REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Multiple-System Atrophy

Alessandra Fanciulli, M.D., and Gregor K. Wenning, M.D., Ph.D.

Multiple-system atrophy is an adult-onset, fatal neurodegenerative disease characterized by progressive autonomic failure, parkinsonian features, and cerebellar and pyramidal features in various combinations. It is classified as the parkinsonian subtype if parkinsonism is the predominant feature and as the cerebellar subtype if cerebellar features predominate.

With its variable clinical presentations, multiple-system atrophy presents a major diagnostic challenge not only in neurology but also in other specialties, including cardiology, gastroenterology, urology, otolaryngology, and sleep medicine. Despite having faster motor progression, multiple-system atrophy may masquerade as Parkinson's disease or idiopathic late-onset cerebellar ataxia until advanced stages of the disease.

The history of multiple-system atrophy reflects the varied clinical manifestations of the disease. The term multiple-system atrophy was first coined in 1969 to pool three previously described neurologic entities: olivopontocerebellar atrophy, the Shy–Drager syndrome, and striatonigral degeneration.[1] These entities correspond to multiple-system atrophy with predominantly cerebellar, autonomic, or parkinsonian features, respectively.

From the Department of Neurology, Division of Neurobiology, Innsbruck Medical University, Innsbruck, Austria (A.F., G.K.W.); and the Department of Neuroscience, Mental Health and Sensory Organs, Sapienza University of Rome, Rome (A.F.). Address reprint requests to Prof. Wenning at the Department of Neurology, Division of Neurobiology, Innsbruck Medical University, Anichstr. 35, A-6020 Innsbruck, Austria, or at gregor.wenning@i-med.ac.at.

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EPIDEMIOLOGIC FEATURES

Multiple-system atrophy is an orphan disease (Orpha number, ORPHA102 [www.orpha.net]). The estimated mean incidence is 0.6 to 0.7 cases per 100,000 person-years, with a range of 0.1 to 2.4 cases per 100,000 person-years.[2] The estimated point prevalence is 3.4 to 4.9 cases per 100,000 population, increasing to 7.8 per 100,000 among persons older than 40 years of age.[3] Cases of the parkinsonian subtype outnumber cases of the cerebellar subtype in most countries by 2:1 to 4:1,[4-6] although the cerebellar subtype is more frequent in Japan,[7] with genetic or epigenetic factors possibly exerting an influence. Disease onset is usually in the sixth decade of life, with both sexes equally affected.[8] The mean survival from the onset of symptoms is 6 to 10 years,[8-10] with few patients surviving more than 15 years.[11]

CAUSES

No environmental factors are known to affect the risk of multiple-system atrophy. As in Parkinson's disease, nicotine use and alcohol consumption are less common among patients with multiple-system atrophy than among healthy controls, which indicates a possible pathophysiological link between Parkinson's disease and multiple-system atrophy.

Multiple-system atrophy is generally considered a sporadic disease. Nevertheless, genetic factors play an etiologic role in some families. In a few European and Japanese pedigrees, multiple-system atrophy has been transmitted in an autosomal domi-

nant or recessive inheritance pattern.[12,13] Recently, a loss-of-function mutation in *COQ2*, encoding the coenzyme Q_{10}–synthesizing enzyme, was reported in Japanese familial and sporadic cases, but the mutation was not detected in patients with multiple-system atrophy who were from North America or Europe.[14] Similarly, a discordant loss of copy number of *SHC2* was found in monozygotic twins and Japanese patients with sporadic multiple-system atrophy but not in patients in the United States.[15,16] Mutations, duplications, and triplications of *SNCA*, encoding α-synuclein, may cause familial Parkinson's disease with features similar to multiple-system atrophy in some affected persons.[17] Two single-nucleotide polymorphisms of the *SNCA* locus showed a significant association with multiple-system atrophy in a large series of European patients.[18] This association was confirmed in follow-up replication studies[19] but not in the preliminary analysis of the first genomewide association study of multiple-system atrophy.[20] A G51D *SNCA* mutation was recently reported in a British pedigree with autosomal dominant juvenile parkinsonism and neuropathological findings compatible with both Parkinson's disease and multiple-system atrophy.[21]

NEUROPATHOLOGICAL FEATURES

Variable degrees of olivopontocerebellar atrophy and striatonigral degeneration are typically found at postmortem examination of patients with multiple-system atrophy, which broadly reflect the presence of ataxia and parkinsonism during life.[22] In addition, neurodegenerative changes affect the central autonomic nervous system, including the hypothalamus, noradrenergic and serotoninergic brain-stem nuclei, dorsal nucleus of the vagus nerve, nucleus ambiguus, intermediolateral columns of the spinal cord, and Onuf nucleus.[23] Frontal-lobe atrophy may be observed after a long disease duration.

