Movement Disorders
CLINICAL PRACTICE
REVIEW

Laboratory-Supported Multiple System Atrophy beyond Autonomic Function Testing and Imaging: A Systematic Review by the MoDiMSA Study Group

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ABSTRACT: Background: Neuroimaging has been used to support a diagnosis of possible multiple system atrophy (MSA). Only blood pressure changes upon standing are included in the second consensus criteria but other autonomic function tests (AFT) are also useful to diagnose widespread and progressive autonomic failure typical of MSA. Additional diagnostic tools are of interest to improve accuracy of MSA diagnosis.
Objectives: To assess the utility of diagnostic tools beyond brain imaging and AFT in enhancing a laboratory-supported diagnosis of MSA to support the upcoming revision of the consensus criteria.
Methods: The International Parkinson and Movement Disorders Society MSA Study Group (MoDiMSA) performed a systematic review of original papers on biomarkers, sleep studies, genetic, neuroendocrine, neurophysiological, neuropsychological and other tests including olfactory testing and acute levodopa challenge test published before August 2019.
Results: Evaluation of history of levodopa responsiveness and olfaction is useful in patients in whom MSA-parkinsonian subtype is suspected. Neuropsychological testing is useful to exclude dementia at time of diagnosis. Applicability of sphincter EMG is limited. When MSA-cerebellar subtype is suspected, a screening for the common causes of adult-onset progressive ataxia is useful, including spinocerebellar ataxias in selected patients. Diagnosing stridor and REM sleep behavior disorder is useful in both MSA subtypes. However, none of these tools are validated in large longitudinal cohorts of postmortem confirmed MSA cases.
Conclusions: Despite limited evidence, additional laboratory work-up of patients with possible MSA beyond imaging and AFT should be considered to optimize the clinical diagnostic accuracy.

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disorder manifesting with autonomic failure, parkinsonism and cerebellar ataxia in any combination. Neuropathologically, MSA is a synucleinopathy characterized by abnormal aggregation of alpha-synuclein in glial cytoplasmic inclusions and neurodegenerative changes in striatonigral or olivopontocerebellar structures. Clinical diagnosis of MSA is currently made according to the consensus criteria which combine clinical features and neuroimaging findings that reflect changes in putamen and infratentorial brain structures such as pons, middle cerebellar

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Keywords: multiple system atrophy, diagnostic tests.
Members of the MoDiMSA Study Group are listed in the Appendix.
Received 10 September 2020; revised 24 December 2020; accepted 11 January 2021.
Published online 10 March 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13158

peduncle (MCP) and cerebellum.[1] In the current diagnostic criteria for MSA, brain MRI and [18F]FDG-PET findings and dopamine transporter imaging contribute to the diagnosis of possible MSA, whereas the diagnosis of probable MSA is exclusively based on clinical features.[1] Two recent clinicopathological studies have shown that the accuracy of MSA diagnosis during lifetime against neuropathologically established diagnosis ranges between 62% and 79%.[2,3] The previous systematic review by the International Parkinson and Movement Disorder Society (MDS)-endorsed MSA Study Group (MoDiMSA) focused on the utility of brain and cardiac imaging and autonomic function tests (AFT) for the early diagnosis of MSA.[4] Neuroimaging features characteristic of MSA may be absent in early disease stages suggesting their suboptimal sensitivity. Recent data suggest that the inclusion of diffusion-weighted MRI sequences and automated volume segmentation in the conventional MRI protocols may allow for an earlier and more accurate diagnosis.[4] However, diagnosis of MSA based on imaging remains challenging due to overlap with Parkinson's disease (PD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), sporadic adult onset ataxia (SAOA) and, less commonly, genetic disorders mimicking MSA. Cardiovascular autonomic tests (excluding blood pressure change upon standing), bladder ultrasonography and urodynamic tests, and [123]I-metaiodobenzylguanidine (MIBG)-scintigraphy are not recognized in the current consensus criteria,[1] although laboratory indices of early, progressive and severe autonomic failure can be useful to improve diagnostic accuracy in individual cases.[4,5] The MoDiMSA review on the utility of AFT for diagnosis of MSA suggested that incomplete bladder emptying or detrusor-sphincter dyssynergia on urodynamic study, neurogenic OH (nOH) on head up tilt test, and normal myocardial sympathetic postgangionic innervation on [123]I-MIBG scintigraphy may increase the accuracy of the revised MSA diagnostic criteria that are underway.[4] In some MSA patients, autonomic dysfunction may be mild or moderate or may appear later in the disease course, resembling that of Lewy body disorders.[6] Patients with PSP and genetic ataxia may occasionally present with urinary or cardiovascular autonomic dysfunction, suggesting overlapping AFT findings between MSA and related disorders.[4] Therefore, laboratory indices of autonomic failure should be regarded as a supportive feature of MSA with a diagnostic yield depending on the clinical context. Given the limitations of brain and cardiac imaging and AFT, inclusion of other diagnostic tools into the revised consensus criteria should be considered to enhance a laboratory-supported diagnosis of MSA.[7] Therefore, the MoDiMSA Study Group conducted a systematic review of the literature to determine the accuracy, benefits and limitations of additional diagnostic tests in the work-up of patients with MSA.

Methods

This systematic literature review was conducted by applying prespecified search terms (available for each domain in the Supplementary systematic evidence Tables S1–S7) in Pubmed (Medline). Original articles published in extenso in English between 1989 and August 1, 2019 were included if the following inclusion criteria were met: at least 10 patients with MSA per study defined either by post-mortem verification, or clinically probable, or clinically probable plus possible MSA according to current consensus criteria,[1,8,9] and at least one reference group of MSA-related disorders, including PD, DLB, PSP, and SAOA. Due to the specific nature of biomarkers and genetic testing, we included studies with unclassified MSA (level of diagnostic accuracy not provided in the paper) and healthy controls as the only comparative group for these two sections.

Data were extracted using prespecified extraction forms including test domain, authors, publication year, number of patients with MSA and their disease duration, reference group(s), level of diagnostic accuracy, methods, sensitivity, specificity, positive and negative predictive values (PPV, NPV), study results and comments. Results are reported in seven systematic domain-specific evidence tables, including biomarkers, genetic testing, neuroendocrine tests, neurophysiological tests, neuropsychological tests, sleep studies, and other tests including olfactory testing and acute levodopa challenge test. Relevant studies that fulfilled the inclusion criteria were critically analyzed by the MoDiMSA Study Group experts allocated to working groups on seven diagnostic domains. Working groups' statements on the assigned domains were summarized in the present manuscript.

Results

The search strategy identified 6531 publications including 1984 publications on biomarkers, 2144 on genetics, 196 on neuroendocrine tests, 356 on neurophysiological tests, 1396 on neuropsychological tests, and 455 on sleep studies. A total of 235 articles met the inclusion citeria (see Fig. 1 for an overview of numbers of publications and patients with MSA per diagnostic domain and Supplementary systematic evidence Tables S1–S7 for data from individual papers).

