Multiple system atrophy: advances in pathophysiology, diagnosis, and treatment

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Multiple system atrophy is an adult-onset, sporadic, and progressive neurodegenerative disease. People with this disorder report a wide range of motor and non-motor symptoms. Overlap in the clinical presentation of multiple system atrophy with other movement disorders (eg, Parkinson's disease and progressive supranuclear palsy) is a concern for accurate and timely diagnosis. Over the past 5 years, progress has been made in understanding key pathophysiological events in multiple system atrophy, including the seeding of α-synuclein inclusions and the detection of disease-specific α-synuclein strains. Diagnostic criteria were revised in 2022 with the intention to improve the accuracy of a diagnosis of multiple system atrophy, particularly for early disease stages. Early signals of efficacy in clinical trials have indicated the potential for disease-modifying therapies for multiple system atrophy, although no trial has yet provided unequivocal evidence of neuroprotection in this rare disease. The advances in pathophysiology could play a part in biomarker discovery for early diagnosis as well as in the development of disease-modifying therapies.

Introduction

Multiple system atrophy is a rare, rapidly progressive, fatal neurodegenerative disease; the median duration from symptom onset to death is less than 9 years.[1] The estimated incidence of multiple system atrophy is 0·6 per 100 000 person-years and increases markedly in people older than 50 years.[2] The crude prevalence of multiple system atrophy differs by geographical region, ranging from 0·5 per 100 000 individuals in Spain to 17 per 100 000 individuals in Japan.[1,2]

Individuals with multiple system atrophy report a wide range of motor and non-motor symptoms and the clinical presentation can overlap with that of other movement disorders. The current understanding is that the disease encompasses various clinical syndromes, including parkinsonism, cerebellar ataxia, and autonomic failure. Any combination of these indications can occur to a variable degree.[3] The clinical diagnosis of multiple system atrophy is based on consensus diagnostic criteria that were revised in 2022 by the Task Force of the International Parkinson and Movement Disorders Society.[4] Although there is rarely a clear difference in the predominance of motor symptoms, two main motor subtypes can be defined, according to the current diagnostic criteria: a parkinsonism-predominant variant and a cerebellar-predominant variant.[4] Early autonomic failure has consistently been reported as a predictor of poor prognosis.[5,6] Advanced disease is characterised by increasing disability (ie, frequent falls, wheelchair dependency, unintelligble speech, severe dysphagia, and residential care) between 5·5 years and 8 years after symptom onset.[7]

Neuropathologically, the features of multiple system atrophy are neuronal loss and accompanying gliosis in the basal ganglia, the pons, the inferior olivary nuclei, the cerebellum, and the spinal cord. The predominant histopathological finding is α-synuclein-immunoreactive inclusion bodies in oligodendrocytes, which are known as glial cytoplasmic inclusions.[4]

In this Review, we aim to provide an overview of the main achievements in multiple system atrophy research over the past 5 years. We discuss the revised clinical diagnostic criteria; describe key pathophysiological advances, including about α-synuclein strains in tissue and biofluids that are specific to multiple system atrophy; analyse developments in fluid and imaging biomarkers; and evaluate therapeutic developments.

Clinical presentation and diagnostic criteria

Due to overlapping clinical presentations, multiple system atrophy is often misdiagnosed as other movement disorders, including Lewy body diseases (eg, Parkinson's disease and dementia with Lewy bodies), progressive supranuclear palsy, and genetic or sporadic adult-onset ataxias.[3] Diagnostic criteria for multiple system atrophy were updated in 2022 by the International Parkinson and Movement Disorders Society.[4] The latest iteration followed a stringent and transparent methodological framework and these criteria distinguish four levels of diagnostic certainty: neuropathologically established multiple system atrophy; clinically established multiple system atrophy; clinically probable multiple system atrophy; and a research category of possible prodromal multiple system atrophy (figure 1).[4]

Neuropathologically established multiple system atrophy is the gold standard diagnosis. The criteria refer to post-mortem findings in the brain of widespread glial cytoplasmic inclusions of phosphorylated α-synuclein, associated with striatonigral or olivopontocerebellar degeneration.[4]