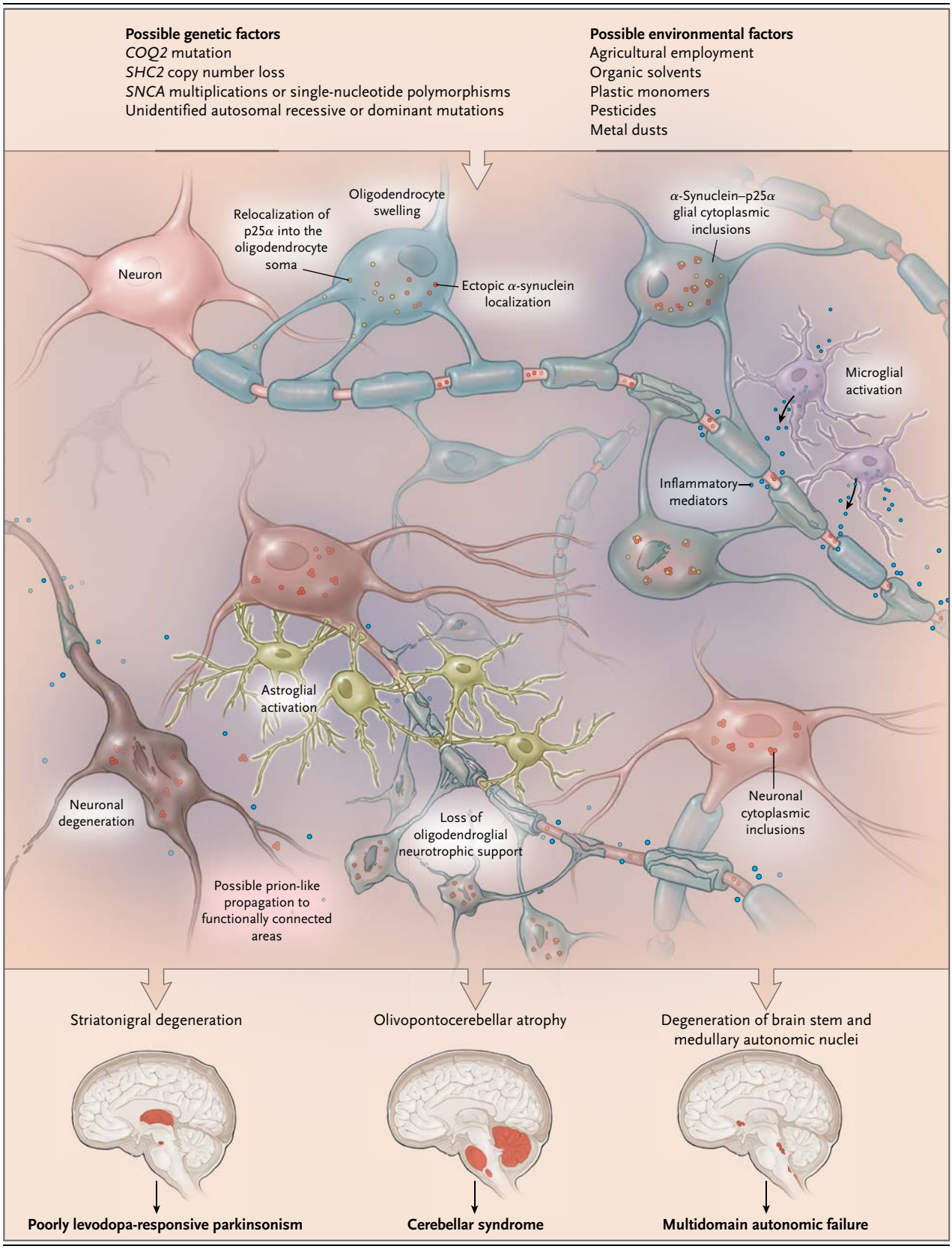
Proteinaceous oligodendroglial cytoplasmic inclusions (also called Papp–Lantos bodies) are the histologic hallmark of multiple-system atrophy.[24] Less frequently, oligodendroglial nuclear, neuronal axonal, cytoplasmic, and nuclear inclusions can be observed as well. The density of glial cytoplasmic inclusions broadly reflects the distribution of neurodegenerative changes in the brains of patients with multiple-system atrophy.[22] Activated microglia and reactive astrogliosis are other common findings.[25] The main constituent of glial cytoplasmic inclusions is misfolded α-synuclein, a protein normally located in neuronal axons and synapses. Hence, multiple-system atrophy is classified as an oligodendroglial α-synucleinopathy, whereas Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure[26] are characterized by neuronal α-synuclein aggregates (Lewy bodies).

Figure 1 (facing page). Pathophysiological Features of Multiple-System Atrophy (MSA).

Genetic and environmental factors may contribute to the initiation of the pathophysiological cascade of MSA. Relocalization of p25α into the oligodendroglial soma is an early event, followed by cellular swelling and abnormal uptake or overexpression of α-synuclein by oligodendroglia. α-Synuclein and p25α precipitate into glial cytoplasmic inclusions, which hinder neuronal trophic support and induce microglial activation. Misfolded α-synuclein released by dysfunctional oligodendrocytes may be taken up by neighboring neurons to form neuronal cytoplasmic inclusions. Neuroinflammation, loss of neurotrophic support, and neuronal dysfunction due to α-synuclein inclusions synergistically contribute to neuronal death in the striatonigral, olivopontocerebellar, and central autonomic pathways, resulting in parkinsonism that is poorly responsive to levodopa, cerebellar ataxia, and multidomain autonomic failure.

PATHOGENESIS

Although the pathogenic mechanisms underlying multiple-system atrophy remain partially unclear, converging evidence from preclinical models and postmortem studies suggests that it is a primary oligodendrogliopathy (Fig. 1).[22,27] Relocalization of p25α, an important stabilizer of myelin integrity, into the oligodendroglial soma appears to precede α-synuclein aggregation.[28] This is followed by oligodendrocyte swelling and abnormal uptake or overexpression of α-synuclein by oligodendroglia.[29,30] The interaction between p25α and α-synuclein promotes phosphorylation and aggregation of synuclein into insoluble oligomers first and glial cytoplasmic inclusions later on. The formation of glial cytoplasmic inclusions, in turn, interferes with neuronal support and activates quiescent microglial cells. As a result, progressively dysfunctional oligodendrocytes release misfolded α-synuclein into the extracellular space; this misfolded α-synuclein may be taken up by neighboring neurons to form neuronal cytoplasmic inclusions. At this point,



neuroinflammation, loss of oligodendroglial neurotrophic support, and neuronal dysfunction due to α-synuclein inclusions may synergistically promote neuronal death and subsequent reactive astrogliosis. Toxic α-synuclein species may then spread in a prion-like fashion to other functionally connected brain areas,[31] leading to the multisystem neuronal involvement that is typical of multiple-system atrophy.