Additional Tests In Patients With Parkinsonism Suggestive of MSA

Evaluation of Levodopa Responsiveness

Levodopa responsiveness should be reviewed in newly diagnosed patients with parkinsonism and at regular intervals afterwards. Parkinsonism that is poorly responsive to levodopa is considered a hallmark of MSA.[1] However, a transient, usually modest, levodopa response is documented in a considerable proportion of patients in clinicopathological and natural history studies, with occasional

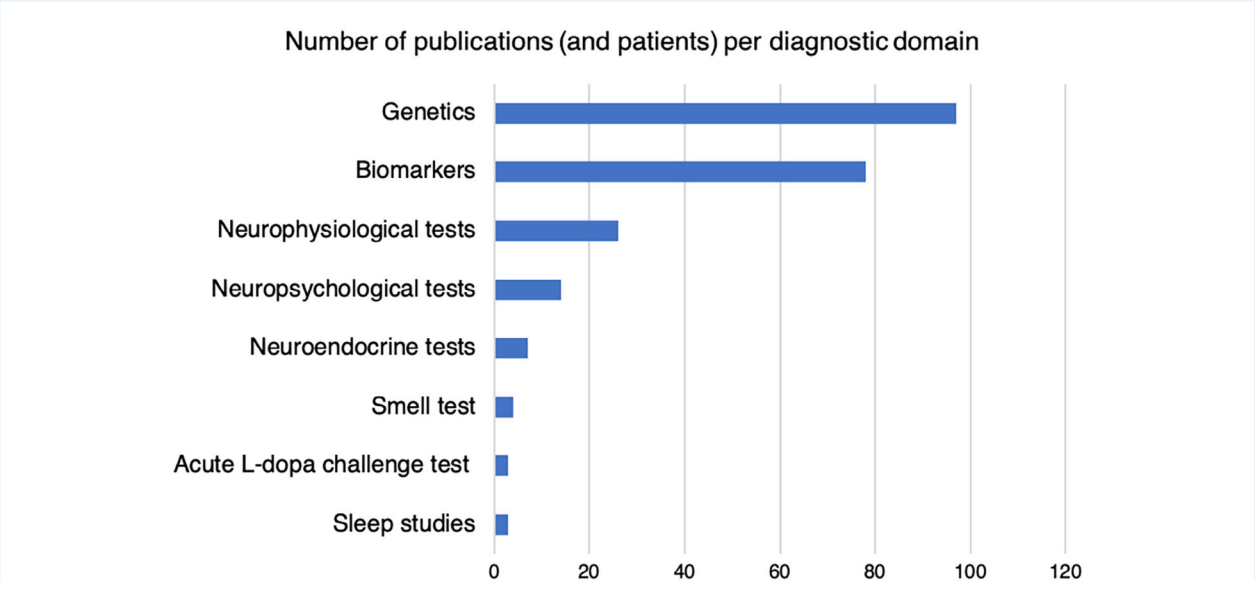

FIG. 1. Number of publications and MSA patients studied (in brackets) per diagnostic domain.

patients experiencing dramatic beneficial responses.[10-12] Levodopa unresponsiveness has usually been defined as either <30% improvement on the Movement Disorder Society Unified PD Rating Scale or Unified MSA Rating Scale motor examination on up to 1000 mg L-dopa with a peripheral decarboxylase inhibitor daily for 1 month, if tolerated, or by applying an acute levodopa challenge test. This test showed poorer response with more frequent side effects upon levodopa administration (eg, nausea) in patients with MSA compared to patients with PD (Table 1).[13]

Olfactory Testing

Olfactory testing is easy, cost-effective and non-invasive. It aids in the differential diagnosis of MSA as most patients with PD have hyposmia in contrast to patients with MSA and PSP who have relatively preserved olfaction (Table 1).[14] A combination of hyposmia and abnormal cardiac MIBG-scintigraphy, reflecting impaired n*orepinephrine analogue* uptake due to degeneration of postganglionic myocardial fibers, should guide clinicians towards the diagnosis of PD versus MSA.[15] Fluctuations of olfactory performance that may affect the test's diagnostic value, especially at early disease stages, have been found in a small but relevant fraction of PD patients during observation periods of 4 to 5 years.[16] Common pitfalls of the smell test include the presence of allergic rhinitis and smoking habits.

Sleep Studies

Neuropathological studies have documented that 98% of patients with video-polysomnography (vPSG)-proven REM sleep behavior disorder (RBD) and a neurodegenerative syndrome (parkinsonism or cognitive impairment) have an underlying synucleinopathy.[17] Therefore, documentation of RBD can help to distinguish MSA from non-synucleinopathy neurodegeneration such as PSP but cannot be used to distinguish MSA from Lewy body disorders. RBD can present before MSA onset; a multicenter prospective study found that 8% of patients with idiopathic RBD who develop neurodegenerative disease after 4 to 5 years, were diagnosed as clinically probable MSA.[18]

Other sleep abnormalities are also common in MSA. They include general disruption of the sleep architecture, upper airway dysfunction (apnea and stridor), loss of REM atonia, and periodic leg movements during sleep. MSA patients have more severe loss of REM atonia compared to patients with PD and idiopathic RBD,[19,20] although an overlap between groups limits the diagnostic potential of REM atonia quantification. Evidence for diagnostic utility of other vPSG sleep parameters is limited. Compared to patients with PD and idiopathic RBD, patients with MSA have more periodic leg movements of sleep, more slow-wave sleep, shorter overall sleep duration, and less wake after sleep onset (Table 1).[19] Apnea (ie, increased apnea/hypopnea index) is commonly observed on vPSG, but not clearly increased compared with other neurodegenerative conditions.[19] Increased snoring is specific for MSA and Lewy body disorders compared to PSP in a clinicopathological series.[3] Symptoms associated with restless legs syndrome are frequent in both patients with MSA (4.8%–28%) and PD (14%).[21]

Inspiratory stridor is commonly observed in MSA and considered a red flag against the diagnosis of PD.[22] Home audio recording is sufficient to make a diagnosis of stridor.[23] Irregular arytenoid cartilage movements were observed on flexible endoscopic evaluation of swallowing in 91% of patients with MSA (of whom, 44% showed clinically overt laryngeal dysfunction with stridor), but in no patients with PD in a recent study published outside of the time

TABLE 1 Diagnostic modalities beyond imaging and autonomic function testing investigated in the work-up of patients with MSA

Diagnostic test	Reference group	Outcome measures	Total number of studies (number of studies providing test accuracy measures)[a]	Total number of MSA patients (number of MSA patients in studies providing test accuracy measures)[a]	Consistency of the results across studies (pro; contra)[b]	Test accuracy
Evaluation of responsiveness to levodopa						
Acute levodopa challenge test (heterogenous levodopa doses and assessment methodology)	PD	• Limited improvement of motor disability in MSA	3 (3)	80 (80)	Pro: 3; Contra: 0	Sensitivity: 75%–94% Specificity: 74%–100%
Olfactory testing						
Smell test	PD	• Normal in MSA	3 (2)	95 (75)	Pro: 3; Contra: 0	Sensitivity: 74%–77% Specificity: 86%–96% (for PD vs. MSA)
Sleep studies						
vPSG-confirmed RBD	PSP, SAOA	• Present in MSA	1 (1)	16 (16) (postmortem confirmed diagnosis)	-	PPV: 98% (for synucleinopathy vs. non- synucleinopathy)
v-PSG abnormalities other than RBD	PD, PSP	• Stridor in MSA • Loss of REM sleep atonia, higher PLM index, less total sleep time, higher apnea-hypopnea index, lowe mean and minimal SaO2 and higher tonic chin EMG density in MSA (overlapping findings with PD)	2 (0)	50 (0)	Pro: 2; Contra: 0	-
Neurophysiological tests						
Anal sphincter EMG	PD	• Abnormal in MSA	11 (8)	557 (518; 30 postmortem confirmed diagnosis)	Pro: 9; Contra: 2	Sensitivity: 35%–100% Specificity: 65%–100% (depending on criteria for abnormal EMG)
Mean MUP duration on sphincter EMG	PD	• Prolonged in MSA (>8 ms, >10 ms, or >13 ms)	8 (3)	501 (424)	Pro: 6; Contra: 2	Sensitivity: 35%–93% Specificity: 54%–100% (depending on cut-off value)
Proportion of prolonged MUP >10 ms on sphincter EMG	PD	• >20% in MSA	3 (1)	294 (263)	Pro: 3; Contra 0	Sensitivity: 66% Specificity: 62%
Other abnormalities in sphincter EMG	PD	• Higher proportion of polyphasic MUP, abnormal MUP amplitude and spontaneous denervation activity in MSA	7 (0)	340 (0)	Pro: 6; Contra: 1	-

(Continues)