The different categories of the criteria were developed to meet different needs. The clinically established category for multiple system atrophy was developed to maximise specificity and address the need for clinical counselling; clinically probable and possible prodromal multiple system atrophy were primarily intended for early diagnosis and research purposes. Entry criteria for all categories are a negative family history and symptom onset after the age

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Neuro-pathological criteria	Neuropathologically established multiple system atrophy • Widespread and abundant CNS α-synuclein-immunoreactive glial cytoplasmic inclusions (Papp-Lantos inclusions) • Neurodegenerative changes in striatonigral or olivopontocerebellar brain regions		
Clinical diagnostic criteria	Sporadic disease with an age at onset of >30 years and a progressive disease course		
	Clinically established multiple system atrophy	Clinically probable multiple system atrophy	Possible prodromal multiple system atrophy*

	• Autonomic failure, at least one of:
	  • Post-void urinary residual volume ≥100 mL
	  • Urinary urge incontinence
	  • ≥20/10 mm Hg blood pressure fall within 3 min in the upright position with insufficient compensatory heart rate increase
	• Clinical motor features, at least one of:
	  • Levodopa-refractory parkinsonism
	  • Cerebellar syndrome (at least two clinical features of cerebellar impairment†)
	• At least two supportive motor‡ or non-motor§ clinical features
	• At least one supportive brain MRI finding¶
		• At least two core clinical features of:
		  • Autonomic failure, defined as (at least one is required):
		  • Unexplained voiding difficulties resulting in urinary post-void residual volume
		  • Unexplained urinary urge incontinence
		  • ≥20/10 mm Hg blood pressure fall within 10 min in the upright position with insufficient compensatory heart rate increase
		  • Parkinsonism
		  • Cerebellar syndrome (at least one clinical feature of cerebellar impairment†)
		• At least one supportive motor‡ or non-motor§ clinical feature
			• At least one of:
			  • REM-sleep behaviour disorder (polysomnography proven)
			  • Neurogenic orthostatic hypotension (≥20/10 mm Hg blood pressure fall within 10 min in the upright position with insufficient compensatory heart rate increase)
			  • Urogenital failure (unexplained erectile dysfunction in males aged <60 years, combined with post-void urinary residual volume >100 mL or unexplained urinary urge incontinence)
			• Clinical motor features, at least one of:
			  • Subtle parkinsonian signs
			  • Subtle cerebellar sign

	Exclusion criteria • Substantial and durable dopaminergic responsiveness (applicable for clinically established and clinically probable multiple system atrophy) • Unexplained loss of olfaction on smell tests or cardiac post-ganglionic noradrenergic denervation on ^{123}I-metaiodobenzylguanidine scintigraphy (latter is only applicable for possible prodromal multiple system atrophy category) • Fluctuating cognitive performance and alertness, with early visuoperceptual impairment • Recurrent visual hallucinations unrelated to medication intake within the first 3 years of disease • Individual fulfils DSM-5 criteria for dementia within the first 3 years of disease • Downgaze supranuclear palsy or slow vertical saccades • Brain MRI findings compatible with other neurological conditions (eg, progressive supranuclear palsy, multiple sclerosis, vascular parkinsonism, cerebellar lesions) • Documentation of an alternative genetic, metabolic, toxic, or immune-mediated condition that might cause autonomic failure, ataxia, or parkinsonism, and can be plausibly associated with the individual's symptoms		