CLINICAL PRESENTATION

Like Parkinson's disease, multiple-system atrophy has a prodromal premotor phase in 20 to 75% of cases, including sexual dysfunction, urinary urge incontinence or retention, orthostatic hypotension, inspiratory stridor, and rapid-eye-movement sleep behavior disorder months to years before the first motor symptoms appear.[32]

MOTOR FEATURES

Parkinsonism, with slowness of movements, rigidity, and a tendency to fall, characterizes the motor presentation of the parkinsonian subtype of multiple-system atrophy.[5] The motor findings are sometimes asymmetrical and may be markedly so. Parkinson-like "pill-rolling" rest tremor is unusual, whereas irregular postural and action tremor with superimposed jerks is seen in as many as 50% of patients with multiple-system atrophy.[5] Progressive degeneration of the striatum accounts for the poor response or lack of response to levodopa, which is a mandatory diagnostic criterion for probable multiple-system atrophy of the parkinsonian subtype. Nevertheless, a transient response to levodopa may be observed in approximately 40% of patients during early disease stages[33]; this is sometimes accompanied by drug-induced involuntary movements, such as head–neck dystonia, an involuntary muscle contraction resulting in abnormal twisting postures.[34]

Cerebellar ataxia predominates in the motor presentation of the cerebellar subtype of multiple-system atrophy.[5,35] Cerebellar features consist of a wide-based gait, uncoordinated limb movements, action tremor, and spontaneous, gaze-evoked, or positional downbeat nystagmus. Spasticity or pyramidal weakness should cast doubts on a diagnosis of multiple-system atrophy, but generalized hyperreflexia, as well as a Babinski sign, may occur in 30 to 50% of cases.[5]

Abnormal postures, including bent spine and disproportionate antecollis (severe forward neck flexion that interferes with eating, speaking, and vision), as well as hand or foot dystonia, are associated with the motor presentation of multiple-system atrophy in 16 to 42% of patients.[36] Recurrent falls, dysphonia (voice-tone changes), dysarthria (difficulty in articulating words), drooling, and dysphagia are defining features of advanced disease.

NONMOTOR FEATURES

Early and severe autonomic failure is a key feature of multiple-system atrophy, and the most frequently affected domains are urogenital and cardiovascular. Erectile dysfunction typically occurs at disease onset in male patients. Genital hyposensitivity during intercourse characterizes the sexual dysfunction in women. Urinary dysfunction includes urinary urgency and frequency, urge incontinence, nocturia, and, less commonly, incomplete bladder emptying.[37] Urinary failure may be masked by concomitant prostatic hypertrophy in men or perineal laxity due to multiple labors or uterine prolapse in women. Remarkably, as many as 50% of these patients undergo futile genitourinary surgery before the correct diagnosis is determined.[38]

Severe orthostatic hypotension, defined as a blood pressure decrease of 30 mm Hg systolic or 15 mm Hg diastolic within 3 minutes after a passive head-up tilt or standing from the recumbent position,[39] is the main feature of cardiovascular autonomic failure in clinically established multiple-system atrophy. It is manifested as recurrent syncope, light-headedness (dizziness), weakness, nausea, tremulousness, headache, or "coat-hanger pain" (pain in the neck and shoulder region) on standing, but it may also be asymptomatic.[40] Postprandial hypotension and supine and nocturnal hypertension accompany orthostatic hypotension in half of patients with multiple-system atrophy.[41]

Respiratory disturbances are characteristic of multiple-system atrophy. Diurnal or nocturnal inspiratory stridor develops in as many as 50% of patients at some time[36] but is more frequent in advanced disease than in earlier stages, and sleep apneas affect about 40% of patients. Episodic nocturnal inspiratory stridor and sleep apnea may occur together.[42] Other features of autonomic failure in multiple-system atrophy include constipation,[43] pupillomotor abnormalities, and vasomotor and thermoregulatory failure with sweating that is diminished and ultimately absent.[44,45]