TABLE 1 *Continued*

Diagnostic test	Reference group	Outcome measures	Total number of studies (number of studies providing test accuracy measures)[a]	Total number of MSA patients (number of MSA patients in studies providing test accuracy measures)[a]	Consistency of the results across studies (pro; contra)[b]	Test accuracy
Bulbocavernosus reflex	PD	• Lower elicitation rates and prolonged latencies in MSA	2 (0)	69 (0)	Pro: 2; Contra: 0	Sensitivity: 24% Specificity: 91–94%
Transcranial magnetic stimulation	PD	• Single-pulse TMS: Prolonged central motor conduction time in MSA	3 (1)	42 (15)	Pro: 2; Contra: 1	Sensitivity: 40% Specificity: 100%
		• Paired-pulse TMS : Similar cortico-cortical inhibition in MSA	3 (0)	37 (0)	Pro: 2; Contra: 1	-
		• Triple stimulation technique: cortico-spinal tract abnormalities	1 (0)	14 (0)	-	Sensitivity: 50% Specificity: 100%
	CBS	• Single-pulse TMS : Normal findings in MSA	***1 (0)***	***13 (0)***	-	-
Trigeminocervical reflexes	PSP	• Normal in MSA	1 (0)	10 (0)	-	Sensitivity: 100% Specificity: 100%
Eyeblink classical conditioning	PD	• Lack of conditioned responses in MSA	1 (0)	11 (0)	-	Sensitivity: 91% Specificity: 75%
Neuropsychological tests						
Dementia Rating Scale	PSP	• Score >125 in MSA	1 (1)	44 (44) (postmortem confirmed diagnosis)	-	Sensitivity: 81% Specificity: 79%
	PSP	• Score >133 in MSA	1 (1)	372 (372)	-	Sensitivity: 80% Specificity: 60%
Frontal Assessment Battery	PSP	• Score >14 in MSA	3 (2)	444 (383)	Pro: 3; Contra: 0	Sensitivity: 68%–92% Specificity: 61%–83%
		• Score >15 in MSA	3 (2)	444 (383)	Pro: 3; Contra: 0	Sensitivity: 58%–78% Specificity: 72%–78%
Verbal fluency + Luria series subitems from FAB	PSP	• Score >4 in MSA	1 (1)	11 (11)	-	Sensitivity: 97% Specificity: 85%
Montreal Cognitive Assessment	PSP	• Score >19 in MSA	1 (1)	35 (35)	-	Sensitivity: 70% Specificity: 89%
Neuroendocrine testing						
Arginine growth hormone stimulation test	PD	• Lack of growth hormone plasma concentrations increase in MSA	2 (2)	69 (69)	Pro: 2; Contra: 0	Sensitivity: 92%–93% Specificity: 91%–96%
	PSP	• Lack of growth hormone concentrations increase in MSA	1 (1)	26 (26)	-	Sensitivity: 78% Specificity: 96%
	SAOA	• Similar in MSA	1 (11)	14 (14)	-	-

(Continues)

TABLE 1 *Continued*

Diagnostic test	Reference group	Outcome measures	Total number of studies (number of studies providing test accuracy measures)[a]	Total number of MSA patients (number of MSA patients in studies providing test accuracy measures)[a]	Consistency of the results across studies (pro; contra)[b]	Test accuracy
Clonidine growth hormone stimulation test	PD	• Lack of growth hormone plasma concentrations increase in MSA reflects the dysregulation of central noradrenergic pathways	2 (2)	34 (34)	Pro: 2; Contra: 1	Sensitivity: 73%–78% Specificity: 57%–85%
Wet biomarkers *(in CSF if not indicated otherwise)*						
α-synuclein[c]	PD	• Similar in MSA	10 (0)	277 (277)	Pro: 9; Contra (decreased in MSA): 1	-
	DLB	• Similar in MSA	3 (0)	20 (20)	Pro: 3; Contra: 0	
	PSP	• Similar in MSA	3 (0)	82 (0)	Pro: 2; Contra (decreased in MSA): 1	
α-synuclein (serum)	PD	• Decreased in MSA	2 (0)	53 (0)	Pro: 1; Contra (similar in MSA): 1	-
Phosphorylated α-synuclein	PD	• Decreased in MSA	1 (1)	25 (0)	-	Sensitivity: 64% Specificity: 86%
DJ-1	PD	• Similar in MSA	3 (0)	64 (0)	Pro: 2; Contra (increased in MSA): 1	-
	DLB	• Similar in MSA	1 (0)	14 (0)	-	
	PSP	• Similar in MSA	1 (0)	14 (0)	-	
Total tau	PD	• Increased in MSA	11 (0)	258 (258)	Pro: 6; Contra (similar in MSA): 5	-
	DLB	• Similar in MSA	3 (0)	73 (0)	Pro: 2; Contra (decreased in MSA): 1	
	PSP	• Similar in MSA	5 (0)	129 (0)	Pro: 5; Contra: 0	
	SAOA	• Similar in MSA	1 (0)	25 (0)	-	
Phosphorylated tau	PD	• Similar in MSA	7 (0)	175 (0)	Pro: 6; Contra (decreased in MSA): 1	-
	DLB	• Decreased in MSA	2 (0)	58 (0)	Pro: 1; Contra (similar in MSA): 1	
	PSP	• Similar in MSA	5 (0)		Pro: 5; Contra: 0	
p-tau/t-tau	PD	• Increased in MSA	2 (0)	57 (0)	Pro: 1; Contra (decreased in MSA): 1	-
t-tau/$A\beta_{42}$	PD	• Increased in MSA	2 (0)	47 (0)	Pro: 1; Contra (similar in MSA): 1	-

(Continues)

TABLE 1 *Continued*

Diagnostic test	Reference group	Outcome measures	Total number of studies (number of studies providing test accuracy measures)[a]	Total number of MSA patients (number of MSA patients in studies providing test accuracy measures)[a]	Consistency of the results across studies (pro; contra)[b]	Test accuracy
Neurofilament light chain	PD	• Increased in MSA	8 (2)	200 (43)	Pro: 7; Contra (similar in MSA): 1	Sensitivity: 80%–83% Specificity: 90%- 97%
	DLB	• Increased in MSA	1 (0)	48 (0)	-	-
	PSP	• Similar in MSA	4 (0)	98 (0)	Pro: 3; Contra (increased in MSA): 1	-
	SAOA	• Increased in MSA	1 (1)	24 (24)	-	Sensitivity: 79% Specificity: 94%
Neurofilament light chain (serum)	PD	• Increased in MSA	2 (0)	52 (0)	Pro: 2; Contra: 0	-
	PSP	• Similar in MSA	2 (0)	52 (0)	Pro: 2; Contra: 0	
	SAOA	• Increased in MSA	1 (0)	25 (0)	-	
Neurofilament heavy chain and phosphorylated neurofilament heavy chain	PD	• Increased in MSA	2 (2)	39 (39)	Pro: 2; Contra: 0	Sensitivity: 61%–83% Specificity: 87%–89%
	PSP	• Similar in MSA	1 (0)	21 (0)	-	-
	SAOA	• Increased in MSA	1 (0)	24 (0)	-	-
Glial fibrillary acidic protein	PD	• Similar in MSA	4 (0)	65 (0)	Pro: 4; Contra: 0	-
	PSP	• Similar in MSA	3 (0)	47 (0)	Pro: 3; Contra: 0	
	SAOA	• Similar in MSA	1 (0)	21 (0)	-	
$A\beta_{42}$	PD	• Similar in MSA	7 (0)	201 (0)	Pro: 6; Contra (decreased in MSA): 1	-
	DLB	• Increased in MSA	2 (0)	58 (0)	Pro: 2; Contra: 0	
	PSP	• Similar in MSA	5 (0)	158 (0)	Pro: 4; Contra (decreased in MSA): 1	
	SAOA	• Similar in MSA	1 (0)	25 (0)	-	
$A\beta_{42}/A\beta_{40}$	DLB	• Increased in MSA	1 (0)	18 (0)	-	-
APPα and APPβ	PSP	• Similar in MSA	1 (0)	31 (0)	-	-
UCH-L1	PD	• Increased in MSA	1 (0)	34 (0)	-	-
FLT-3 ligand	PD	• Similar in MSA	3 (0)	89 (0)	Pro: 2; Contra (decreased in MSA): 1	-
	PSP	• Similar in MSA	1 (0)	30 (0)	-	
Complement C3/factor H	PD	• Decreased complement C3 and similar factor H in MSA[a]	1 (1)	32 (0)	-	Sensitivity: 80% Specificity: 87%
MCP-1	PD	• Similar in MSA	1 (0)	31 (0)	-	-
	PSP	• Similar in MSA	1 (0)	31 (0)	-	
YKL-40	PD	• Similar in MSA	2 (0)	68 (0)	Pro: 1; Contra (increased in MSA): 1	-
	PSP	• Similar in MSA	1 (0)	31 (0)	-	
Solubile CD14 receptor	PD, PSP, CBS	• Similar in MSA	1 (0)	37 (0)	-	-
Urate (CSF and serum)	PD, PSP, CBS	• Similar in MSA	1 (0)	13 (0)	-	-
Myelin basic protein	PD	• Increased in MSA	1 (0)	28 (0)	-	-
	SAOA	• Similar in MSA	1 (0)	25 (0)	-	