Figure 1: **International Parkinson and Movement Disorders Society clinical diagnostic criteria for multiple systems atrophy**
DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition. REM=rapid eye movement. *Category devised for research purposes, to enable diagnosis of individuals with multiple system atrophy at the earliest symptomatic stage. †Clinical features of cerebellar impairment are gait ataxia, limb ataxia, cerebellar dysarthria, and cerebellar oculomotor features. ‡Supportive motor features: rapid progression; moderate-to-severe postural instability; severe speech impairment or severe dysphagia within 3 years from the beginning of motor symptoms; craniocervical dystonia induced by levodopa in the absence of limb dyskinesia; unexplained Babinski sign; jerky myoclonic postural or kinetic tremor; and postural irregularities (ie, antecollis, camptocormia, Pisa syndrome, contractures of the hands and feet). §Supportive non-motor features: stridor; inspiratory sighs; cold violaceus hands or feet; erectile dysfunction (for male individuals aged <60 years; if isolated, it does not fulfill the autonomic criterion for the diagnosis of clinically probable multiple system atrophy); and emotional incontinence. ¶For parkinsonism-predominant multiple system atrophy: atrophy of the putamen, middle cerebellar peduncle, pons, or cerebellum; increased diffusivity of the putamen and the middle cerebellar peduncle; and the hot-cross-bun sign. For cerebellar-predominant multiple system atrophy: atrophy of the putamen, middle cerebellar peduncle, and pons; increased diffusivity of the putamen; and hot-cross-bun sign.

of 30 years. Core clinical features for a diagnosis of clinically established multiple system atrophy are severe autonomic failure (ie, urogenital failure or neurogenic orthostatic hypotension) accompanied by poorly levodopa-responsive parkinsonism or two or more cerebellar signs, including gait ataxia, limb ataxia, cerebellar dysarthria, and oculomotor dysfunction.[4] In addition to the core clinical features, at least two supportive motor or non-motor clinical features of multiple system atrophy, and at least one brain MRI finding, must be present (figure 2). Clinical findings or MRI findings that suggest an alternative diagnosis of Parkinson's disease (eg, substantial and persistent dopaminergic responsiveness or unexplained anosmia), dementia with Lewy bodies (eg, cognitive fluctuations, variations in attention and alertness, and early decline in visuoperceptual abilities), progressive supranuclear palsy (eg, downgaze supranuclear palsy, slowing of vertical saccades), vascular parkinsonism (eg, strategic infarcts affecting the basal ganglia on neuroimaging), or other secondary or hereditary causes of parkinsonism or cerebellar ataxia should be carefully excluded.[4]

Criteria for a diagnosis of clinically probable multiple system atrophy aim to achieve a balance between sensitivity and specificity, and have fewer requirements than for clinically established multiple system atrophy. A combination of at least two core clinical features—ie, autonomic failure, parkinsonism, or cerebellar ataxia—should be present. Autonomic failure can be milder for a diagnosis of clinically probable multiple system atrophy, including delayed orthostatic hypotension and voiding difficulties with post-void residual volumes (ie, <100 mL). For people with parkinsonism-predominant multiple system atrophy, parkinsonism (bradykinesia plus an additional symptom) is required; variable levodopa responsiveness is possibly observed in the first few years after drug initiation. One cerebellar sign is sufficient for individuals with cerebellar-predominant multiple system atrophy.

