity, 98%; PPV, 89%).[47] However, a more recent study demonstrated suboptimal diagnostic accuracy in discriminating MSA-P and PSP from PD.[48] Similar diagnostic performance of transcranial sonography (TCS) has been reported in drug-naïve patients with disease duration <3 years (sensitivity, 50%; specificity, 94%).[49] A combination of positive results for TCS, cardiac [123I]MIBG scintigraphy, and olfactory testing yielded 100% specificity but low sensitivity (25%) in one study; diagnostic accuracy was increased by combining any 2 of the 3 testing modalities.[48] Notably, 10% to 15% of patients cannot be assessed with TCS owing to insufficient temporal acoustic bone windows. A comparable diagnostic potential of TCS and [18F]FDG-PET has also been reported.[49] There is a lack of studies addressing the use of TCS to distinguish MSA-P versus PSP and MSA-C versus SAOA.

Recommendations and Limitations

Current diagnostic criteria include atrophy of the putamen, middle cerebellar peduncle, pons, or cerebellum on conventional MRI and evidence of hypometabolism on FDG-PET in the putamen, middle cerebellar peduncles, pons, and cerebellum as supporting features for the diagnosis of possible MSA-P and MSA-C.[7] Moreover, presynaptic nigrostriatal denervation on DAT imaging with SPECT or 18F-fluorodopa PET is an additional feature for possible MSA-C.[7]

Suboptimal accuracy of neuroradiological diagnosis, particularly in the early disease stages, may be improved by implementing diffusion-weighted MRI sequences and other advanced techniques.

Increased diffusivity in the posterior putamen and MCP with spared superior cerebellar peduncles on diffusion-weighted sequences is highly predictive for an early diagnosis of MSA-P.[16]

Automated brain segmentation using conventional MRI sequences may provide an objective measure to discriminate early to moderately advanced MSA, PSP, and PD with short disease durations from each other at the individual patient level and at first attendance to a specialist clinic.[23]

A major shortcoming of most imaging studies is the lack of neuropathological confirmation, so this should be improved in future studies. Moreover, most studies reported data related to clinically established diseases and only a few studies evaluated patients in the early disease stages. However, as the aforementioned features discriminate clinically proven MSA from other conditions, the presence of these features early in the disease should also have discriminatory power, although this has to be proven with prospective studies. A direct comparison of different imaging modalities was rarely performed; hence, there is no evidence to recommend a single imaging modality as the marker. Several studies focusing on D_2 receptor imaging, TCS, and $^{[123I]}$MIBG scintigraphy pooled atypical parkinsonian disorders, which makes it impossible to draw conclusions regarding the diagnostic accuracy for MSA with these imaging modalities.[49,50] Significant and persistent between-study variability suggests that there is an urgent need for harmonization of imaging protocols. Finally, there is a noteworthy lack of studies on neuroimaging to distinguish MSA-C versus SAOA.

Section 2: Autonomic Function Testing

Cardiovascular Autonomic Function Testing

Autonomic failure in the synucleinopathies is a consequence of dysfunction in both peripheral and central autonomic areas. The site of the autonomic lesion accounts for the phenotypic variability observed among the synucleinopathies. In MSA, autonomic failure is a consequence of predominant central involvement, whereas in the Lewy body disorders (PD, DLB) autonomic involvement is predominantly peripheral. However, a minority of patients with MSA also have peripheral autonomic involvement; and central autonomic involvement is apparent also in the Lewy body disorders, particularly in advanced stages.[51] Autonomic dysfunction in DLB is similar to that of PD but usually more severe, with a degree of involvement that is intermediate between PD and MSA. In all of the synucleinopathies, one of the most disabling manifestations of autonomic failure is neurogenic orthostatic hypotension (nOH), which is defined as a sustained drop in systolic or diastolic blood pressure within 3 minutes of standing up or head-up tilt. PAF is a clinical diagnosis characterized by isolated autonomic failure in the absence of motor or cognitive impairment.[52] Although autonomic involvement in PAF was often considered to be peripheral, the evolution of PAF into other synucleinopathies, including MSA, DLB, and PD (sometimes after 15–20 years), indicates that PAF, in many cases, may be a premotor stage of a central nervous system synucleinopathy.[51,52]