(Continues)

TABLE 1 *Continued*

Diagnostic test	Reference group	Outcome measures	Total number of studies (number of studies providing test accuracy measures)[a]	Total number of MSA patients (number of MSA patients in studies providing test accuracy measures)[a]	Consistency of the results across studies (pro; contra)[b]	Test accuracy
S100B	PD	• Increased in MSA	1 (0)	28 (0)	-	-
	SAOA	• Similar in MSA	1 (0)	25 (0)	-	
Uric adic (serum)	PD	• Similar in MSA	1 (0)	40 (0)	-	-
Homocysteine (serum)	PD	• Similar in MSA	1 (0)	47 (0)	-	-
CoQ10	PD	• Decreased in MSA	3 (0)	78 (0)	Pro: 2; Contra (similar in MSA): 1	-
	PSP	• Decreased in MSA	1 (0)	20 (0)	-	
α-synuclein + p-tau/t-tau	PD	• Decreased α-synuclein and increased p-tau/t-tau in MSA	1 (1)	31 (32)	-	Sensitivity: 90% Specificity: 65% (for PD vs. MSA)
NFL + t-tau	PD	• Increased NFL and t-tau in MSA	1 (1)	25 (25)	-	Sensitivity: 76% Specificity: 97%
NFL + FLT3 ligand	PD	• Increased NFL and similar FLT3L in MSA	1 (1)	25 (25)	-	Sensitivity: 83% Specificity: 97%
NFL + FLT3 ligand + t-tau	PD	• Increased NFL and t-tau, similar FLT3 in MSA	1 (1)	25 (25)	-	Sensitivity: 82% Specificity: 97%
NFL + sAPPα + sAPPβ + Aβ42 + t-tau + p-tau + α-synuclein + YKL-40 + MCP-1	PSP	• NFL increased in MSA, other biomarkers from panel similar in MSA	1 (1)	31 (31)	-	Sensitivity: 80% Specificity: 78% (for PSP vs. MSA)
DJ-1 + t-tau + p-tau	PD	• Increased DJ-1 in MSA • Decreased t-tau in PD • No difference in p-tau	1 (1)	21 (21)	-	Sensitivity: 82% Specificity: 81%

[a]Refer to the Supplementary systematic evidence Tables S1–S7 for details on disease duration of MSA subjects, study design, methods, results and validity measures from individual studies that met the inclusion criteria for this review.
[b]Pro: number of studies supporting the statement given in the outcome measures column; Contra: number of studies providing conflicting results and not supporting the statement given in the outcome measures column.
[c]Excluding data on Real-Time Quaking-Induced Conversion assay and α-synuclein-protein misfolding cyclic amplification assay.
Abbreviations: APP, amyloid precursor protein; CD, carbidopa; CoQ10, coenzyme Q10; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; EMG, electromyography; FAB, Frontal Assessment Battery; FLT3 ligand, fms-like tyrosine kinase ligand; MCP-1, monocyte chemoattractant protein-1; MSA, multiple system atrophy; NFL, neurofilament light chain; p-tau, phosphorylated tau; PD, Parkinson's disease; PSP, progressive supranuclear palsy; RBD, REM sleep behavior disorder; REM, rapid eye movements; SAOA, sporadic adult onset ataxia; t-tau, total tau; TMS, transcranial magnetic stimulation; UCH-L1, Ubiquitin carboxy-terminal hydrolase L1; UPDRS, Unified Parkinson's Disease Rating Scale; vPSG, video-polysomnography.

window of this review.[24] Stridor onset within the first 3 years from disease onset was present in 16% of patients with MSA, indicating low sensitivity in early stages.[25] It has been only rarely documented in other degenerative parkinsonian disorders suggesting high specificity, although controlled studies are lacking.

Pelvic Neurophysiology

Evaluation of bladder function in patients with MSA comprises simple (ie, post-void ultrasonography and uroflowmetry) and advanced methods such as urodynamic tests and sphincter electromyography (EMG). Post-void bladder ultrasonography is a non-invasive, widely available, highly specific tool for diagnosing MSA versus PD. However, in early disease stages when symptoms of overactive bladder may be present in both MSA and PD patients, the sensitivity of bladder ultrasonography is suboptimal.[4] Urodynamic testing is useful for investigation of the pathophysiology of both urinary incontinence and retention in patients with MSA.[4]

EMG recordings from the external anal and urethral sphincters are commonly abnormal in MSA.[26,27] In a series of 30 definite MSA cases, 24 had abnormal sphincter EMG, five had borderline results, and only one was normal.[28] Neurogenic changes in MSA occur as a result of involvement of anterior horn cells in the Onuf's nucleus of the sacral spinal cord, and the most consistent abnormalities are prolonged duration of motor unit potentials (MUPs) compared to PD, suggestive of chronic reinnervation (Table 1).[29,30] The value of sphincter EMG in the differential diagnosis of parkinsonism has been debated over the years and a false-negative result can arise if the Onuf's nucleus is yet to be involved. Moreover, machine-automated MUP analysis tends to exclude long-duration polyphasic potentials with satellite potentials, so that additional manual MUP analysis is advisable in cases where MSA is suspected.[31] Changes of chronic reinnervation similar to those seen in MSA, may be found, though usually to a lesser degree, in long standing PD and other parkinsonian syndromes such as PSP (which also affects Onuf's nucleus), DLB and spinocerebellar ataxia (SCA) type 3, following cauda equina injury, and following damage to the sphincter muscle such as haemorrhoid surgery and obstetric pelvic floor tears. The prevalence of neurogenic changes increases with duration of disease and worsening neurological disability.[32] A highly abnormal EMG in the absence of other obvious causes in a patient with suspected MSA in the first 5 years is significant. In contrast, an entirely normal result after 5 years makes the diagnosis of MSA very unlikely; thus, the test is of limited usefulness in between.[28] Lower elicitation rates and prolonged latencies of the bulbocavernosus reflex were observed in patients with MSA compared to patients with PD with early urogenital symptoms (Table 1).[33]

Among other neurophysiological tests, auditory startle reflex has occasionally been used for distinguishing PSP (absent or reduced due to pathology in the reticular formation) from MSA (normal response) in small unblinded studies.[34]

Neuropsychological Tests

Despite prevalence rates of cognitive impairment of up to 32% in clinical and autopsy confirmed MSA series,[35,36] neuropsychological testing is valuable in the differential diagnosis of MSA and other dementia disorders such as DLB, PD dementia (PDD) and PSP.[37,38] Disproportionate deficits in attention, executive functions and visual processing relative to memory and naming are typical for DLB.[38] PDD, characterized by frontal-executive dysfunction, initially is mild but often evolves after a mean of 10 years from the onset of motor symptoms.[39] In comparative studies patients with DLB and PDD performed worse than patients with MSA across all cognitive domains.[40] In patients with PSP, global cognitive performance is poor compared with MSA patients 4 years after symptom onset, with more profound executive dysfunction and more rapid progression.[36] However, in early stages the difference in cognitive performance may not be present. One study reported that the Dementia Rating Scale might separate autopsy confirmed MSA from PSP patients with moderate sensitivity and specificity.[41] The Frontal Assessment Battery (FAB)[42] and Montreal Cognitive Assessment[43] also showed good discriminative power that was even better for the verbal fluency and Luria series subitems of the FAB (Table 1).[42] More severe deterioration also occurs in other cognitive domains in patients with PSP than in those with MSA.[41,44,45]

A test battery specific for the cognitive screening of patients with MSA has not yet been developed. Level-1 examination of the diagnostic procedures for PDD (cognitive deficits severe enough to impact daily living, MMSE<26 and impairment in at least two of the following tests: months backward or serial 7 subtraction, lexical fluency or clock drawing, MMSE pentagons, 3-word recall)[39] showed excellent specificity of 96.9% and a negative predictive value of 94.1% for detecting dementia in MSA, while a sensitivity of 84.6% was achieved by applying a cut-off MMSE score of 27 instead of 26.[46] Neuropsychological testing is of limited value in the differentiation of patients presenting with ataxia.