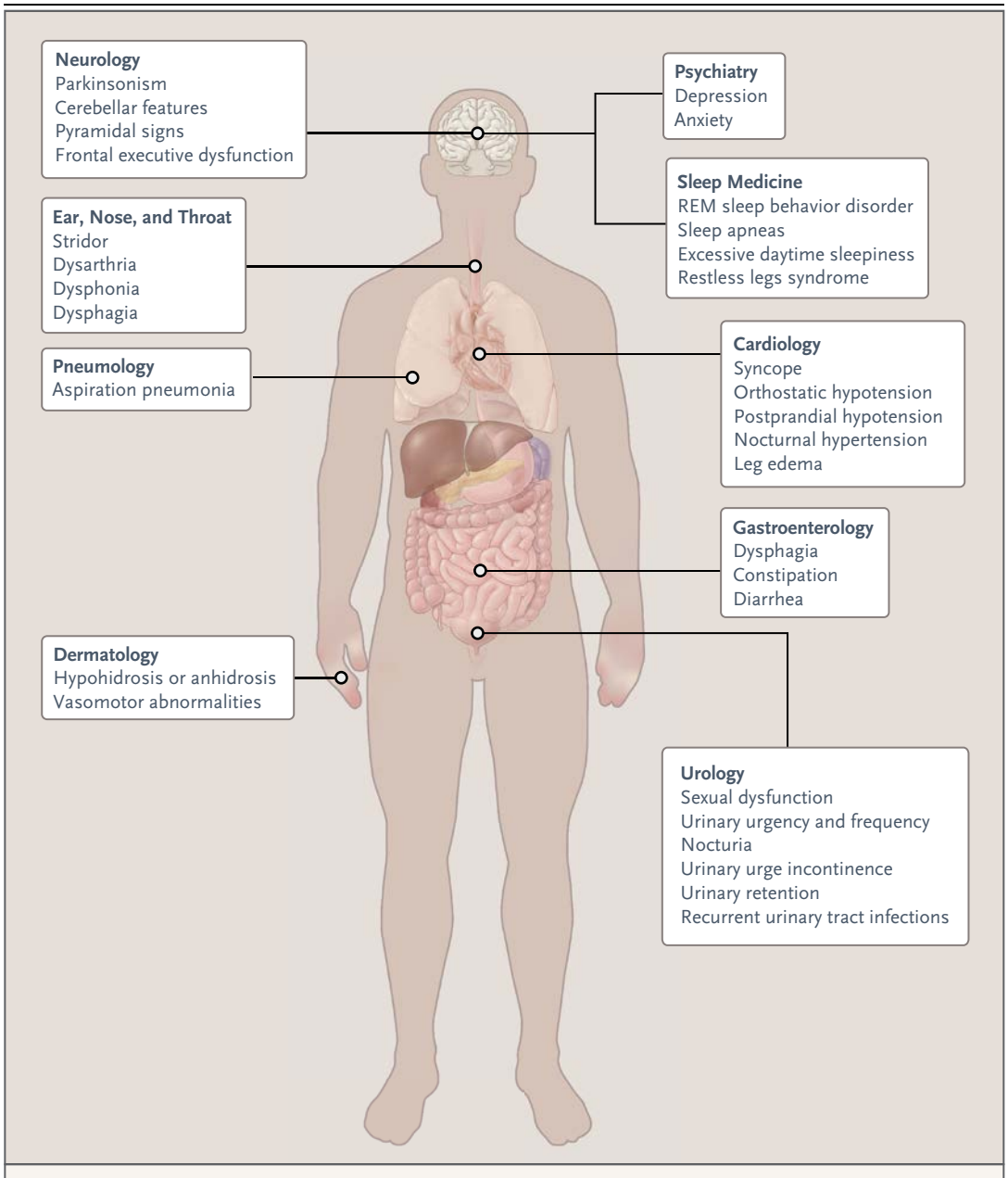


Figure 2. Multidisciplinary Presentation of MSA.

Dementia or visual hallucinations are not consistent with a diagnosis of multiple-system atrophy; these symptoms in the presence of parkinsonism and autonomic failure should prompt consideration of dementia with Lewy bodies.[39] However, frontal-lobe dysfunction with attention deficits has been reported in one third of cases.[46] Emotional incontinence (i.e., inappropriate laughing or crying in the absence of the appropriate emotional context) can occur,[36] as well as behavioral changes, including depression, anxiety, panic attacks, and suicidal ideation. Finally, as many as 50% of patients report disabling pain; advanced disease, dystonia, and female sex are possible risk factors for this symptom.[47] A visual summary of the varied clinical manifestations of multiple-system atrophy is provided in Figure 2.

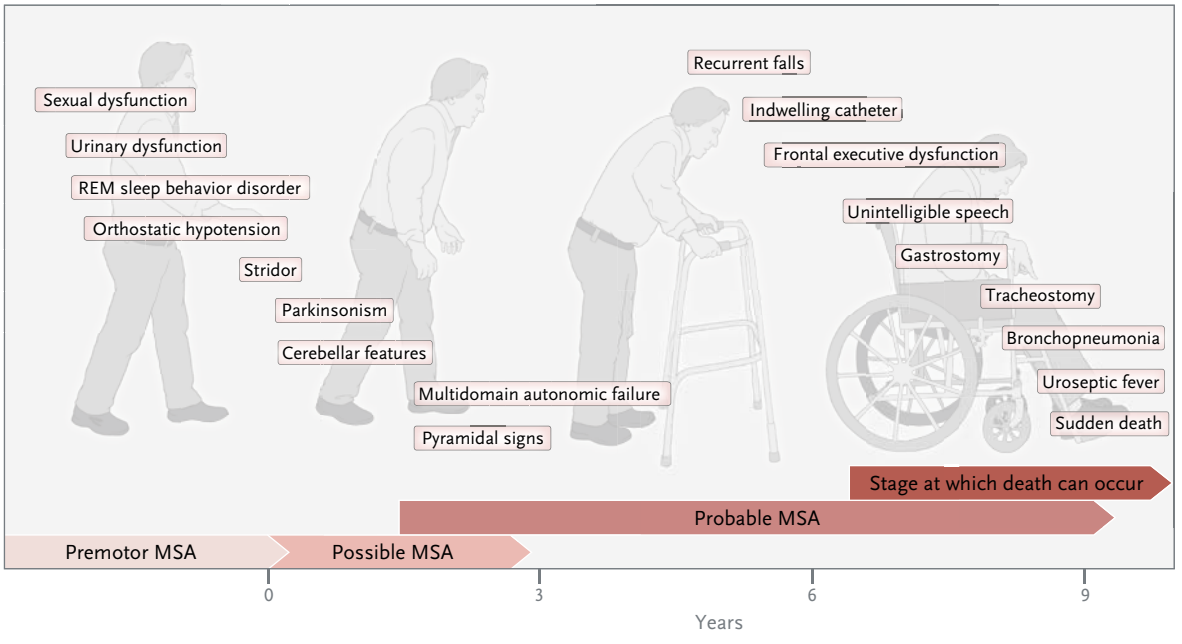


Figure 3. Natural History of MSA.

The premotor phase of MSA can last for months to years. Year 0 denotes the time of onset of motor symptoms. A diagnosis of definite MSA is not possible until the postmortem examination is performed.

DISEASE PROGRESSION AND PROGNOSIS

Multiple-system atrophy is characterized by a relentless worsening of motor and nonmotor symptoms during an average time frame of 10 years, with more rapid progression at the onset (Fig. 3).[9] Approximately 50% of patients require walking aids within 3 years after the onset of motor symptoms,[7] 60% require a wheelchair after 5 years,[10] and the median time before the patient is bedridden is 6 to 8 years.[7] The causes of death in multiple-system atrophy commonly include bronchopneumonia, urosepsis, or sudden death. Sudden death often occurs at night as a result of either acute bilateral vocal-cord paralysis or acute disruption of the brain-stem cardiorespiratory drive. Counseling patients on life expectancy can be challenging for the treating physician, because there are reports of both aggressive variants with a disease duration of less than 3 years[48] and more benign cases with prolonged survival.[11] Older age at onset,[7,8,10,49-51] a parkinsonian phenotype,[9,50] and early development of severe autonomic failure[7,50,52,53] are negative prognostic factors, whereas a cerebellar phenotype[8] and later onset of autonomic failure[11] predict slower disease progression.