Standard cardiovascular autonomic function testing batteries include head-up tilt, Valsalva maneuver, heart rate variability during deep breathing, and sustained handgrip.[53] During head-up tilt, patients with MSA often have a greater degree of orthostatic hypotension (OH),[54,55] often associated with supine hypertension,[56,57] and blunted orthostatic plasma noradrenaline increase compared with patients with PD.[54,55] The prevalence of nOH appears to be similar in MSA and PD. However, rather than its presence, it is the early development of nOH that usually points toward MSA instead of PD. Less impaired heart rate response on standing along with a higher nocturnal heart rate in MSA compared with synucleinopathies with peripheral autonomic nervous system involvement reflects a relatively spared sympathetic postganglionic innervation of the heart in MSA.[58,59] Absent or reduced blood pressure overshoot in late phase II and phase IV of the Valsalva maneuver (a sign of impaired sympathetic function),[57,60] as well as reduced Valsalva ratio and heart rate variability during deep breathing (signs of parasympathetic dysfunction),[54,55,57,60] are more common in MSA than in PD. Overall, cardiovascular autonomic findings in MSA and PD overlap and do not reliably distinguish these disorders,[55,57] however, more severe and generalized autonomic failure is characteristic of MSA. Cardiovascular autonomic function tests may be helpful to discriminate MSA-C from SAOA,[61] but nOH may not be sensitive to distinguish MSA-C versus spinocerebellar ataxia (SCA)-1, SCA-2, SCA-6, or SCA-17.[62]

The presence of nOH is specific for MSA versus PSP and corticobasal degeneration (CBD), particularly in the early stages. Specificity ranges from 85% to 100%, but sensitivity is low in early disease (21%).[4,63–66] The presence of nOH is of limited usefulness to distinguish MSA versus DLB.[4,5]

An orthostatic decrease of blood pressure by at least 30 mmHg systolic or 15 mmHg diastolic required for the diagnosis of probable MSA[2] can also be diagnosed by a bedside standing test.[67] Expanding orthostatic blood pressure measurements from 3 to 10 minutes during standing test significantly increases the sensitivity to detect delayed OH (ie, a drop in blood pressure when

standing beyond 3 minutes) and correctly diagnose additional patients with MSA.[68]

Plasma norepinephrine levels in the supine position >100 pg/mL have a good sensitivity (82%–100%) and specificity (75%–100%) to distinguish MSA from isolated autonomic failure (also at premotor stages), but not MSA from PD (36%–100%).[56,61,69] Some studies reported that the norepinephrine increase on standing was more blunted in MSA and isolated autonomic failure than in PD, but no cutoffs were available.[56,69] Thus, there is insufficient evidence regarding the diagnostic value of plasma norepinephrine levels on standing.

Until recently, it was considered that patients with PAF were primarily at risk to phenoconvert to Lewy body disease. However, several retrospective and one prospective study have shown that some patients with PAF can evolve into MSA as well.[52,70] Patients presenting with PAF who phenoconverted to MSA were younger at the onset of autonomic failure and had preserved olfaction and shorter times to phenoconversion diagnosis when compared with patients presenting with PAF phenoconverting to PD and DLB. In patients presenting with PAF, a heart rate response upon tilt >10 bpm, severe bladder dysfunction (ie, requiring intermittent catheterization), and a preganglionic pattern of sweat loss (ie, impaired thermoregulatory sweat test with preserved sweat axon reflex test) have been suggested as autonomic features predicting future phenoconversion to MSA.[70]

Cardiac Sympathetic Imaging

In most patients with MSA, cardiac postganglionic sympathetic innervation is preserved, whereas a majority of patients with Lewy body disorders present degeneration of peripheral postganglionic sympathetic fibers.[51] Consequently, cardiac uptake of radiolabeled catechols and plasma norepinephrine concentrations are preserved in most patients with MSA and reduced in most patients with Lewy body disorders.[51]