Biomarkers

Alpha-Synuclein

Decreased α-synuclein levels have been reported in cerebrospinal fluid (CSF) of patients with MSA, but most studies have failed to discriminate between patients with MSA and PD.[47-52] Most recently and outside of the time window of this review, a Real-Time Quaking-Induced Conversion (RT-QuIC) assay was reported to accurately detect α-synuclein seeding activity across Lewy body synucleinopathies but not in MSA.[53] Further research has shown that α-synuclein aggregates associated with PD and MSA corresponded to different conformational strains of α-synuclein[54] and that an α-synuclein-protein misfolding cyclic amplification (PMCA) assay can discriminate between these disorders with an excellent overall sensitivity.[55] In addition, α-synuclein oligomers detected by PMCA analysis together with CSF neurofilament light chain (NfL) were able to discriminate patients

with early MSA from those with Lewy body synucleinopathies.[56] Ultrasensitive single molecule array ELISA is another quantification method with the potential to detect plasma and CSF or exosomal α-synuclein. The lower number of oligodendrogial-derived plasma exosomes in MSA compared to PD (sensitivity: 62%, specificity: 81%) was reported in another very recent study.[57] Inconclusive results on plasma α-synuclein levels in MSA have been reported; some of the variability may be ascribed to the influence of blood contamination, age and different detection procedures (Table 1).[47,58]

Markers of Axonal and Glial Damage

Neurofilament light and heavy chain (NfH) concentrations in CSF are increased in patients with atypical parkinsonism including MSA compared to patients with PD (Table 1).[50,59] Higher NfL levels were also found in serum in patients with atypical parkinsonism including MSA compared to patients with PD, showing good discriminative power in the detection (sensitivity: 82%, specificity: 92%) and validation cohorts (sensitivity: 80%, specificity: 92%), as well as in the cohort of patients with disease duration less than 3 years (sensitivity: 70%, specificity: 80%), and a strong correlation with CSF levels of NfL.[60]

Amyloid Markers

Decreased CSF levels of Aβ1-42, a 42-amino acid long peptide that forms toxic β-amyloid aggregates, and a lower ratio of Aβ1-42/Aβ1-40, may be used to discriminate patients with DLB from patients with MSA (Table 1).[61,62]

Panels of Biomarkers

Combining different wet biomarkers is a promising approach to increase diagnostic accuracy. A set of 9 CSF biomarkers (NfL, sAPPα, sAPPβ, Aβ1-42, total tau, phosphorylated tau, α-synuclein, YKL-40, MCP-1), as well as disease duration and severity were shown to differentiate patients with PD from those with atypical parkinsonism with a sensitivity and specificity of 91%. Among them NfL, α-synuclein and sAPPα independently predicted the diagnosis of PD versus atypical parkinsonism. The same panel was able to differentiate between MSA and PSP patients (Table 1).[48] However, the applied methodology needs standardization of the procedures and validation in future prospective studies. Serum miR-24, miR-34b, and miR-148b were upregulated in MSA compared to PD in one study.[63]

Arginine Stimulation Test

The arginine stimulation test is based on the ability of this amino acid to induce growth hormone (GH) secretion through the inhibition of somatostatin release, which is possibly mediated by the cholinergic system. In small unblinded studies it was reported that the GH response to arginine is blunted in patients with MSA, and relatively preserved in patients with PD and PSP.[64]

Genetic Screening

An increasing number of heredodegenerative syndromes that can occasionally mimic MSA have been described (Table 2). Among these, a combination of parkinsonism and ataxia may be observed in SCA2, SCA3, SCA6 and SCA17. A complex phenotype with L-dopa unresponsive parkinsonism and central hypoventilation requires attention towards *DCTN1* mutation. In patients of European ancestry, screening for the *C9orf72* hexanucleotide repeat expansion should be considered, especially in cases with a family history of amyotrophic lateral sclerosis or frontotemporal dementia.

Additional Tests In Patients With Ataxia Suggestive of MSA

Sleep Studies

Adult onset progressive ataxia and autonomic failure, that initially presents with urogenital failure followed by nOH, with cerebellar, brainstem and MCP atophy on brain imaging is highly suggestive of MSA-cerebellar type.[65] The presence of RBD in the ataxic patient may point towards the diagnosis of MSA-C versus SAOA (Table 1). In a recent prospective study, probable RBD was present in 83% of MSA-C patients and 11% of SAOA patients.[66] Sleep abnormalities can be also seen in patients with genetic ataxias.[67,68]

Exclusion of Common Causes of Adult Onset Progressive Ataxia

A progressive course of ataxia starting in midlife requires screening for the common causes of cerebellar degeneration including toxic (ie, alcohol, phenytoin, lithium, barbiturates), metabolic (ie, vitamin B12, or B1 deficiency syndromes), paraneoplastic and non-cancer related immune mediated disorders (ie, ataxia associated with antigliadin antibodies, or with anti-glutamic acid decarboxylase antibodies), infections (ie, cerebellitis), parainfectious syndromes, brain mass lesions and multiple sclerosis.

Genetic Screening

Typically, MSA occurs sporadically in the community. Several pathologically confirmed MSA cases occurring in the same family have been reported.[69,70] The diagnostic value of genetic testing in MSA is evaluated in the setting of a suspected monogenic inheritance. Homozygous or compound heterozygous loss-of-function mutations in *COQ2* gene, involved in the coenzyme Q_{10} (COQ_{10}) biosynthesis, are the only monogenic mutations that have been suggested to cause MSA in two Japanese families.[70] Furthermore, the common *COQ2* polymorphism V393A identified in the East Asian populations has been suggested as a

TABLE 2 Neurogenetic MSA mimic syndromes (adapted from Stankovic I, et al.)[5]

Genetic characteristics			Clinical characteristics		
Gene	Locus	Inh.	Typical presentation	Typical AAO	Red flag(s)
ABCD1	Xq28	XR	ALD	1st–3rd decade	Adrenal insufficiency, leukodystrophy on MRI, psychiatric symptoms, elevated very long chain fatty acids
LMNB1	5q23	AD	ALD	4th–6th decade	Extensive, U-fiber sparing white matter lesions on MRI, cognitive impairment in advanced stages
ATXN1	6p22.3	AD	SCA1	3rd–4th decade	Axonal sensory neuropathy, hyporeflexia, loss of vibration/proprioception
ATXN2	12q24.1	AD	SCA2	4th decade	Chorea, dystonia, cognitive impairment, slow saccades
ATXN3	14q21	AD	SCA3	4th decade	Upper motor neuron signs, executive dysfunction, ophthalmoparesis
ATXN7	3p21.1-p12	AD	SCA7	3rd–4th decade	Retinal degeneration
ATXN8	13q21	AD	SCA8	4th decade	Slowly progressive, hyperreflexia
C9orf72	9p21.2	AD	ALS/FTD	4th-7th decade	Motor neuron signs, cognitive impairment, psychiatric symptoms
CACNA1A	19p13.13	AD	SCA6	5th–6th decade	Family members can present with episodic ataxia or hemiplegic migraine
CYP27A1	2q35	AR	CTX	2nd–3rd decade	Diarrhea, cataracts, xanthomas, cognitive and psychiatric symptoms
DCTN1	2p13.1	AD	Perry syndrome	5th decade	Hypoventilation, weight loss, psychiatric symptoms
ATN1	12p13.31	AD	DRPLA	4th decade	Choreoathetosis, dementia, epilepsy, psychiatric symptoms
FMR1	Xq27.3	XR	FXTAS	6th–7th decade	Female pre-mutation carriers can present with primary ovarian insufficiency, family history of fragile-X syndrome
FXN	9q21.11	AR	FRDA	2nd–3rd decade	Hyporeflexia, loss of vibration/position sense, cardiomyopathy, diabetes
GBA	1q22	AR	GD	1st–2nd decade	Cognitive impairment, common in patients of Ashkenazi Jewish ancestry
		AD	PD/LBD	6th decade	
LRRK2	12q12	AD	PD	6th decade	Family history of L-dopa-responsive Parkinson disease
NOP56	20p13	AD	SCA36	5th–6th decade	Hearing loss, motor neuron involvement, slow progression
PDYN	20p13	AD	SCA23	5th–6th decade	Slow progression
POLG1	15q15	AR, AD	Mitochondriopathy	1st–4th decade	Ophthalmoplegia, hearing loss, neuropathy, epilepsy, dementia
RFC1	4p14	AR	CANVAS	4th–6th decade	Late-onset ataxia, sensory neuronopathy, bilateral vestibulopathy, chronic cough, and autonomic dysfunction
PRNP	20p13	AD	Prion disease	3rd–9th decade	Myoclonus, dementia, psychiatric symptoms, seizures, rapid progression
PPP2R2B	5q32	AD	SCA12	4th decade	Cerebellar ataxia, hyperreflexia, tremor
SNCA	4q22.1	AD	PD, LBD	3rd–4th decade	Dementia, early-onset L-dopa responsive parkinsonism
SPG7	16q24.3	AD, AR	HSP	3rd–4th decade	Spastic paraplegia, cerebellar ataxia, executive dysfunction
SPG11	15q21.1	AR	HSP	3rd–4th decade	Severe spastic paraplegia
TBP	6q27	AD	SCA17	2nd–5th decade	Psychiatric symptoms, dementia, chorea

