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A Critique of the Second Consensus Criteria for Multiple System Atrophy

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Multiple system atrophy (MSA) is an adult-onset progressive neurodegenerative disorder that manifests clinically with autonomic failure, parkinsonism, and ataxia in any combination. Oligodendroglial cytoplasmic inclusions consisting of misfolded α -synuclein are a pathological hallmark of disease.¹ The clinical diagnosis of MSA is typically delayed as a result of incomplete or nonspecific manifestations during early disease stages.^{2,3} Quinn first published diagnostic criteria for MSA in 1989.⁴ Since then, the first consensus criteria in 1998⁵ and their revision in 2008⁶ have been widely accepted as diagnostic guidelines for MSA. In a clinico-pathological study examining the validity of the second consensus criteria,⁶ the sensitivities for possible and probable MSA at first visit were 41% and 18%, respectively, increasing to 92% and 63% at last visit.⁷ In a recent brain bank study on 134 patients retrospectively assigned a diagnosis of possible or probable MSA according to the second consensus criteria,⁶ only 83 (62%) met the pathological criteria for MSA: the most common causes of misdiagnosis were dementia with Lewy bodies (DLB) in 19 (37%) followed by progressive supranuclear palsy (PSP) in 15 (29%) and Parkinson's disease (PD) in 8 (15%) cases.⁸ Developing good diagnostic tools in the early disease stages is a prerequisite for an estimation of disease prognosis and evaluation of novel disease-modifying treatments in clinical trials. Therefore, it is of paramount importance to achieve very good specificity and to overcome the poor sensitivity of the existing criteria at the first neurological visit. The Movement Disorder Society (MDS) MSA Study Group developed a questionnaire (see Table 1) highlighting the critical issues associated with the second consensus criteria for the diagnosis of MSA.⁶ The questionnaire was distributed among the coauthors who provided feedback resulting in the present critique.

Issue 1: Levels of Diagnostic Accuracy

The second consensus criteria⁶ define 3 levels of diagnostic certainty (definite, probable, and possible) and 2 motor phenotypes (parkinsonian [MSA-P] and cerebellar [MSA-C]). The criteria require *postmortem confirmation* for a definite diagnosis, which is obviously impossible while the patient is alive. A future revision of the criteria should therefore include a category of *clinically established* MSA, which is expected to improve specificity (for example, to >90%) at the expense of sensitivity. Balanced sensitivity (including the majority of MSA cases, for example >80%) and specificity (excluding the majority of non-MSA cases, for example >80%) would likely improve on the current consensus criteria for *clinically probable* MSA. Laboratory support should be included in the definition of *clinically established* or *clinically probable* MSA to supplement clinical presentations that are highly suggestive of MSA but yet fail to fulfill all the requirements for the clinically established or probable diagnoses. For example, in a patient with more advanced parkinsonism than would be expected to PD for the duration and without autonomic failure, MRI features strongly suggestive of MSA would enable earlier diagnosis with highest clinical diagnostic certainty.⁹ Validation in a *postmortem* series is a priority to define which combinations of the laboratory supporting tests have sufficient specificity to justify

enrollment in clinical trials with disease-modifying agents. The term *clinically possible* MSA is defined already in the second consensus criteria.⁶ However, it should be conceptualized more explicitly to capture early patients with isolated autonomic failure or rapid eye movement sleep behavior disorder (RBD) and likely additional clinical or instrumental features suggestive of MSA who require additional follow-up for diagnostic confirmation (see Table 1). However, even this diagnostic category should have satisfactory specificity.