$^{[123I]}$MIBG scintigraphy uses an analog of norepinephrine to evaluate the functional integrity of myocardial sympathetic fibers. Cardiac MIBG uptake is typically impaired in PD and normal in most patients with MSA.[71] However, the diagnostic performance of cardiac MIBG is limited by the fact that some patients with early PD may have normal MIBG uptake, whereas some patients with MSA (about 30%) have reduced MIBG uptake.[72] A recent meta-analysis comprising 625 patients with PD and 220 patients with other neurodegenerative parkinsonism showed a very good accuracy of both early (pooled sensitivity, 82.6%; specificitym 89.2%) and delayed heart-to-mediastinum ratio (pooled sensitivity, 89.7%; specificity, 82.6%).[71] Similarly, in early parkinsonism (Hoehn and Yahr stage 1–2) a good diagnostic accuracy has been shown using the delayed heart-to-mediastinum ratio (sensitivity, 94%; specificity, 80%).[71] Both early and delayed heart-to-mediastinum ratios were lower in patients with PAF and DLB compared with patients with MSA and PSP.[73,74] There are anecdotal reports indicating that a normal MIBG myocardial scintigraphy, in patients with PAF, may predict phenoconversion to MSA.[75] There are little data on the use of $^{[123I]}$MIBG scintigraphy to distinguish patients with MSA from those with sporadic or genetic late-onset ataxias.

Urinary Function Testing

Lower urinary tract dysfunction is an early feature of MSA that often precedes other neurological symptoms, including cardiovascular autonomic failure, possibly more in the cerebellar than parkinsonian subtype.[76] The prominence and magnitude of lower urinary tract symptoms in patients with early MSA are typically greater compared with those of advanced PD.[77] The presence of urinary urgency, frequency, and incontinence distinguishes definite MSA-C from SAOA both at initial presentation and throughout the disease course.[78] Patients with SAOA have a mild degree of detrusor overactivity, whereas detrusor underactivity and urinary retention are extremely uncommon.

Urinary urgency and increased frequency, reflecting detrusor overactivity, are characteristic of early MSA and frequently evolve to overt incontinence already in the first years of disease. Urinary retention with increased postvoid residual (PVR) volume can already be present at early stages,[79] but usually emerges in advanced disease as a result of bladder neck dysfunction and external sphincter denervation as well as detrusor underactivity/atonia.[80,81] Other urodynamic findings in MSA, such as detrusor sphincter dyssynergia, are also seen in later disease stages.[80] In contrast, the most frequent bladder abnormality in PD is detrusor overactivity, whereas detrusor sphincter dyssynergia is uncommon and the PVR volume is generally low.[81] There are limited urinary function data in early disease stages of MSA.[81] An average PVR volume of 70 mL was reported in the first year after disease onset,[80] but whereas this finding was specific for MSA, it had a sensitivity of <20%.[81] The presence of urinary retention can help distinguish MSA from PD, but not from PSP because equivalent PVR volumes have been reported in patients with MSA and patients with PSP.[81]

Sudomotor Function Testing

More widespread, severe, and progressive anhidrosis on thermoregulatory sweat testing can distinguish MSA from PD with a specificity of 85% to 100% and from DLB with a specificity of 92%.[61,62,71,82] Notably, in a recent study, 95% of 232 patients with MSA had abnormal thermoregulatory sweat testing, but only 59% had abnormal postganglionic sudomotor test, whereas abnormalities on both tests were reported in 41% of patients.[83]

Recommendations and Limitations

Cardiovascular and sudomotor function testing assists in delineating the presence, magnitude, and distribution of autonomic

TABLE 1 Utility of diagnostic tests for the differential diagnosis of MSA versus related disorders based on predominant clinical presentation (diagnostic accuracy values presented where available)