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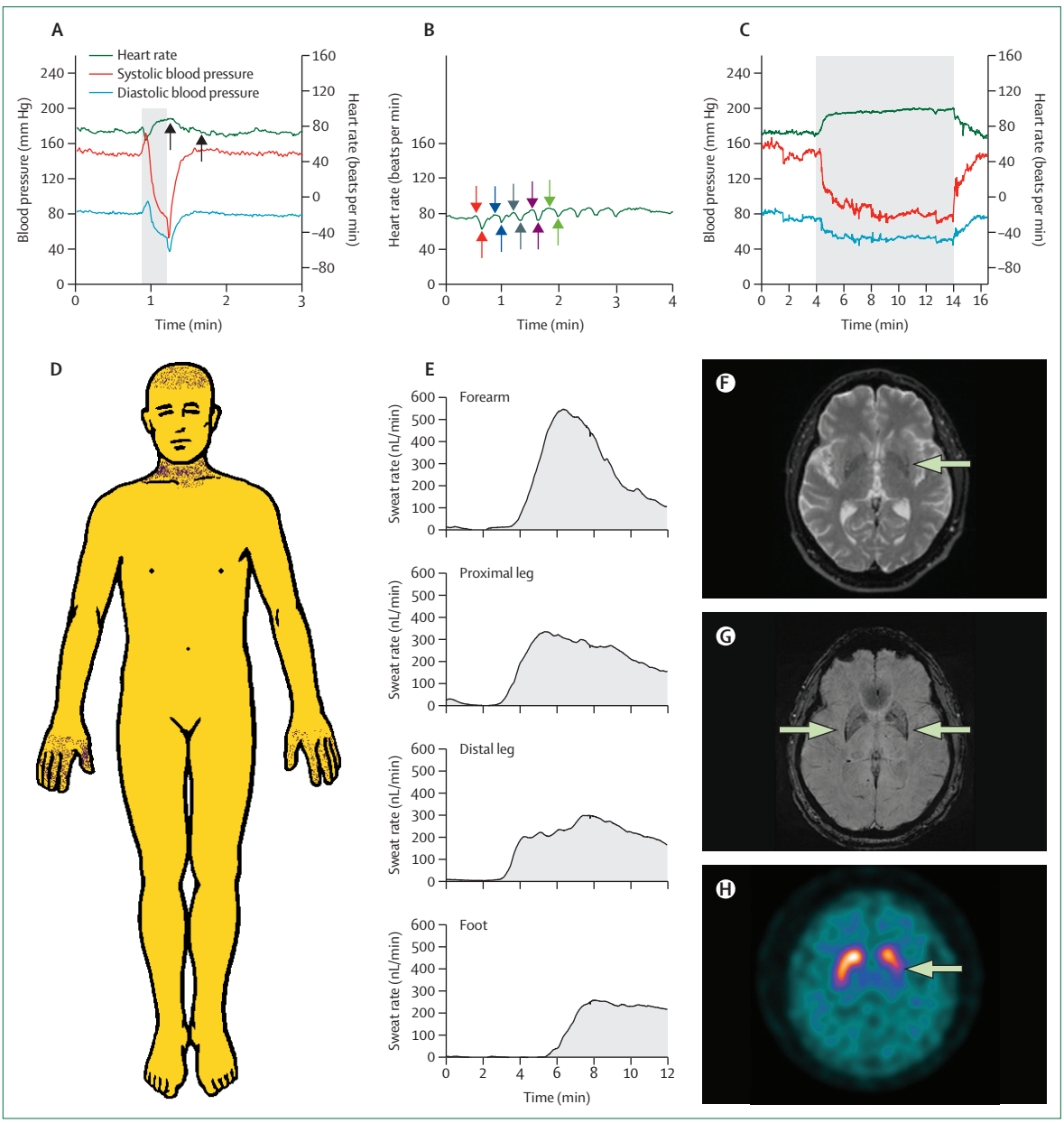

Figure 2: **Findings characteristic of multiple system atrophy**
(A) Blood pressure responses to the Valsalva manoeuvre (shown in grey), showing absent late phase 2, prolonged blood pressure recovery time, and absent phase 4 overshoot with normal heart rate response (maximum and minimum heart rate shown with arrows). (B) Heart rate responses to deep breathing (inhalation shown with downward arrows and exhalation shown with upward arrows), which are normal. (C) Tilt table testing, which shows blood pressure of 168/90 mm Hg after 5 min of lying supine, falling to 100/74 mm Hg after 3 min of head-up tilt to 70°. Heart rate rose from 74 bpm to 97 bpm with neurogenic orthostatic hypotention criteria fulfilled at the 10 min read-out (tilt shown in grey). (D) Thermoregulatory sweat test, which shows anhidrosis (yellow) of 98% of the body, with preserved sweating (purple) over the forehead and hands. (E) Quantitative sudomotor axon reflex testing, which shows normal sweat responses at the forearm, proximal and distal leg, and foot. (F) Head MRI shows a slight increase in diffusion (green arrow) over the left putamen, (G) with bilateral putaminal hypointensity on susceptibility-weighted imaging (green arrows). (H) Ioflupane [^{123}I] SPECT imaging shows reduced uptake in the left putamen (green arrow).