Issue 2: Clinical Heterogeneity

The current division into parkinsonian and cerebellar subtypes reflects initial clinical manifestations. Importantly, there is a substantial overlap of cerebellar and parkinsonian features (termed by some authors as MSA *P+C*), reflecting mixed neuropathological findings of oligodendroglial cytoplasmatic inclusion distribution and neuronal loss in the striatonigral and olivopontocerebellar pathways.¹⁰ Approximately half of MSA-P patients show additional cerebellar signs, and 75% of MSA-C patients develop parkinsonism during the disease course.^{11,12}

Early and severe autonomic failure is a hallmark of both MSA-P and MSA-C. It is therefore a mandatory feature in the current consensus criteria.⁶ Depending on the study setting, rates of autonomic failure of up to 50% are reported at MSA disease onset. Urogenital dysfunction typically predates cardiovascular autonomic failure.¹³ Until recently it was considered that patients with pure autonomic failure (PAF) are primarily at risk of Lewy body disease. However, several studies have shown that PAF commonly evolves into MSA as well.^{14,15} These patients were younger at the onset of autonomic failure and had shorter times to evolution to MSA diagnosis when compared with patients evolving to PD and DLB.¹⁵ Preserved olfaction and RBD in patients with PAF strongly predicted a progression to MSA, whereas impaired olfaction was associated with phenoconversion to Lewy body disease.¹⁵ The presence of red flags provides important clues for a correct and early diagnosis of MSA patients presenting with PAF¹⁶ (see Table 1). Secondary causes of autonomic failure and alternative conditions mimicking autonomic symptoms in patients suspected of MSA may lead to a misdiagnosis and need to be ruled out (see Table 2).

During the past decade, new MSA variants have been recognized, including young-onset (between 30–40 years)¹⁷ and late-onset (>75 years)¹⁸ long-duration MSA extending for more than 15 years,¹⁹ corticobasal presentation,^{20,21} and mild cognitive impairment^{22,23} or infrequently dementia syndromes mimicking frontotemporal dementia,^{21,24} DLB, and PSP.⁸ In addition, an increasing range of genetic MSA mimics (ie, MSA look-alikes)²⁵ has been identified (see Table 3).

Novel diagnostic criteria for MSA would need to take into account the frequent presence of mixed-motor presentations (MSA-P/C), PAF as a risk factor for MSA (MSA-AF), and a new delineation of variants (young-onset MSA, late-onset MSA, long-duration MSA, and MSA-corticobasal presentation). Given the lower diagnostic specificity, these cases could only reach *clinically possible* diagnostic certainty if supported by clinical red flags, imaging, or other biomarkers.

Issue 3: Response to Levodopa

Current criteria require a poor response to levodopa as qualifier for a diagnosis of probable MSA.⁶ Although many patients with MSA have a poorer or absent response to levodopa when compared with patients with PD, some may have a good or excellent responses, sometimes for many years (see Table 1). A major issue with the criterion of poor levodopa responsiveness arises from 2 large, prospective natural history studies that showed beneficial levodopa response in 42% to 57% of MSA-P patients.^{11,12} In addition, 13% to 25% of MSA-C patients also manifested some improvement.^{11,12} Weighting of several factors together supporting a diagnosis of MSA is needed. For example, a patient with a classical combination of early autonomic failure and ataxia with moderately levodopa responsive parkinsonism could still reach high levels of diagnostic certainty. Dysarthria and other features of mild ataxia and postural instability usually remain present at the best ON state in patients with MSA. Enhancing sensitivity for early MSA stages should therefore include a revision of the current definition of levodopa responsiveness of parkinsonism in MSA. In contrast, issues carrying less diagnostic weight such as positive family history and disease onset after the age of 75 years should be categorized under “low” yield category.

Issue 4: Nonsupporting and Exclusion Features for MSA Diagnosis

The second consensus criteria⁶ provide a list of features not supporting the diagnosis of MSA. Although certain features not previously described in definite MSA may be classified as absolute exclusions (see Table 1), other features, such as classic pull-rolling tremor, although uncommon, still occur in 10% of patients and thus do not exclude the diagnosis. Early multidomain cognitive deficits and visual hallucinations in a patient with autonomic failure argue for DLB diagnosis. However, these features may also be present in a minority of patients with MSA^{8,22} (see Table 4). Revised MSA criteria should take this distinction into account similarly to the approach used in the MDS criteria for PD.²⁶