	Predominant parkinsonism			Predominant autonomic failure	Predominant ataxia
	MSA vs. PD	MSA vs. PSP	MSA vs. DLB	MSA vs. PAF	MSA vs. SAOA
Conventional MRI	• Putaminal (sensitivity, 43%–100%; specificity, 61%–100%), pontine (sensitivity, 43%–63%; specificity, 75%–100%), MCP (sensitivity, 33%–100%; specificity, 100%), and/or cerebellar atrophy (sensitivity, 42%–58%; specificity, 86%–100%) • Increased putaminal diffusivity (sensitivity, 77%–100%; specificity, 80%–100%)	• Pontine (sensitivity, 44%–76%; specificity, 60%–100%), MCP (sensitivity, 33%–56%; specificity, 83%–86%), and/or cerebellar atrophy (sensitivity, 58%; specificity, 59%), normal midbrain (midbrain atrophy for diagnosis of PSP vs. MSA: sensitivity, 86%–100%; specificity, 67%–100%), and SCP (SCP atrophy for diagnosis of PSP vs. MSA: sensitivity, 57%; specificity, 83%) • Increased MCP (sensitivity, 91%; specificity, 84%) and normal SCP diffusivity (increased rADC in SCP for diagnosis of PSP vs. MSA: sensitivity, 96%; specificity, 93%)	• Putaminal and infratentorial abnormalities • Increased putaminal and MCP diffusivity	• Putaminal and infratentorial abnormalities • Increased putaminal and MCP diffusivity	• Atrophy of putamen, MCP (sensitivity, 41%–93%; specificity, 82%–90%) and pons (sensitivity, 73%–100%; specificity, 82%–90%)
MRI with automated segmentation	• Volume loss in the putamen and cerebellar gray matter (sensitivity, 100%; specificity, 100%)		• No data available	• No data available	• No data available
$^{[18F]}$FDG-PET	• Hypometabolism in putamen, brainstem, or cerebellum (sensitivity, 85%–87%; specificity, 93%–96%)		• Limited data available	• No data available	• Limited data available
DAT SPECT	• Not useful			• Presynaptic nigrostriatal denervation	• Presynaptic nigrostriatal denervation
Transcranial sonography	• Normal echogenicity of substantia nigra (sensitivity, 52%–91%; specificity, 70%–98%) • Areas of increased echogenicity in the lenticular nucleus (sensitivity, 75%; specificity, 75%)	• Not useful	• Normal echogenicity of substantia nigra	• No data available	• No data available

(Continues)

TABLE 1 *Continued*

	Predominant parkinsonism			Predominant autonomic failure	Predominant ataxia
	MSA vs. PD	MSA vs. PSP	MSA vs. DLB	MSA vs. PAF	MSA vs. SAOA
$^{[123I]}$MIBG cardiac scintigraphy	• Normal early (sensitivity, 83%; specificity, 89%) and delayed heart to mediastinum ratio (sensitivity, 90%–94%; specificity, 80%–83%)	• Not useful	• Normal early and delayed heart to mediastinum ratio	• Normal early and delayed heart to mediastinum ratio	• Not useful
Cardiovascular autonomic function testing	Early and severe OH (sensitivity, 45%–64%; specificity, 48%–80%)	Presence of OH (sensitivity, 60%; specificity, 87%)	• Not useful	• Cardiac chronotropic response upon tilt >10 bpm and mild degree of cardiovagal impairment predict phenoconversion from PAF to MSA	• Presence of OH
Urinary function testing	• Increased postvoid residual (sensitivity, 14%–55%; specificity, 79%–95%) • Detrussor underactivity/atonia (sensitivity, 16%–52%; specificity, 50%–99%)	• Detrussor underactivity/atonia	• Limited data available	• Severe bladder dysfunction may predict phenoconversion from PAF to MSA	• Early urinary urgency and incontinence • Increased postvoid residual
Sudomotor function tests	• More widespread and severe anhidrosis (sensitivity, 66%; specificity, 54%)	• Limited data available	• More widespread and severe anhidrosis	• Preganglionic pattern of sweat loss may predict phenoconversion to MSA	• Limited data available
Supine norepinephrine level	• >100 pg/mL	• Not useful	• Limited data available	• >100 pg/mL may predict phenoconversion to MSA	• Limited data available

MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; DLB, dementia with Lewy bodies; PAF, pure autonomic failure; SAOA, sporadic adult onset ataxia; MRI, magnetic resonance imaging; rADC, relative apparent diffusion coefficient; $^{[18F]}$FDG-PET, fluorodeoxyglucose–positron emission tomography; DAT SPECT, dopamine transporter–single photon emission computerized tomography; [^{123}I]MIBG, metaiodobenzylguanidine; MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle; OH, orthostatic hypotension.

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More severe, generalized, and rapidly progressive autonomic failure is typical for MSA compared with PD particularly in the early stages. The presence of nOH is even more valuable when the differential diagnosis includes tauopathies (PSP, CBD) or SAOA. Intact functional integrity of myocardial sympathetic fibers on $^{[123I]}$MIBG scintigraphy is a useful supporting feature for the diagnosis of MSA, as it is typically impaired in PD and DLB but normal in MSA-P. The diagnostic accuracy of MIBG imaging in early parkinsonism is overall high, although specificity may be reduced by normal findings in some patients with early PD. MIBG imaging cannot discriminate MSA-P from PSP or CBD. Further studies are needed to assess the utility of MIBG scintigraphy for the early diagnosis of MSA with isolated cerebellar or autonomic presentation. Confounding factors (comorbidities, comedications) should be carefully controlled before analyzing the results of MIBG scintigraphy. However, it must be acknowledged that specialized autonomic testing (eg, thermoregulatory sweat testing, tilt-table test) and MIBG scintigraphy may not be available in all locations, limiting their routine application.

Bladder sonography and abnormal urodynamic findings can discriminate MSA from PD. An elevated PVR in the early stages may help to distinguish MSA from both PD and SAOA. Repeated cardiovascular and urodynamic/sonographic tests are encouraged in patients with suspected MSA who have no evidence of OH and/or urinary involvement at their initial neurological evaluation.

Conclusion

Current evidence on the accuracy of diagnostic tests for the early diagnosis of MSA is mostly available for patients presenting with parkinsonism (Table 1); however, specific findings that can support early clinical diagnosis of patients presenting with cerebellar and autonomic dysfunction have been also discussed and are summarized in Table 1.

Overall, most diagnostic markers have good specificity but suboptimal sensitivity to distinguish MSA from related disorders. This is particularly true for the early disease stages when specific clinical features may still be absent or overlap with other neurodegenerative disorders. Several investigations, in particular MRI, $^{[18F]}$FDG-PET, and $^{[123I]}$MIBG scintigraphy as well as cardiovascular autonomic and urodynamic tests have proven efficacious in supporting a diagnosis of MSA in individual patients. The use of automated algorithms in clinical routine is expected to improve the accuracy of early MSA diagnosis in the coming years. The costs and/or availability may be a limitation for a more extensive use in routine clinical practice of autonomic function tests and cardiac MIBG scintigraphy.

A major shortcoming of all diagnostic tests is the lack of sufficient validation in postmortem MSA series. Moreover, most studies are cross-sectional and do not evaluate patients at the very earliest stage, following them prospectively until they do fulfill diagnostic criteria for MSA. Further prospective studies are necessary to identify diagnostic markers that can reliably predict an autopsy-proven diagnosis of MSA even in the early or prodromal stages of the disease.

Author Roles

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APPENDIX

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Summary of studies on imaging in MSA. A total of 1836 articles were identified in PubMed using the search terms on July 20, 2019. A total of 118 relevant papers were included in the analysis.

Table S2. Summary of studies on autonomic function testing in MSA. A total of 5901 articles were identified in PubMed using the search terms on July 20, 2019. A total of 55 relevant papers were included in the analysis.