No brain MRI finding is required for a diagnosis of clinically probable multiple system atrophy; nevertheless at least one supportive motor or non-motor clinical feature must be present, and no exclusion criterion among those that are also valid for diagnosing clinically established multiple system atrophy should be reported.

Several ancillary investigations—eg, functional neuroimaging, neurophysiological assessments, and analysis of fluid biomarkers—might support the diagnosis of clinically established and clinically probable multiple system atrophy, especially in unclear cases. These tests, however, have not been included in the mandatory

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examinations for multiple system atrophy diagnostic investigations, due to their unavailability outside of tertiary referral centres.[4]

Possible prodromal multiple system atrophy has been introduced as a category in the updated diagnostic criteria, for research purposes. This new category acknowledges that, years before motor features emerge, individuals with multiple system atrophy might develop non-motor features,[8–11] such as isolated rapid eye movement (REM)-sleep behaviour disorder or pure autonomic failure (panel). The presence of REM-sleep behaviour disorder and cardiovascular or urogenital autonomic failure are entry criteria for a diagnosis of possible prodromal multiple system atrophy in individuals older than 30 years who show subtle parkinsonian or cerebellar signs. Up to 80% of individuals with isolated REM-sleep behaviour disorder develop a clinically overt α-synucleinopathy over time, with Lewy body diseases (eg, Parkinson's disease) more commonly evolving from REM-sleep behaviour disorder than multiple system atrophy.[8] By comparison with people who go on to develop Lewy body diseases, individuals with multiple system atrophy more often have preserved olfaction and cognition.[12] Likewise, up to one-third of individuals with pure autonomic failure might, over time, develop a Lewy body disease or multiple system atrophy.[9] In this context, intact olfaction, severe bowel and bladder disturbances, and a central pattern of autonomic dysfunction (ie, preserved cardiac noradrenergic innervation and serum noradrenalin levels above 100 pg/mL) might suggest multiple system atrophy at a premotor stage.[9,11] Rigorous exclusion criteria reduce the likelihood of misdiagnosing prodomal multiple system atrophy as Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy, and other secondary or genetic presentations that resemble multiple system atrophy. Ancillary investigations are especially important to distinguish individuals with a high probability of developing multiple system atrophy in the future versus those whose condition will develop into a Lewy body disease or retain a non-motor clinical presentation.[4]

The 2022 International Parkinson and Movement Disorders Society diagnostic criteria for clinically established and clinically probable multiple system atrophy were validated retrospectively in three large neuropathological case series.[13–15] A validation of the possible prodromal multiple system atrophy category has not been published yet. The validation studies showed variable accuracy for the category of clinically probable multiple system atrophy; however, all studies confirmed high specificity for the category of clinically established multiple system atrophy,[13–15] albeit at the expense of low sensitivity. In one of the three studies,[15] omitting MRI criteria from the clinically established criteria did not result in a change in specificity but improved the sensitivity. Further prospective studies are necessary to identify any potential biases associated with retrospective validation of diagnostic criteria and to ascertain whether the diagnostic importance of MRI features has been underestimated. Overall, a combination of clinical features and advanced MRI algorithms (possibly supported by machine learning[16]) could provide the highest diagnostic yield in clinical practice.

Panel: A case of autonomic failure with subtle motor symptoms followed by parkinsonism and ataxia

A man aged 52 years initially presented for orthostatic hypotension with a 2-year history of intermittent light-headedness. He reported a 5-year history of erectile dysfunction followed by urinary frequency and urgency. Post-void residual volume was 254 mL and he subsequently required urinary catheterisation for retention. His partner reported that he thrashed in bed while acting out his dreams. On examination, he had a fine, postural high-frequency tremor, a reduced right-sided arm swing, and brisk reflexes. Autonomic function tests (figure 2) showed cardiovascular adrenergic failure with orthostatic hypotension on tilt with blunted heart rate response, whereas cardiovagal function and postganglionic sudomotor function were preserved. Thermoregulatory sweat test showed global anhidrosis (98%), suggestive of a central thermoregulatory disorder in the setting of normal quantitative sudomotor axon reflex testing. Laboratory testing was notable for supine norepinephrine of 203 pg/mL, which rose to 290 pg/mL after 10 min of standing. He was diagnosed with pure autonomic failure, with recommendations for non-pharmacological and pharmacological treatment of autonomic symptoms.