Issue 5: Genetic Factors

Several observations have implicated genetic factors in MSA and challenge the weighting of a positive family history of parkinsonism or ataxia as a nonsupporting criterion for the diagnosis of MSA (see Table 1). Causative loss-of-function mutations in the *COQ2* gene were found in 2 siblings diagnosed with definite and probable MSA-P from a consanguineous family and in 2 siblings with probable MSA-C from another family in Japan.²⁷ However, in other pedigrees no monogenic mutation has been found as a cause of MSA. The calculated heritability of MSA as a result of common genetic variance using Genome-Wide Complex Trait Analysis is 2.09% to 6.65%, and this number could be explained by the small cohort size and possible presence of misdiagnosed cases.²⁸

Evidence favoring a role of genetic predisposition in MSA is not strong at present. In the context of the enrollment of patients in clinical trials, MSA should be regarded as a sporadic disease and Mendelian families as phenocopies. A continuum from genetic, complex trait and sporadic factors underlying MSA should be confined to the research setting. A concept of familial MSA reflecting rare, multiplex families or MSA phenocopies as evidenced by

positive family history might be considered. The inclusion of patients with a positive family history of MSA or degenerative cerebellar disorder into the clinical category of *familial* MSA will reduce the specificity at the expense of sensitivity. In these cases, a *clinically possible* diagnosis can be allowed only if counterbalanced with multiple red flags or strongly supportive biomarkers.

Issue 6: Diagnostic Tests

Conventional MRI and fludeoxyglucose PET indices of neurodegeneration in the putamen, middle cerebellar peduncle (MCP), pons, and cerebellum and presynaptic nigrostriatal denervation on single-photon emission computed tomography or ¹⁸F-fluorodopa PET are additional features of possible MSA in the second consensus criteria.⁶ Suboptimal accuracy of neuroradiological diagnosis, particularly in the early disease stages,^{29,30} may be improved by implementing diffusion-weighted sequences and advanced MRI techniques (see Table 1). Patterns highly predictive for an early diagnosis of MSA-P include increased diffusivity in the posterior putamen and MCP with spared superior cerebellar peduncles on diffusion-weighted sequences³¹ and volume loss in the putamen and cerebellar gray matter in the absence of severe midbrain atrophy on automated observer-independent volumetric MRI based on the segmentation of subcortical regions.³² Current evidence suggests that intact functional integrity of myocardial sympathetic fibers on ¹²³I-metaiodobenzylguanidine-SPECT is a useful supporting feature for MSA diagnosis.³³ Extending the duration of orthostatic blood pressure measurements from 3 to 10 minutes significantly increases sensitivity to capture delayed orthostatic hypotension and correctly diagnose a number of additional MSA patients.^{13,34,35} An emphasis on the severity of adrenergic failure using robust indices such as blood pressure recovery time instead of a reliance on sensitivity in the detection of (mild) orthostatic hypotension improves the diagnosis of MSA.^{36,37} Similarly, the distribution of anhidrosis on a thermoregulatory sweat test distinguishes MSA from PD with good sensitivity and specificity.³⁶ Open bladder neck during filling, detrusor-sphincter dyssynergia during voiding, and postvoid residual volume >100 mL are characteristic urodynamic/sonographic findings of MSA.^{38,39} The diagnostic characteristics of cutaneous alpha-synuclein deposition in MSA patients are not definitively established. Introducing additional biomarkers as supporting features in the new criteria is therefore needed to achieve a higher proportion of correctly diagnosed MSA patients, particularly in the early disease stages. To achieve diagnostic criteria that can be widely applied for the inclusion of patients into multinational or multi-institutional disease-modifying clinical trials, the general availability of certain diagnostic tests needs to be considered.

Conclusion

In conclusion, this article highlights the need for a revision of the second consensus criteria for an MSA diagnosis.⁶ Current poor diagnostic sensitivity and suboptimal specificity^{7,8} should be enhanced especially at the early disease stages to permit the recruitment of patients with a very high likelihood of MSA into future disease-modifying trials. New MSA diagnostic categories, which would ideally serve the earlier diagnosis, will be proposed based on existing evidence. The goal of the recently established MDS MSA Criteria Revision Task Force is to define the methodological principles for the criteria revision and

drive the revision process. A validation exercise on the novel criteria in a prospective clinicopathological study is needed to determine their diagnostic accuracy.