DIAGNOSIS

Because of its protean manifestations, multiple-system atrophy may be misdiagnosed, especially at disease onset. An autonomic presentation can be indistinguishable from pure autonomic failure, and parkinsonism with autonomic involvement may be misdiagnosed as Parkinson's disease. Patients with the cerebellar subtype generally present with late-onset cerebellar ataxia and additional features of autonomic failure. The cerebellar phenotype can mimic ataxias induced by toxins (e.g., alcohol, chemotherapeutic agents, lead, lithium, and toluene) or by vitamin B_1 deficiency, as well as immune-mediated or genetic ataxias, such as fragile X–associated tremor ataxia syndrome, spinocerebellar ataxia (especially type 6), or late-onset Friedreich's ataxia.[54]

CLINICAL DIAGNOSTIC CRITERIA

The consensus guidelines define three degrees of certainty for the diagnosis of multiple-system atrophy: definite, probable, and possible.[39] A diagnosis of definite multiple-system atrophy requires postmortem evidence of widespread α-synuclein–

Table 1. Diagnostic Criteria for Multiple-System Atrophy (MSA).*

Definite MSA
Neuropathological findings during postmortem examination must include the following:
Widespread and abundant cerebral α-synuclein–positive GCIs
Neurodegenerative changes in striatonigral or olivopontocerebellar region
Probable MSA
Sporadic, progressive disease in adults (onset after 30 yr of age) characterized by autonomic failure, including urinary incontinence (with erectile dysfunction in men), or an orthostatic decrease in blood pressure by at least 30 mm Hg systolic or 15 mm Hg diastolic within 3 min of standing, plus one of the following:
Parkinsonism (slowness of movements, rigidity, and tendency to fall) with poor response to levodopa (parkinsonian subtype [MSA-P])
A cerebellar syndrome (wide-based gait, uncoordinated limb movements, action tremor, and nystagmus) (cerebellar subtype [MSA-C])
Possible MSA
A sporadic, progressive, adult-onset disease characterized by the following:
Parkinsonism (slowness of movements, rigidity, and tendency to fall) or a cerebellar syndrome (wide-based gait, uncoordinated limb movements, action tremor, and nystagmus)
At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency or frequency, incomplete bladder emptying, erectile dysfunction in men, or a substantial orthostatic blood-pressure decline that does not meet the level required for probable MSA)
At least one of the following additional features:
Possible MSA-P or MSA-C: Babinski sign with hyperreflexia, stridor
Possible MSA-P: rapidly progressive parkinsonism; poor response to levodopa; recurrent falls within 3 yr after the onset of motor symptoms; cerebellar features (wide-based gait; cerebellar dysarthria; uncoordinated limb movements; or spontaneous, gaze-evoked, or positional downbeat nystagmus); recurrent choking within 5 yr after the onset of motor symptoms; atrophy on MRI of the putamen, middle cerebellar peduncle, pons, or cerebellum; hypometabolism on FDG-PET in the putamen, brain stem, or cerebellum
Possible MSA-C: parkinsonism; atrophy on MRI of the putamen, middle cerebellar peduncle, or pons; hypometabolism on FDG-PET in the putamen; presynaptic nigrostriatal dopaminergic denervation on SPECT or PET
Features supporting the diagnosis of MSA (red flags) and features not supporting the diagnosis
Supporting: head–neck dystonia; disproportionate antecollis; bent spine (forward, lateral, or both); contractures of the hands or feet; inspiratory sighs; severe dysphonia; severe dysarthria; new or increased snoring; cold hands and feet; emotional incontinence (pathologic laughter or crying); jerky, irregular, or postural or action tremor
Not supporting: classic "pill-rolling" rest tremor, clinically significant neuropathy, hallucinations not induced by drugs, onset after 75 yr of age, family history of ataxia or parkinsonism, dementia (in accordance with DSM-IV criteria), white-matter lesions suggesting multiple sclerosis

* The information is adapted from Gilman et al.,[39] with permission. DSM-IV denotes *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; FDG-PET [^{18}F]-fluorodeoxyglucose–positron-emission tomography; GCI glial cytoplasmic inclusion; and SPECT single-photon-emission computed tomography.

positive glial cytoplasmic inclusions with concomitant olivopontocerebellar atrophy or striatonigral degeneration. Probable multiple-system atrophy is defined as a sporadic, progressive disorder in adults (onset after the age of 30 years), characterized by severe autonomic failure plus predominantly levodopa-refractory parkinsonism (in the parkinsonian subtype) or cerebellar ataxia (in the cerebellar subtype).

Finally, a diagnosis of possible multiple-system atrophy can be made if a sporadic, progressive, adult-onset disorder with predominant parkinsonism or cerebellar ataxia is accompanied by at least one feature suggestive of autonomic failure and at least one of the additional features listed in Table 1. The additional presence of one or more "red flags" further supports a diagnosis of multiple-system atrophy. Exclusion criteria need to be considered as well (Table 1).