Abbreviations: Inh, inheritance; Mt. DNA, mitochondrial DNA; XR, X-chromosomal recessive; AD, autosomal dominant; AR, autosomal recessive; AAO, age at onset; ALD, adrenoleukodystrophy; SCA, spinocerebellar ataxia; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; CTX, cerebrotendinous xanthomatosis; DRPLA, dentatorubral pallidoluysian atrophy; FXTAS, fragile X tremor ataxia syndrome; FRDA, Friedreich ataxia; GD, Gaucher disease; PD, Parkinson disease; LBD, Lewy body dementia; HSP, hereditary spastic paraplegia.

possible risk variant.[71] This variant is extremely rare in the Caucasian population, which could explain the lack of disease associations in North American or European MSA cohorts.[72,73] Several additional heterozygous variants of unknown significance have been reported in *COQ2*, but their role in disease pathogenesis is unclear and requires further investigation. In addition, decreased concentrations of COQ2 in serum, CSF and cerebellum of MSA patients suggest that COQ_{10} deficiency may contribute to the pathogenesis of MSA (Table 1).[74]

In patients presenting with ataxia, either the presence of a family history or non-supportive features for MSA should guide the physician towards neurogenetic mimicry. These "red flags," however, may not be present in a given case. Genetic screening, as a second tier after exclusion of the other common causes of midlife onset progressive ataxia, should be considered in selected cases to refine the clinical diagnosis by excluding of the most common mimicries due to the pathogenic mutations in the *ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *PPP2R2B*, *FMR1*, and *TBP* genes. Repeat expansion mutations in the *RFC1* gene is an underrecognized cause and has been observed in 22% of patients with late-onset cerebellar ataxia.[75] Fragile X–associated tremor/ataxia syndrome resulting from a premutation in the *FMR1* gene more frequently poses a differential diagnosis challenge to MSA than the other syndromes due to overlapping clinical and MRI features including hyperintensities in the MCP. In Japanese patients, screening for *DRPLA* needs consideration.

Notably, however, in a large postmortem series, none of the patients with a clinical diagnosis of MSA in life had a final diagnosis of neurogenetic mimic syndrome.[3] Other rare neurogenetic mimic syndromes have been described in the literature, but more detailed discussion goes beyond the scope of this article.

Biomarkers and Arginine Stimulation Test

Patients with MSA-C have increased NfL and NfH levels in CSF compared to patients with SAOA (Table 1).[76]

Arginine GH stimulation test failed to show efficacy in differentiating between patients with MSA-cerebellar type from patients with SAOA, genetic ataxia and healthy controls (Table 1).[77]

Conclusion And Test Limitations

Data assessed in this systematic review suggest that several diagnostic tools beyond imaging and AFT may support the diagnosis of MSA in individual cases. The diagnostic discrimination of each tool depends on the clinical context (ie, predominant clinical presentation and differential diagnosis) and changes over the disease course. The paucity of studies in patients with MSA presenting with isolated autonomic failure (ie, distinguishing premotor MSA from pure autonomic failure due to Lewy body disease) prevented us from analyzing the evidence in this specific population. Although severe, widespread and progressive autonomic failure is specific for MSA, there are very few comparative studies on diagnostic accuracy of autonomic function testing versus other diagnostic tests. A major limitation of the available evidence is an absence of postmortem diagnostic confirmation in the majority of studies. Because most studies were cross-sectional, including patients with advanced disease stages, the evaluation of the test performance in the first 2 to 3 years from onset (when the sensitivity for a diagnosis of MSA is most required) is poor.

In patients presenting with parkinsonism, a history of the levodopa response is required, as a poor response to levodopa is characteristic of MSA compared to PD. Studies addressing the performance of an acute levodopa challenge test were difficult to interpret, as they analyzed different MSA populations, and used different levodopa doses, assessment methodologies and outcome measures. There is no information on the value of an acute levodopa challenge in de novo drug-naïve MSA patients. Given the methodological diversity, the proportion of MSA patients in early disease stages with levodopa-responsive parkinsonism, and the high number of false-negative cases due to common peripheral side-effects we conclude that the acute levodopa challenge test cannot assist in the earlier diagnosis of MSA. Consequently, a negative levodopa challenge – when available – should not deter clinicians from initiating chronic levodopa maintenance therapy, until a daily dose of 1000 mg has been tried for at least a month if needed and tolerated. The moderate discriminative power of olfactory testing in distinguishing MSA (where the test is normal) from PD (where olfaction is typically impaired) suggests that it might be useful to support a diagnosis of MSA, despite a lack of blinded data. There are no studies on the efficiency of combined olfactory testing and cardiac sympathetic imaging in differentiating MSA from PD+nOH. Otherwise unexplained neurogenic findings in sphincter EMG within a few years from disease onset are suggestive of MSA. However, due to overlapping denervation patterns between MSA and PD such changes may not support the diagnosis in individual patients. Given some denervation in healthy subjects, the test should be interpreted with caution. Limitations of the sphincter EMG include discomfort for the patient, difficulties in interpreting the results, effects of age, sex, multiple childbirths, and comorbidities such as prostate hypertrophy, bladder neck stenosis, or stress incontinence.

Careful neuropsychological screening is useful to exclude dementia, which is, based on current evidence, rare in MSA but is an essential feature of DLB and PDD. Assessment of global cognitive functions employing the Dementia Rating Scale, or executive functions by applying the FAB may help differentiate patients with MSA from patients with PSP. However, differentiation made on the basis of cognitive state is not likely to be helpful in early stages. There is a need to define a specific cognitive battery with tests whose performance would not be affected by motor disability.[78]

VPSG-documented RBD and severe loss of REM atonia are highly indicative of a neurodegenerative synucleinopathy such as MSA; hence, their absence makes a diagnosis of MSA unlikely. Documentation of inspiratory stridor by home audio recording or vPSG is very specific for MSA.[23] Based on a small number of relevant studies we conclude that vPSG is useful to distinguish patients with MSA from patients with tauopathies and sporadic, symptomatic and genetic ataxias (although RBD has been documented in selected disorders such as SCA3). VPSG cannot assist in the differential diagnosis of MSA vs. other synucleinopathies.

In patients presenting with progressive adult onset ataxia, immune mediated (including paraneoplastic and non-cancer related disorders), metabolic, toxic, and infectious/postinfectious causes should be excluded. As a second tier, genetic screening for the most common SCAs is recommended, particularly in cases with positive family history or non-supportive features for MSA. Other rare MSA neurogenetic mimicries have been described in the literature (Table 2) but broad genetic testing beyond the common SCAs is currently not recommended.