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TABLE 1.
Pros and cons for the revision of selected items of the second consensus criteria for the diagnosis of MSA

Question	Cons	Pros
Do we need a revision of the second consensus criteria ⁶ on the diagnosis of MSA?	<ul style="list-style-type: none"> The second consensus criteria⁶ are the worldwide acknowledged gold-standard for the diagnosis of MSA, with >2000 citations since publication. 	<ul style="list-style-type: none"> Sensitivity of the second consensus criteria⁶ at first visit as well as specificity in <i>postmortem</i> series are suboptimal.^{7,8} The implementation of recently identified clinical and MRI MSA-specific red flags may enable an earlier and more accurate diagnosis.^{16,29}
Should we revise the existing categories of MSA-P and MSA-C?	<ul style="list-style-type: none"> Early division into the motor subtypes is useful to predict the clinical outcome (MSA-P being reported as more aggressive in European cohorts).¹¹ With the existing categories, non-motor features support the differential diagnosis of MSA-P and MSA-C versus related disorders. Inclusion of atypical MSA phenotypes that are rare would significantly reduce diagnostic specificity in the absence of reliable biomarker. 	<ul style="list-style-type: none"> Clinical heterogeneity of MSA may justify inclusion of new MSA variants if counterbalanced with multiple red flags and supported with imaging or other biomarkers: <ul style="list-style-type: none"> MSA-AF: MSA presenting with predominant autonomic failure MSA-P/C: mixed parkinsonian and cerebellar MSA YOMSA: MSA with onset between 30 and 40 years of age LOMSA: MSA with onset after 75 years of age LDMSA: MSA surviving more than 15 years MSA-CBS: MSA presenting with features of corticobasal syndrome
Definite diagnosis of MSA depends on autopsy. Should we improve diagnostic certainty during life?	<ul style="list-style-type: none"> Only <i>postmortem</i> examination can secure a definite diagnosis as specific biomarkers and clinical features are missing. Insufficient validation of neuroimaging and wet biomarkers against <i>postmortem</i> proven MSA cases. 	<ul style="list-style-type: none"> A definite diagnosis based on autopsy largely confines the use of the criteria to the research setting. Three levels of clinical diagnostic certainty should be pursued: <ul style="list-style-type: none"> <i>clinically established</i>: maximizing specificity <i>clinically probable</i>: balancing sensitivity and specificity <i>clinically possible</i>: requires follow-up
Should we exclude family history of 1 or more affected relatives with apparent MSA or degenerative cerebellar disease from the list of non-supporting features for MSA diagnosis?	<ul style="list-style-type: none"> MSA is sporadic, with only very rare exceptions. Family history of a neurodegenerative disorder is not a risk factor for MSA. Calculated MSA heritability is low.²⁸ Genetic MSA look-alikes have been described (see Table 3).²⁵ In the context of MSA-C, a positive family history strongly suggests an alternative diagnosis. Inclusion of patients with positive family history of MSA or degenerative cerebellar disease would significantly reduce diagnostic specificity. 	<ul style="list-style-type: none"> Definite MSA cases with familial aggregation of both MSA-P and MSA-C phenotypes have been reported. Positive family history for parkinsonism is reported in 11 % of definite MSA cases.⁸ Parkinsonism is more common in the first-degree relatives of patients with MSA. Causative loss-of-function mutations in the <i>COQ2</i> gene are found in 2 families from Japan.²⁷ Clinical category of <i>familial</i>/MSA might be considered.