ANCILLARY INVESTIGATIONS

The diagnosis of multiple-system atrophy is based on the medical history and neurologic findings. Nevertheless, ancillary investigations may help

Table 2. Ancillary Investigations in MSA.*

Investigation	Characteristic Findings	Notes
Neuroimaging		
CT	Ruling out of MSA-mimicking brain lesions	CT is recommended for patients with contraindications to MRI.
1.5-Tesla MRI	In MSA-P: atrophy of putamen, middle cerebellar peduncle, pons, or cerebellum; "putaminal rim sign" (hyperintense signal of the dorsolateral border of putamen) plus putaminal hypointensity in T_2-weighted sequences; in MSA-C: atrophy of putamen, middle cerebellar peduncle, or pons; "hot-cross-bun sign" (cruciform hyperintensity in the pons) in T_2-weighted sequences	Putaminal rim sign and hot-cross-bun sign have high specificity but low sensitivity for the diagnosis of MSA.[55]
Diffusion-weighted MRI	Increased putaminal diffusivity, differentiating MSA-P from PD; increased diffusivity in the middle cerebellar peduncle, differentiating MSA-P from PD and PSP	Diffusion-weighted MRI has high sensitivity and specificity.[55] Increased diffusivity in the middle cerebellar peduncle has been also observed in fragile X–associated tremor ataxia syndrome.[56]
FDG-PET	Hypometabolism in putamen, brain stem, or cerebellum, which indicates possible MSA-P in patients with atypical parkinsonism[39]; hypometabolism in putamen, which indicates possible MSA-C in patients with idiopathic late-onset cerebellar ataxia[39]	FDG-PET is recommended for patients with contraindications for MRI.
^{18}F-dopa PET, ^{123}Iβ-CIT SPECT, and ^{123}I-FP SPECT	Presynaptic nigrostriatal dopaminergic denervation	This finding is suggestive of MSA-C in patients with idiopathic, late-onset cerebellar ataxia.[39]
^{11}C-raclopride PET and ^{123}I-IBZM SPECT	Postsynaptic dopamine-receptor loss in the striatum, differentiating MSA-P from PD	These tests have suboptimal diagnostic accuracy.
^{18}F-fluorodopamine PET and ^{123}I-MIBG scintigraphy	Normal cardiac radiotracer uptake, differentiating MSA-P from PD[57]	These tests have suboptimal diagnostic accuracy. Normal uptake indicates the presence of spared cardiac postganglionic sympathetic fibers in MSA.
Transcranial ultrasonography†	Hyperechogenicity of the lentiform nucleus (putamen plus globus pallidus) combined with normal echogenicity of the substantia nigra, differentiating MSA-P from PD[58]	The test cannot be performed in about 10% of patients because of the absence of an acoustic temporal bone window.
Autonomic testing		
Urologic domain		
Urodynamic examination	Vesical detrusor overactivity, absence of detrusor–sphincter coordination, bladder atony	Masses, relevant surgical scars, prolapses, and urinary tract infections need to be ruled out in advance; videourodynamics can provide additional anatomical information in particular cases.
Ultrasonography	Large postvoiding residual urine volumes (>100 ml)	The test is recommended for patients reporting voiding difficulties.
Cardiovascular domain		
Standing test	OH with blunted heart-rate increase on standing[39]	Perform the test after the patient has been in the supine position for 10 min. OH can be symptomatic or asymptomatic.
Passive head-up tilt test	OH with blunted heart-rate increase on tilting[39]; decreased heart-rate variability at rest and during orthostatic challenge[59]; normal supine plasma noradrenaline levels, differentiating MSA from PAF[60]†; lack of plasma vasopressin rise during head-up tilt, differentiating MSA from PAF[61]†	The test requires devices for continuous heart rate and blood-pressure monitoring. OH can be symptomatic or asymptomatic. Assessment of noradrenaline levels provides suboptimal diagnostic accuracy. Consider dietary and environmental factors as well as drugs modifying noradrenaline levels. A lack of plasma vasopressin rise during head-up tilt indicates disruption of baroreceptive pathways in MSA.

Valsalva maneuver	Impaired cardiovascular autonomic reflexes with an absence of blood-pressure overshoot during late phase II and phase IV of the maneuver[62,63]	The test requires devices for continuous heart rate and blood-pressure monitoring.
24-hr ambulatory blood-pressure monitoring	Nocturnal hypertension	
Respiratory domain		
Sleep laryngoscopy†	Nocturnal stridor, subclinical paralysis of vocal-cord abductors	
Polysomnography	Sleep apnea	The test is recommended for patients with snoring or excessive daytime sleepiness; it is also indicated for the diagnosis of RBD.
Gastrointestinal domain		
Videofluoroscopic swallow test	Silent aspiration	The test is recommended for patients with swallowing difficulties, excessive cough, or drooling (high suspicion of incipient dysphagia).
Measurement of colon-transit time[43] and rectal manometry†	Loss of anal-sphincter relaxation, decreased anal tone	
Anal-sphincter electromyography†	Anal-sphincter abnormalities, differentiating MSA-P from PD and MSA-C from idiopathic late-onset cerebellar ataxia[64]	The test has suboptimal diagnostic accuracy; it does not distinguish MSA-P from PSP. A history of multiple or traumatic deliveries, lower abdominal surgery, prostatectomy, hemorrhoidectomy, and chronic constipation may produce abnormal results.
Thermoregulatory domain		
Thermoregulatory sweat test†	Rapidly progressive failure of whole-body sweating, differentiating MSA-P from PD[44]	
Quantitative sudomotor axon reflex test†	Normal findings, differentiating MSA-P from PD[65]	Normal findings indicate sparing of skin postganglionic sympathetic innervation in MSA.
Laboratory investigations		
Clonidine growth hormone stimulation test†	Absence of rise in plasma growth hormone level, differentiating MSA-P from PD and PSP[65,66]	The test has suboptimal diagnostic accuracy. The absence of an increase in plasma growth hormone indicates α_2 adrenoreceptor loss in the hypothalamus in MSA.
Arginine growth hormone stimulation test†	Absence of rise in plasma growth hormone level, differentiating MSA-P from PD[67]	The absence of an increase in plasma growth hormone indicates disruption of the hypothalamopituitary axis in MSA. The test does not distinguish between MSA-C and idiopathic, late-onset cerebellar ataxia.
Genetic testing	*COQ2* mutations (in Japanese patients)[14]; absence of mutations associated with fragile X–associated tremor ataxia syndrome, Friedreich's ataxia, and SCA types 1, 2, 3, 6, and 17[54] in cases of a cerebellar presentation	
Other testing	Normal results of tests for vitamin B_1 deficiency, paraneoplastic ataxia, anti-GAD ataxia, gluten ataxia, post–Epstein–Barr virus cerebellitis, and Hashimoto's thyroiditis[54] for patients with a cerebellar presentation	
Neuropsychological testing	Frontal executive dysfunction,[46] ruling out overt dementia[39]	