Although there are several promising biomarker candidates such as α-synuclein (RT-QuIC and PMCA assays allowed differentiation between MSA and Lewy body synucleinopathies) or NfL (that allowed differentiation between MSA and PD, but not MSA versus tauopathies) in CSF and plasma none of them is sufficiently robust to support a diagnosis of MSA. By applying panels with multiple biomarkers, diagnostic accuracy could be improved. The high variability of findings on fluid biomarkers across the literature highlights the need to standardize analytical methods and harmonize standard operating procedures. The

validation of current biomarkers in large prospective studies is needed before any wet biomarker can be used for MSA diagnosis. The arginine growth hormone stimulation test provided conflicting results in different MSA cohorts. The role of this and other neuroendocrine tests remains to be defined in future, larger studies.

As with all systematic reviews, this study has several limitations. First, we may have missed original studies due to potential publication bias. Second, we did not report uncertainty of accuracy data, for example, 95% confidence intervals sensitivity and specificity. Third, PPV and NPV must be judged in the light of prevalence, which was not available for most settings. Fourth, data on the same patients could have been published in more than one study; hence, the cumulative number of patients in studies from which the range of diagnostic accuracy measures was derived (Table 1) may not be correct. Fifth, diagnostic test accuracy characteristics alone are not sufficient to inform clinical decision making. Further aspects including the benefits and harms to patients with false negative and false positive results as well as cost effectiveness must be included in the decision-making process, which may require decision-analytic modeling approaches.[79]

In summary, current best evidence suggests that in patients with parkinsonism suggestive of MSA, evaluation of history of levodopa responsiveness and olfactory function is useful. Neuropsychological testing should be performed to exclude dementia at the time of diagnosis. When MSA-cerebellar type is suspected, a screening for the common causes of adult onset progressive ataxia is useful. Genetic screening beyond the most common SCAs is not currently recommended. Diagnosing sleep abnormalities is useful in both motor MSA subtypes. The results of pelvic neurophysiology should be interpreted with caution, and the role of this testing is limited due to overlapping finding with PD and other common non-neurological diseases. Based on current evidence, we conclude that the laboratory work-up should be extended beyond brain and cardiac imaging and autonomic function tests in selected patients with MSA to improve diagnostic accuracy during lifetime. Cohort studies enrolling patients with MSA within the first 2 years after symptom onset with blinded test results and postmortem diagnostic confirmation are required to generate sufficient evidence on test accuracies in early disease stages.

Appendix

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Acknowledgments

One of the coauthors of this research (Dr S. Scholz) was supported in part by the Intramural Research Program of the National Institutes of Health (National Institute of Neurological Disorders and Stroke; project number: 1ZIANS003154).

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T.O.: 1A,B; 2B
A.P.: 1A,B; 2B
M.T.P.: 1A,B; 2B
R.P.: 1A,B; 2B
N.Q.: 1A,B; 2B
O.R.: 1A,B; 2B
M.S.: 1B,C; 2B
R.S.: 1A,B; 2B
C.S.: 1A,B; 2B
J.D.S.: 1A,B; 2B
S.S.: 1A,B,C; 2B
J.M.S.: 1A,B; 2B
M.S.: 1A,B; 2B
W.S.: 1A,B; 2B
M.S.: 1A,B; 2B
A.T.: 1A,B; 2B
E.T.: 1A,B; 2B
S.T.: 1A,B; 2B
L.V.: 1A,B; 2B
U.W.: 1A,B; 2B
T.W.: 1A,B; 2B
H.W.: 1A,B; 2B
D.W.: 1A,B; 2B
U.S.: 1A,B; 2B
W.P.: 1A,B; 2B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. No informed consent was required. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 months: Dr J. Bang reports serving on the Advisory Board of Wave Life Science. Dr P. Barone reports funding from Lundbeck, UCB, Zambon, Chiesi, Roche, Bial, and Biogen (scientific advisory boards, speakter activities). Dr D. Berg reports consultancies/advisory boards fees from Biogen, BIAL, UCB Pharma GmbH and Zambon, honoraria from AbbVie, Biogen, BIAL, UCB Pharma GmbH, Zambon, Desitin and GE and grants from Deutsche Forschung sgemeinschaft (DFG), German Parkinson's Disese Association (dPV), Bundesministerium für Bildung und Forschung (BMBF), Parkinson Fonds Deutschland GmbH, UCB Pharma GmbH, EU, Novartis Pharma GmbH, Ludbeck, and Damp foundation. Dr I. Biaggioni reports consultancy fees from Theravance Biopharma. Dr B. Bloem reports consultancy fees from Biogen, AbbVie, Walk and Path and UCB, grants/research support from Netherlands Organization for Scientific research, Michael J Fox Foundation, Parkinson Vereniging, Parkinsons's Foundation, Gatsby Foundation, Verily Life Sciencies, Horizon 2020, Topsector Life Sciencies and Health, Stichting Parkinson Fonds, UCB and AbbVie and fees for speaking at conferences from AbbVie, Zambon, BIAL and Roche. Dr C. Colosimo reports grant from Ipsen. Dr A. Fanciulli reports royalties from Springer Nature and Thieme Verlag, speaker fees and honoraria from the Ordensklinikum Linz, Austrian Parkinson Society, International Parkinson Disease and Movement Disorder Society