Question	Cons	Pros
Should we exclude dementia from the list of non-supporting features for MSA diagnosis? How do we define dementia in this context?	<ul style="list-style-type: none"> MSA versus DLB: Cognitive impairment with mental fluctuations and visual hallucinations usually indicate DLB rather than MSA. MSA versus PDD: An overlapping pattern of dominant frontal-executive type of mild cognitive impairment in MSA and nondemented PD patients is a diagnostic trap. MSA versus PSP: Severe and early frontal executive dysfunction is distinctive of PSP. The MoCA, the FAB, verbal fluency items and Luria series are tools to distinguish PSP from MSA. 	<ul style="list-style-type: none"> Around 30% of patients with MSA develop mild cognitive impairment early in the disease, most commonly in a form of executive dysfunction.^{22,23} Criteria for MSA-related mild cognitive impairment or dementia are not yet developed.
Is it still reasonable to have onset age >75 years as a non-supporting feature?	<ul style="list-style-type: none"> Limiting the onset age to 75 years increases specificity of MSA diagnosis against DLB that manifest with dementia and autonomic failure but approximately 1 decade later. With increased age, vascular burden increases, producing vascular levodopa unresponsive mimics. Disease onset after 75 years of age in MSA is rare. 	<ul style="list-style-type: none"> Definite MSA cases manifesting after 75 years of age have been reported.^{8,18} Late-onset MSA patients may have been underestimated in population-based cohorts because of arbitrary inclusion criteria. Among the current diagnostic criteria for atypical parkinsonian disorders, only those for MSA define an upper age limit.
Should we allow for diagnosis of MSA in patients with a good levodopa response?	<ul style="list-style-type: none"> Levodopa responsiveness is a temporary characteristic of a substantial minority of MSA patients. Clear and dramatic levodopa responsiveness is highly specific for PD and supports its differential diagnosis from MSA. 	<ul style="list-style-type: none"> Natural history studies have shown a beneficial levodopa response in significant proportion of both MSA-P and MSA-C patients.^{11,12} Levodopa responsiveness may last 3 to 4 years in MSA.^{11,12} Given that patients with suspected MSA, but definite levodopa responsiveness, only qualify for possible MSA, a long delay in diagnosing probable MSA occurs if this criterion is applied. Several factors may influence judgment of levodopa responsiveness (eg, minimal clinically relevant improvement, disease progression, acute side effects of levodopa administration, and levodopa-induced dyskinesias).
Should we incorporate a numerical scoring system that allows building up a score out of a list of red flags?	<ul style="list-style-type: none"> A score is unable to capture the breadth of MSA phenotype. Scoring systems are complex and difficult to apply in the routine clinical practice. 	<ul style="list-style-type: none"> The presence of 2 or more MSA-specific red-flags out of early instability, rapid progression, abnormal postures, bulbar dysfunction, respiratory dysfunction, and emotional incontinence shows a good diagnostic accuracy for probable MSA-P and may anticipate its diagnosis in patients with possible MSA-P.¹⁶
What genetic tests are reasonable in the differential diagnosis of MSA?	<ul style="list-style-type: none"> With the exception of the <i>COQ2</i> mutation in Japanese MSA families,²⁷ no monogenic mutation has been found to cause MSA. Genetic testing should not be performed on a routine basis. In patients with features not suggestive of typical MSA, genetic testing may be considered. 	<ul style="list-style-type: none"> There is a growing list of MSA genetic look-alikes.²⁵ The predominant phenotype should guide the diagnostic algorithm (see Table 3) and testing for the most common look-alike syndromes could increase diagnostic accuracy. <i>COQ2</i> mutation screening is desirable only in familial MSA cases from Japan.
What nongenetic tests are reasonable or necessary in the differential diagnosis of MSA and why?	<ul style="list-style-type: none"> Most nongenetic tests have not been evaluated in prospective clinico-pathological cohorts. 	<ul style="list-style-type: none"> Ancillary tests may increase the diagnostic accuracy at early MSA stages. Conventional MRI:

Question	Cons	Pros
		<p>Atrophy, hypointensity, and slit-like hyperintensity of posterior putamen as well as increased iron deposition in putamen differentiate MSA-P from PD, but not PSP.</p> <p>Compared with other degenerative parkinsonism, MCP atrophy and hyperintensity can predict MSA diagnosis on autopsy in 100% of cases.²⁹</p> <p>The specificity of the hot cross bun sign in MSA is 100% versus PD or PSP, but it may be also present in genetic ataxia, most frequently SCA2.²⁹</p>
		<ul style="list-style-type: none"> Quantitative neuroimaging: <ul style="list-style-type: none"> 1.5 T diffusion-weighted imaging: Increased putamen diffusivity differentiates between MSA-P and PD (sensitivity, 90%; specificity, 93%).³¹ Increased diffusivity in MCP differentiates MSA from PSP (sensitivity 91 %–100%, specificity 84%–100%).⁴⁰ MRI volumetry: Volumes of the midbrain, putamen, and cerebellar gray matter calculated with automated segmentation of T1-weighted MRI imaging are highly predictive for the diagnosis of MSA with respect to PD and PSP at first clinical visit.³²
		<p>Functional imaging:</p> <ul style="list-style-type: none"> FDG-PET: Cerebellar, brain stem, and striatal glucose metabolism is abnormal in patients with MSA when compared with other degenerative parkinsonisms (specificity >90%, sensitivity >75%).³⁰ Dopaminergic imaging: DAT-SPECT is not specific for MSA when tested against PD and PSP. It may be useful in differential diagnosis of MSA-C. Reduced dopamine transporter imaging is described also in genetic ataxia.
		<ul style="list-style-type: none"> Cardiac MIBG-SPECT: In the presence of OH, a preserved cardiac sympathetic innervation points toward MSA rather than PD.³³
		<p>Cardiovascular autonomic function testing: More generalized, severe, and progressive autonomic failure can help distinguish MSA from PD.³⁶ Presence of autonomic failure in a patient with apparently SAOA may indicate MSA. Supine plasma catecholamine levels help distinguishing MSA with autonomic onset from PAF. In PSP, autonomic failure is uncommon.</p>
		<ul style="list-style-type: none"> Neuro-urological studies: Open bladder neck during filling, detrusor-sphincter dyssynergia during voiding, sphincter EMG abnormality, and increased postvoid residual volume are useful for the differential diagnosis of MSA versus pd.^{38,39}
		<ul style="list-style-type: none"> Wet biomarkers: No biomarker is sufficiently robust for a laboratory diagnosis of MSA. Neurofilament light chain is currently the most promising candidate to distinguish MSA from PD, but standardization of operating procedures is needed.

Question	Cons	Pros
		<ul style="list-style-type: none"> Videopolysonnography: May distinguish between MSA and PSP or between MSA-C and other ataxias by diagnosing RBD. Olfactory testing: Differentiates between MSA and PD and PAF and is cost- and time-effective. It does not differentiate between MSA and PSP or SAOA. Neuroendocrine tests: May differentiate between MSA, PD, and PAF, but yield an inadequate diagnostic accuracy. Exclusion of acquired causes of ataxia: An alternative, immune-mediated cause should be considered in patients with rapidly progressive presentation (over weeks). Separate lists of nonsupporting (ie, unusual for MSA) and exclusion criteria (ie, never described in MSA) are needed based on weighting of clinical features.
Should we include nonsupporting and exclusion features?	<ul style="list-style-type: none"> Only exclusion criteria are needed: <ul style="list-style-type: none"> Age at onset <30 years, sudden onset and relapsing remitting course, amnesic dementia with predominant storage problems, marked frontotemporal behavioral syndrome, marked cortical sensory loss, and acquired causes of parkinsonism or ataxia¹⁸ Core clinical features for MSA-related disorders (see Table 4). 	

DAT, dopamine transporter; DLB, dementia with Lewy bodies; EMG, electromyography; FAB, Frontal Assessment Battery; FDG-PET, fluodeoxyglucose positron emission tomography; LDMSA, long-duration multiple system atrophy; LOMSA, late-onset multiple system atrophy; MCP, middle cerebellar peduncle; MIBG, 123I-metaiodobenzylguanidine; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; MSA, multiple system atrophy; MSA-AF, multiple system atrophy–autonomic failure; MSA-C, multiple system atrophy–cerebellar; MSA-CBS, multiple system atrophy–corticobasal syndrome; MSA-D, multiple system atrophy–dementia; MSA-MCI, multiple system atrophy–mild cognitive impairment; MSA-P, multiple system atrophy–parkinsonian; MSA-P/C, multiple system atrophy–mixed parkinsonian and cerebellar; OH, orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PSP, progressive supranuclear palsy; RBD, rapid eye movement sleep behavior disorder; SAOA, sporadic adult-onset ataxia; SCA2, spinocerebellar ataxia type 2; SPECT, single-photon emission computed tomography; YOMSA, young-onset multiple system atrophy.