* There are no established guidelines for ancillary testing in cases of suspected MSA. Test results that may help rule out conditions that mimic MSA or that support the clinical diagnosis are listed. CT denotes computed tomography, ^{123}Iβ-CIT 2β-carbomethoxy-3β-(4-iodophenyl)tropane, ^{123}I-FP ioflupane, ^{123}I-IBZM iodobenzamide, ^{123}I-MIBG metaiodobenzylguanidine, MRI magnetic resonance imaging, OH orthostatic hypotension, PAF pure autonomic failure, PD Parkinson's disease, PSP progressive supranuclear palsy, RBD rapid-eye-movement sleep behavior disorder, and SCA spinocerebellar ataxia.

† This test is not routinely used and therefore should be considered investigational.

confirm the diagnosis, rule out alternative causes, and tailor management strategies (Table 2).

PRINCIPLES OF THERAPY

Only symptomatic therapy is available at present, including pharmacologic and nonpharmacologic approaches (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Unfortunately, the evidence level is low for these approaches, with few exceptions. Most of the commonly used drugs are prescribed off-label.[68] We recommend a multidisciplinary management approach to optimally address the patients' needs.[69]

SYMPTOM MANAGEMENT

Motor Features

In the parkinsonian subtype of multiple-system atrophy, a slow increase in the levodopa dose is advisable to minimize exacerbation of orthostatic hypotension, edema, and nausea. A transient beneficial response to levodopa is seen in as many as 40% of patients.[5] Levodopa withdrawal in patients with no apparent response occasionally causes abrupt and sometimes irreversible worsening of motor abnormalities. Complete discontinuation of levodopa treatment is therefore not recommended for patients who do not have major side effects. Dopamine agonists are less likely to provide a motor benefit in multiple-system atrophy but may be tried in cases of levodopa-induced dystonia; evidence for the effectiveness of amantadine, a selective antagonist of NMDA receptors, is controversial.[70] Treatment with amantadine can be attempted, but if no amelioration is achieved, it should be discontinued. Local botulinum toxin injections can be helpful for disabling hand, foot, or axial dystonia.

There is no specific therapy available for cerebellar symptoms. Clonazepam may ameliorate myoclonus or action tremor in multiple-system atrophy. Open-label gabapentin[71] and buspirone[72] have also been effective in single cases.

Complementary neurorehabilitation programs, including occupational, physical, and speech therapy, can be helpful for patients with the parkinsonian or cerebellar subtype in preventing choking and falls and in augmenting general coping and communication abilities.[73]

Nonmotor Features

Patients with multiple-system atrophy who have neurogenic bladder symptoms should be screened regularly for urinary tract infections. Urinary urge incontinence due to detrusor overactivity can be treated with antimuscarinic agents. However, anticholinergic side effects, such as confusion and cognitive worsening, must be monitored. Botulinum toxin injections in the detrusor muscle may be tried for patients whose condition does not respond to treatment with antimuscarinic agents, and a 10° to 20° head-up tilt during sleep and bedtime administration of desmopressin can ameliorate nocturia. Clean intermittent self-catheterization is the first-line therapy for urinary retention with postvoid residual volumes above 100 ml. Unfortunately, this approach can cause urethral ulceration in the long term, and suprapubic indwelling catheterization may become necessary. Preliminary evidence suggests the use of a bladder stimulator as a possible alternative to self-catheterization for patients with multiple-system atrophy. Add-on pharmacologic therapies for urinary retention are designed either to enhance vesical detrusor contractility (cholinergic agents) or to promote urethral smooth sphincter relaxation (α_1-adrenoreceptor antagonists).[74] Sildenafil, a phosphodiesterase type 5 inhibitor, can reverse erectile dysfunction in men with multiple-system atrophy, but worsening of orthostatic hypotension is a recognized side effect.[75] Intracavernous injection of vasodilatory prostaglandins (e.g., alprostadil) can be used as an alternative approach. No data are available on the management of sexual dysfunction in women with multiple-system atrophy.

Patients with orthostatic hypotension should be trained to recognize and avoid triggers such as rapid postural change, heavy meals, straining while coughing or passing stool, and exposure to hot temperatures. If patients feel light-headed (dizzy), physical countermaneuvers such as crossing the legs, squatting, or tensing muscles may prevent syncope. Other nonpharmacologic measures to ameliorate orthostatic hypotension include increasing water and salt intake, keeping the head of the bed raised during sleep, and using compression stockings or abdominal binders.[40]

In patients with severe orthostatic hypotension, pharmacologic measures are advisable to

minimize the risk of injurious falls. Drugs with hypotensive side effects (e.g., long-acting calcium antagonists and antianginal agents) should be avoided or at least administered in the evening. Midodrine and droxidopa, sympathomimetic agents that increase arteriolar tone, are specifically licensed by the Food and Drug Administration for the symptomatic treatment of neurogenic orthostatic hypotension.[76-79] Off-label administration of fludrocortisone can be helpful, in addition to increasing the intravascular volume.[80] Beneficial effects have also been reported for a range of other drugs used off-label to treat orthostatic hypotension associated with autonomic failure.[81-85] Exacerbation of supine hypertension is a frequent side effect of therapies for orthostatic hypotension, and patients receiving such therapies should therefore be monitored. In the case of supine hypertension, recumbence should be avoided in the daytime, and a snack before bedtime as well as a head-up tilt position during sleep may control milder forms of nocturnal hypertension. If a reverse-dipping profile (i.e., a nocturnal increase in blood pressure with respect to daytime) is documented during 24-hour ambulatory blood-pressure monitoring and does not respond to nonpharmacologic measures, bedtime administration of short-acting antihypertensive agents may be considered. Postprandial hypotension can be minimized by avoiding both alcohol and excessive single-meal caloric intake or by increasing water and coffee consumption. In severe cases, caffeine,[86] octreotide,[87] or acarbose[88] administration before eating may be helpful.