3 years later, the same individual presented with new symptoms of imbalance, impaired fine motor skills, and raspy speech. On examination, he had dysarthria with inspiratory sighs, right hemi-parkinsonism, and subtle ataxia. Ioflupane [^{123}I] SPECT imaging showed loss of dopaminergic terminals in the left putamen. Head MRI showed increased diffusivity of the left putamen and bilateral putaminal hypointensity on susceptibility-weighted imaging. Repeat autonomic function testing showed a similar pattern and degree of autonomic failure.

The initial presentation was autonomic failure with evidence of CNS involvement, based on autonomic function testing, supine norepinephrine levels higher than 100 pg/mL, and a history of rapid eye movement-sleep behaviour disorder. Motor findings were subtle; there was no overt parkinsonism or ataxia. Using the current Movement Disorders Society criteria for multiple system atrophy,[4] this individual would meet diagnostic criteria for possible prodromal multiple system atrophy at initial presentation. The early clinical and laboratory features suggest a high risk for development of multiple system atrophy. At the 3-year repeat examination, he met the criteria for clinically established multiple system atrophy.

Advances in pathophysiology and pathogenesis

The core neuropathological feature of multiple system atrophy is accumulation of aggregated α-synuclein in oligodendrocytes, which form glial cytoplasmic inclusions (figure 3). Neuronal cytoplasmic inclusions are also comprised of misfolded α-synuclein and can be observed in the brains of individuals with multiple system atrophy, albeit less frequently than glial cytoplasmic inclusions. The presence of these inclusions, as well as associated neurodegenerative changes in striatonigral or olivopontocerebellar structures, confirms the diagnosis of neuropathologically established multiple system atrophy.[4] The main component of glial cytoplasmic inclusions in multiple system atrophy is α-synuclein phosphorylated at serine residue 129, and the density of these inclusions

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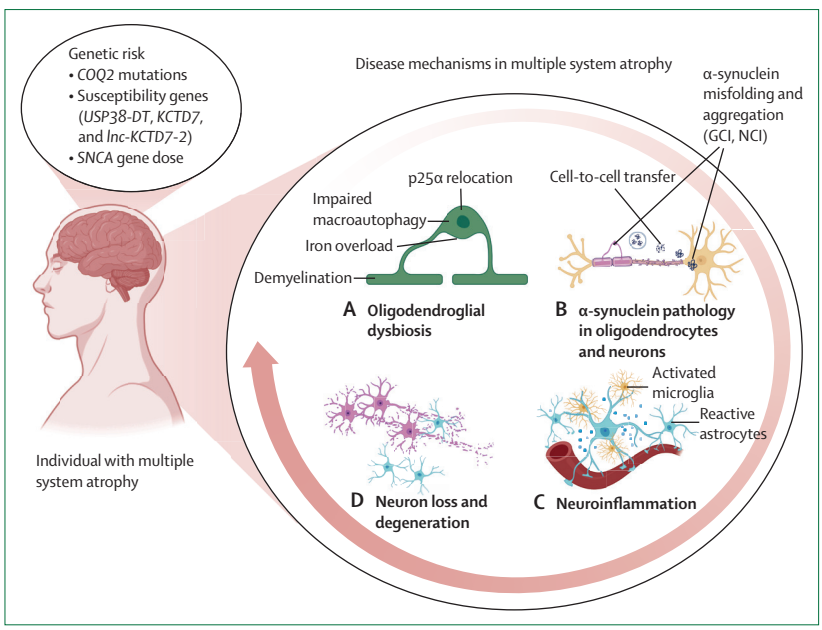