TABLE 2.
Secondary causes and alternative etiologies of autonomic failure resulting in misdiagnosis of MSA

Secondary causes of autonomic neuropathy	
Diabetes mellitus (most frequent)	
Uremia	
Liver disease	
Chemotherapy and radiotherapy	
Borelliosis, syphilis, and HIV infection	
Paraneoplastic syndromes (autoimmune autonomic ganglionopathy, paraneoplastic autonomic neuropathy, and acute autonomic and sensory neuropathy) (rapid progression)	
Autoimmune diseases (Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and celiac disease)	
Amyloidosis	
Alternative etiologies of key autonomic symptoms	
Orthostatic hypotension	Polypharmacy <ul style="list-style-type: none"> • Dopaminergic drugs, especially levodopa (intestinal > oral) • Antihypertensive drugs and diuretics • Neuroleptic drugs • Vasoactive drugs
	Anaemia
	Hypovolemia (diarrhea, blood loss)
	Cardiopulmonary diseases (aortic stenosis, tachy- or bradyarrhythmia, ischemic cardiac disease, pulmonary embolism)
	Hypoglycemia
	Intoxication
	Epileptic or psychogenic nonepileptic seizure
	Benign prostatic hypertrophy (men)
Urinary storage problems	Pelvic floor relaxation/prolapse after multiple labors (women)
	Urinary infections
	Pelvic surgery
	Benign prostatic hypertrophy (men)
	Pelvic masses
	Pelvic surgery
	Cauda equina syndrome
Voiding problems	

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Sexual dysfunction	Cardiovascular disease
	Smoking (men)
	Alcohol (men)
	Menopause (women)
	Thyroid disease
	Psychogenic
Dysphagia	Upper gastrointestinal tract masses
	Radiotherapy
	Achalasia and diffuse spasms
Constipation/ diarrhea	Lower gastrointestinal tract masses
	Irritable bowel
	Inflammatory bowel disease
	Infectious diseases
	Antibiotics/food
	Thyroid and parathyroid disease
	Disorders of calcium metabolism
	Anal fissure
	Spinal cord injury
Stridor, dysphonia, and inspiratory sighs	Chronic laryngeal infection and laryngeal masses
	Chest masses causing extrinsic stenosis or affecting recurrent laryngeal nerve latrogenic lesions of recurrent laryngeal nerve during surgery
Hypo/anhydrosis	Hypothyroidism Primary skin diseases
Blurred vision, photophobia, and diminished nocturnal vision	Cataract and other primary eye disorders
Cold hands and feet	Peripheral artery disease

HIV, human immunodeficiency virus.

TABLE 3.
Decision flow for diagnosis of MSA-mimic genetic syndromes based on predominant phenotype