and Theravance Biopharma and research grants from the Stichting ParkinsonFond, the MSA Coalition and the Österreichischer Austauschdienst. Dr J. Ferreira reports grants from GlaxoSmithKline, Grunenthal, Fundacao MSD (Portugal), TEVA, MSD, Allergan, Novartis, and Medtronic, serving at advisory board for BIAL, testimony to Novartis and consultancy fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, BIAL, Merck-Serono, Mez, Ipsen, Biogen, Acadia, Allergan, AbbVie, and Sunovion Pharma. Dr S. Fox reports research Funding from Michael J Fox Foundation for Parkinson Research, NIH (Dystonia Coalition), CIHR, and Parkinson Canada, honoraria from the International Parkinson and Movement Disorder Society and American Academy of Neurology, Site PI for clinical trials for Biotie, Cynapsus, Eisai, and Revance, consultancy/speaker fees from Acadia, Atuka, Sunovion, Teva, and Paladin and royalties from Oxford University Press. Dr B. Frauscher reports advisory board fees and speaker engagements from Eisai and UCB Pharma, discovery grant from NSERC, and infrastructure grant from CFI. Dr V. Fung reports unrestricted research grants from Michael J. Fox Foundation, Abbvie and Merz. He is on Advisory Boards and/or has received travel grants from Abbvie, Allergan, Cavion, Ipsen, Merz, Praxis, Seqirus, Stada, Teva and UCB, and receives royalties from Health Press Ltd. Dr T. Gasser reports grants from Bundesministerium für Bildung und Forschung (BMBF), Deutsche Forschung sgemeinschaft (DFG), speaker honoraria from UCB Pharma, Novartis, Teva and MedUpdate and serving as a chairman of the scientific advisory board of the "Joint Programming for Neurodegenerative Diseases" program, funded by the European Commission. Dr A. Gerhard reports research grant from MRC UK. Dr M. Hallett is an inventor of patents held by NIH for an immunotoxin for the treatment of focal movement disorders and the H-coil for magnetic stimulation; in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health and Brainsway. He has research grants from Allergan for studies of methods to inject botulinum toxins, Medtronic, Inc. for a study of DBS for dystonia, and CALA Health for studies of a device to suppress tremor. Dr G. Halliday is supported in part by funding from the National Health and Medical Research of Australia, MJ Fox Foundation, Shake-it-up Australia, MSA Coalition, and the University of Sydney. Dr H. Kaufmann reports compensation as a consultant/advisory board member for Lundbeck and Theravance Biopharma Inc. Dr. Klockgether receives/has received research support from the Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF), the Bundesministerium für Gesundheit (BMG), the Robert Bosch Foundation, the European Union (EU), and the National Institutes of Health (NIH). He has received consulting fees from Biohaven, Roche, UBC, Uniqure, and Vico Therapeutics. He has received a speaker honorarium from Novartis and Bayer. Dr V. Kostic has received speaker honoraria from Roche and Alkaloid and receives research supports from the Swiss Pharm, Serbian Ministry of Education, Science and Development and Serbian Academy of Sciences and Art. Dr. F. Krismer reports a research grant from the MSA Coalition. Dr. Lang has served as an advisor for Abbvie, AFFiRis, Biogen, Janssen, Lilly, Lundbeck, Merck, Paladin, Roche, Sun Pharma, Theravance, and Corticobasal Degeneration Solutions, received honoraria from Sun Pharma, AbbVie and Sunovion, received grants from Brain Canada, Canadian Institutes of Health Research, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, and W. Garfield Weston Foundation and received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press. Dr H. Ling reports research grant from CBD Solutions. Dr I. Litvan research is supported by the National Institutes of Health grants: 5P50AG005131–33, 2R01AG038791-06A, U01NS090259, U01NS100610, U01NS80818, R25NS098999, P20GM109025, U19 AG063911-1, 1R21NS114764-01A1, Parkinson Study Group, Michael J Fox Foundation, Parkinson Foundation, Lewy Body Association, Roche, Abbvie, Biogen, EIP- Pharma and Biohaven Pharmaceuticals. She was member of a Lundbeck Advisory Board and Corticobasal Degeneration Solutions. She is a Chief Editor of Frontiers in Neurology. Dr W. G. Meissner has received fees for editorial activities with Springer Nature and Elsevier, has served as advisor for Lundbeck and Biohaven, and has received teaching honoraria from UCB. Dr Y. Miki reports grant from the Sakurai Memorial Fund for Medical Research. Dr A. Palma reports salary from Novartis Gene Therapies, research funding from the NIH, Michael J. Fox Foundation, MSA Coalition, Familial Dysautonomia Foundation, FDA, and Biogen. He is advisory board member for Lundbeck, Biogen, PTC Therapeutics, Astellas, and Dr. Reddy's Laboratories, managing editor of Clinical Autonomic Research and principal investigator in MSA studies funded by Biohaven Pharmaceuticals, Theravance, and Biogen. Dr J. Panicker is supported in part by funding from the United Kingdom's Department of Health NIHR Biomedical Research Centres. Dr W. Poewe reports personal fees from Alterity, AbbVie, Affiris, Astra Zeneca, BIAL, Biogen, Britannia, Lilly, Lundbeck, Neuroderm, Neurocrine, Denali Pharmaceuticals, Novartis, Orion Pharma, Roche, Takeda, Teva, UCB and Zambon (consultancy and lecture fees in relation to clinical drug development programmes for PD), royalties from Thieme, Wiley Blackwell, Oxford University Press and Cambridge University Press and grant support from MJFF, EU FP7 and Horizon 2020. Dr R. Postuma reports grants and personal fees from Fonds de la Recherche en Sante, the Canadian Institute of Health Research, Parkinson Canada, the Weston-Garfield Foundation, the Michael J. Fox Foundation, the Webster Foundation, and personal fees from Takeda, Roche/Prothena, Teva Neurosciences, Novartis, Biogen, Boehringer Ingelheim, Theranexus, GE HealthCare, Jazz Pharmaceuticals, Abbvie, Jannsen, Curasen and Otsuko. Dr C. Sampaio reports consultancy honoraria from Kyowa Kirin, Pinteon Pharmaceuticals, Neuraly, Green Valley Pharmaceuticals, and Pfizer. Dr J. Schmahmann reports clinical trial support from Biohaven Pharmaceuticals and consultancy to Cadent Therapeutics. Dr K. Seppi reports personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal and Abbvie, honoraria from the International Parkinson and Movement Disorders Society, research grants from

FWF Austrian Science Fund, Michael J. Fox Foundation, and International Parkinson and Movement Disorder Society. Dr M. Stamelou reports serving on the advisory board for Biogen and PD neurotechnology, advisory services to UCB, speaker honoraria from MDS, EAN, UCB, Abbvie, research funding from MJFF (genetic PPMI), and honoraria from Oxford and Cambridge University Press. She is an associate editor in MDJ. Dr E. Tolosa reports honoraria for consultancy from TEVA, Bial, Prevail, Boehringer Ingelheim, Roche and Biogen and funding for research from Spanish Network for Research on Neurodegenerative Disorders (CIBERNED) Instituto Carlos III (ISCIII), and The Michael J. Fox Foundation for Parkinson's Research (MJFF). Dr S. Tsuji reports grant from Nobelpharma Co., Ltd. and consultancies from i-TRS, Ono Pharmaceutical, Daiichi Sankyo Company, Sanofi K. K., and Aeglea Biotherapeutics. Dr U. Walter reports grants from Bundesministerium für Bildung und Forschung, Germany, and personal fees from Merz Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Thieme, and Elsevier Press. Dr T. Warner reports grants received from Medical Research Council, Reta Lila Weston Medical Trust, Corticobasal Degeneration Solutions Inc., UCLH BRC, ABN and RoseTrees. Dr D. Weintraub reports research funding or support from Michael J. Fox Foundation for Parkinson's Research, Alzheimer's Therapeutic Research Initiative (ATRI), Alzheimer's Disease Cooperative Study (ADCS), the International Parkinson and Movement Disorder Society (IPMDS), and National Institute on Aging (NIA), honoraria for consultancy from Acadia, Aptinyx, CHDI Foundation, Clintrex LLC (Alkahest, Aptinyx, Avanir, Otsuka), Eisai, Great Lake Neurotechnologies, Janssen, Sage, Scion, Signant Health and Sunovion and license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS. Dr G. K. Wenning reports grants from Biogen, Biohaven, Minoryx, Lundbeck and Theravance. Drs A. Antonini, Dr S. Bajaj, A. Berardelli, Dr D. Brooks, Dr G. Calandra Buonaura, Dr P. Cortelli, Dr R. Freeman, Dr D. Goldstein, Dr G. Hoglinger, Dr H. Houlden, Dr V. Iodice, Dr P. Low, Dr T. Nomura, Dr S. Orimo, Dr T. Ozawa, Dr A. Pantelyat, Dr M. T. Pellecchia, Dr N. Quinn, Dr O. Rascol, Dr M. Sabanovic, Dr R. Sakakibara, Dr S. Scholz, Dr J. M. Senard, Dr M. Sharma, Dr U. Siebert, Dr W. Singer, Dr I. Stankovic, Dr A. Takeda, Dr L. Vignatelli, Dr H. Watanabe report no financial disclosures for the past 12 months. ■

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Supporting Information

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

Table S1. Summary of studies on biomarkers in MSA. Search terms: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (blood OR plasma OR "cerebrospinal fluid" OR CSF). A total of 1984 papers were identified in Pubmed using the search terms on July 20th, 2019. A total of 77 relevant papers were included in the analysis.

Table S2. Summary of studies on genetic screening in MSA. Search terms: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (genetic OR genetics OR familial OR mutation). A total of 2144 papers were identified in Pubmed using the search terms on July 20th, 2019. A total of 95 relevant papers were included in the analysis.

Table S3. Summary of studies on neuroendocrine tests in MSA. Search terms: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (neuroendocrine OR arginine OR "growth hormone" OR GH OR clonidine). A total of 196 papers were identified in Pubmed using the search terms on July 20th, 2019. A total of 7 relevant papers were included in the analysis.

Table S4. Summary of studies on neurophysiological tests in MSA. Search terms: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (neurophysiology OR "evoked potentials" OR EVP OR electromyography OR EMG). A total of 356 papers were identified in Pubmed using the search terms on July 20th, 2019. A total of 26 relevant papers were included in the analysis.

Table S5. Summary of studies on neuropsychological tests in MSA. Search terms: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (neuropsychology OR neuropsychological OR dementia OR cognition OR cognitive OR frontal-executive OR memory). A total of 1396 papers were identified in Pubmed using the search terms on July 20th, 2019. A total of 14 relevant papers were included in the analysis.

Table S6. Summary of sleep studies in MSA. Search terms: ("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "shy drager syndrome") AND (sleep OR "REM sleep behavior disorder" OR RBD OR REM sleep without atonia). A total of 455 papers were identified in Pubmed using the search terms on July 20th, 2019. A total of 3 relevant papers were included in the analysis.

Table S7. Summary of other tests in MSA. Relevant papers on other tests were searched manually. A total of 13 relevant papers were included in the analysis.