Continuous positive airway pressure — or, in resistant cases, biphasic positive airway pressure — is the therapy of choice for patients with multiple-system atrophy who have isolated nocturnal inspiratory stridor or sleep apnea.[89] Unilateral botulinum toxin injection in the vocal-cord adductors[90] may be considered for more severely affected patients. Tracheostomy[89] may effectively relieve airway obstruction at the laryngeal level and prevent respiratory crisis due to acute bilateral paralysis of the vocal-cord abductors, but it cannot eliminate the risk of sudden death, because fatal sleep apnea can still occur.

Oral glycopyrrolate[91] or botulinum toxin injections in the salivary glands[92] (both of which decrease saliva production) can relieve the drooling that results from impaired swallowing in advanced multiple-system atrophy. Liquid thickeners (e.g., honey) and a chin-down posture while swallowing can prevent choking in dysphagic patients. In advanced stages, a percutaneous endoscopic gastrostomy allows for enteral feeding and lowers the risk of aspiration pneumonia, but it needs to be discussed with the patient well in advance in order to obtain informed consent. Constipation can be very difficult to treat in patients with multiple-system atrophy. Satisfying results are likely to be achieved if alimentary measures are combined with regular administration of osmotic bulking agents.[93]

Low-dose clonazepam at bedtime can be considered as treatment for severe rapid-eye-movement sleep behavior disorder, but it may aggravate nocturnal stridor or sleep apnea. Preliminary evidence suggests that melatonin may be an alternative treatment in this situation.[94]

Cognitive impairment in patients with multiple-system atrophy does not usually require treatment, but pharmacologic intervention may be needed for those with severe depression, anxiety, or emotional incontinence. Selective serotonin-reuptake inhibitors are preferable to tricyclic antidepressants because they are more effective and less likely to worsen orthostatic hypotension and urinary retention.

TOWARD DISEASE MODIFICATION

Multiple-system atrophy–specific biomarkers are needed to facilitate the early identification and enrollment of patients in disease-modifying clinical trials, at early or even presymptomatic disease stages. Perhaps surprisingly, blood and cerebrospinal fluid α-synuclein levels appear to be neither sensitive nor specific for multiple-system atrophy. Phosphorylated oligomeric α-synuclein or other markers, such as neurofilament light chain, FLT3 ligand, total tau, or amyloid β42, which may also be combined with α-synuclein, need to be explored further as candidate biomarkers in body fluids.[95] Preliminary evidence suggests that positron-emission tomography (PET) with ^{11}C-2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy) benzoxazole, an α-synuclein ligand, may allow visualization of the density of glial cytoplasmic inclusions in regions of the brain in vivo.[96] If

replicated and standardized, this approach may become an effective diagnostic and prognostic molecular imaging marker of multiple-system atrophy.

Thanks to research consortia such as the European Multiple System Atrophy Study Group, the French Multiple System Atrophy Reference Center, and the U.S. Autonomic Disorders Consortium, several intervention trials of orally active candidate neuroprotective agents have been completed in the past decade, using rates of motor decline as primary outcome measures and findings from magnetic resonance imaging or PET imaging as secondary outcome measures (see Table S2 in the Supplementary Appendix). Despite preclinical evidence in favor of neuroprotection, thus far, riluzole,[35] minocycline,[97] rifampin (also called rifampicin),[98] and rasagiline[99] have shown no benefit. Several factors may account for the therapeutic failure seen in these trials. Currently available multiple-system atrophy preclinical models may not reflect the pathologic complexity of multiple-system atrophy, preclinical interventional protocols may be substantially different from human ones, and clinical end points may be insufficient to detect disease-modifying effects in the short term. Moreover, a putative neuroprotective compound might be effective in early or even preclinical stages of the disease but be futile in later stages, when much of the neuronal reserve has already been lost.

A randomized, placebo-controlled trial showed that intraarterial infusion of autologous mesenchymal stem cells, followed by three intravenous stem-cell infusions, 1 month apart, in patients with the cerebellar subtype attenuated clinical progression as well as the loss of cerebral glucose metabolism and gray-matter density at 1 year of follow-up. However, cerebral ischemic lesions (asymptomatic in all but one patient) were seen in both the placebo group and the treatment group.[100] These may have been related to the administration procedure itself, but stem-cell–induced asymptomatic strokes in some patients cannot be ruled out. The exact mechanism of action of stem-cell therapy in multiple-system atrophy is also unclear at present. If they do not replace lost neurons, stem cells might prevent neurodegeneration by releasing neurotrophic factors or attenuating neuroinflammation.[100,101] In our opinion, the outcome of mesenchymal stem-cell therapy for multiple-system atrophy will depend on carefully designed trial protocols that are informed by preclinical studies.

Future trials will benefit from accelerated interventional target discovery, biomarker development, and early patient recruitment. To this purpose, a global multiple-system atrophy registry (GLOMSAR) has been established by the International Parkinson and Movement Disorder Society Study Group on Multiple System Atrophy with the support of the U.S. Multiple System Atrophy Coalition (www.multiple-system-atrophy.org).

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We dedicate this review to Kerry Simon and all patients with multiple-system atrophy under our care, whose fight against this challenging disease we admire. We thank Sid Gilman and Ryan Walsh for providing their expert opinion on the review.

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