Predominant phenotype	Gene	Inheritance pattern	Typical phenotype	AAO (decade)	Red flags
Ataxia	<i>ATXN1</i>	AD	SCA1	3 rd -4 th	Axonal sensory neuropathy, hyporeflexia, loss of vibration/proprioception
	<i>ATXN2</i>		SCA2	4 th	Chorea, dystonia, cognitive impairment, slow saccades
	<i>ATXN3</i>		SCA3	4 th	Upper motor neuron signs, executive dysfunction, ophthalmoparesis
	<i>CACNA1A</i>		SCA6	5 th -6 th	Family members can present with episodic ataxia or hemiplegic migraine
	<i>ATXN7</i>		SCA7	3 rd -4 th	Retinal degeneration
	<i>ATXN8</i>		SCA8	4 th	Slowly progressive, hyperreflexia
	<i>PPP2R2B</i>		SCA12	4 th	Cerebellar ataxia, hyperreflexia, tremor
	<i>TBP</i>		SCA17	2 nd -5 th	Psychiatric symptoms, dementia, chorea
	<i>ATN1</i>		DRPLA	4 th	Choreoathetosis, dementia, epilepsy, psychiatric symptoms
	<i>NOP56</i>		SCA36	5 th -6 th	Hearing loss, motor neuron involvement, slow progression
	<i>FMR1</i>	XR	FXTAS	6 th -7 th	Female premutation carriers can present with primary ovarian insufficiency, family history of fragile-X syndrome, periventricular white matter hyperintensities on MRI
Parkinsonism	<i>FXN</i>	AR	FRDA	2 nd -3 rd	Axonal sensory neuropathy, hyporeflexia, loss of vibration/position sense, cardiomyopathy, diabetes, slow progression
	<i>DCTN1</i>	AD	Perry syndrome	5 th	Hypoventilation, weight loss, psychiatric symptoms
	<i>SNCA</i>		PD/LBD	3 rd -4 th	Dementia, early onset levodopa responsive parkinsonism
	<i>GBA</i>			1 st -2 nd	Cognitive impairment, common in patients of Ashkenazi Jewish ancestry
				6 th	
	<i>LRRK2</i>			6 th	Family history of levodopa responsive PD
Spastic gait	<i>SPG7</i>	AD/AR	HSP	3 rd -4 th	Spastic paraplegia, cerebellar ataxia, executive dysfunction
	<i>SPG11</i>	AR		3 rd -4 th	Severe spastic paraplegia
Autonomic failure	<i>LMNB1</i>	AD	Leukodystrophy	4 th -6 th	Extensive, U-fiber sparing white matter lesions on MRI, cognitive impairment in advanced stages
Complex phenotypes	<i>POLG1</i>	AD/AR	Mitochondriopathy	1 st -4 th	Ophthalmoplegia, hearing loss, neuropathy, epilepsy, dementia
	<i>CYP27A1</i>	AR	CTX	2 nd -3 rd	Diarrhea, cataracts, xanthomas, cognitive and psychiatric symptoms
	<i>PRNP</i>	AD	Priori disease	3 rd -9 th	Myoclonus, dementia, psychiatric symptoms, seizures, rapid progression
	<i>C9orf72</i>	AD	FTD/ALS	4 th -7 th	Motor neuron signs, cognitive impairment, psychiatric symptoms

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AAO, age at onset; AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CTX, cerebrotendinous xanthomatosis; DRPLA, dentatorubral pallidoluysian atrophy; FRDA, Friedreich ataxia; FTD, frontotemporal dementia; FXTAS, fragile X tremor ataxia syndrome; HSP, hereditary spastic paraplegia; LBD, Lewy body disease; MRI, magnetic resonance imaging; PD, Parkinson's disease; SCA, spinocerebellar ataxia; XR, X-linked recessive.

TABLE 4.

Features strongly supportive for non-MSA disorders presenting with parkinsonism

Differential diagnosis	Core clinical features for non-MSA disorder
MSA versus PD	<ul style="list-style-type: none"> • “Pill-rolling” tremor • Sustained levodopa response after 5 years from onset • Motor fluctuations and marked peak dose appendicular dyskinesia after 5 years from disease onset • Absence of defining autonomic features after first 5 years
MSA versus DLB	<ul style="list-style-type: none"> • Early dementia (specifically visuospatial or language in addition to executive dysfunction) • Early visual hallucinations • Fluctuating cognition with profound variations in attention/alertness not related to orthostatic hypotension
MSA versus PSP	<ul style="list-style-type: none"> • Supranuclear vertical downward gaze paresis • Frontal lobe type symptomatology commonly with behavioral abnormalities • Recurrent falls backward within the first 3 years
MSA versus CBS	<ul style="list-style-type: none"> • Apraxia • Cortical sensory loss • Aphasia • Persistent unilaterality

DLB, dementia with Lewy bodies; CBS, corticobasal syndrome; MSA, multiple system atrophy; PD, Parkinson’s disease; PSP, progressive supranuclear palsy.