Figure 3: **Hypothesis on pathophysiological events in multiple system atrophy**
Key pathophysiological events include (A) early oligodendroglial dysbiosis, (B) aggregation of α-synuclein, and (C) neuroinflammation, eventually leading to (D) cell death and neurodegeneration; direction of arrow indicates hypothesised sequential cascade. Somatic copy number gains in the *SNCA* gene and differential *SNCA* overexpression might contribute to the aggregation of α-synuclein in multiple system atrophy. GCI=glial cytoplasmic inclusions. NCI=neuronal cytoplasmic inclusions.

correlates with neuron loss. In addition to α-synuclein, glial cytoplasmic inclusions contain multiple proteins and are enriched with lysosomes and peroxisomes.[17,18]

Glial cytoplasmic inclusions comprise two types of α-synuclein filaments, each consisting of two protofibrils.[19] These filaments are distinct from those forming Lewy bodies in Parkinson's disease and dementia with Lewy bodies as they are characterised by a specific β-sheet structure.[19–21] These findings support the idea that synucleinopathies are characterised by disease-specific α-synuclein conformers or strains, which might account for differences in affected cell types or brain regions. Seed aggregation assays and PET ligands, which are being developed for diagnostic purposes, exploit these differences in α-synuclein strains.[22,23]

Although substantial progress has been made over the past decade in understanding the mechanisms underlying α-synuclein misfolding and aggregation in oligodendrocytes, these processes remain incompletely understood. Early autopsy and in vitro studies in post-mortem brain tissue and induced pluripotent stem cells confirmed the presence of *SNCA* gene transcripts and the expression of α-synuclein mRNA in oligodendrocytes.[24,25] However, the expression of α-synuclein in oligodendrocytes might be insufficient to initiate the aggregation process, and other mechanisms, such as relocation to the cytoplasm of the tubulin polymerisation-promoting phosphoprotein p25α (figure 3)—a protein essential for myelin formation—could be necessary. Overexpression of p25α in oligodendrocytes facilitates the recruitment of endogenous α-synuclein to form aggregates, which provides additional support for an early alteration of p25α cellular homoeostasis in the pathogenesis of multiple system atrophy.[26] Furthermore, glial cytoplasmic inclusions in oligodendrocytes show an increased number of *p25α* gene transcripts and an experimental study showed that the presence of p25α in the cellular milieu had an effect on the secondary stucture of the α-synuclein strain, causing larger inclusion bodies and eliciting pro-degenerative properties, eventually leading to a more severe motor phenotype in animal models.[25,27]

Another possible mechanism for α-synuclein misfolding and aggregation is that neurons could be the primary (or at least a highly contributing) source of α-synuclein, with α-synuclein being a protein tightly connected to synapses (figure 3).[28,29] This hypothesis aligns with the observation that the formation of α-synuclein-positive nuclear inclusions might be an early event in disease development and that oligodendrocytes can take up extracellular α-synuclein, which can recruit endogenous α-synuclein to form insoluble, highly aggregated assemblies.[26,30,31] Another mechanism could be the incorporation of neuronal α-synuclein aggregates by oligodendrocytes via pruning of diseased axonal segments.[32] The substantial overlap of the sarkosyl-insoluble proteome in multiple system atrophy and Parkinson's disease brain extracts provides additional evidence for a possible neuronal origin of α-synuclein in glial cytoplasmic inclusions.[18] Finally, additional mechanisms could contribute to the accumulation of α-synuclein aggregates in oligodendrocytes, such as reducing its extracellular secretion via the SNARE complex or impaired lysosomal function.[33]

Not much is known about the progression of glial synucleinopathy in multiple system atrophy, and no hypothesis similar to that for Parkinson's disease (ie, the Braak model or the brain-first *vs* body-first model) has yet been formulated. Studies in animal models have induced a progressive neuronal (but not an oligodendroglial) synucleinopathy after inoculation with α-synuclein derived from post-mortem brain tissue or brain homogenates from people with multiple system atrophy.[34–36] Moreover, inoculation of α-synuclein could not reliably induce a synucleinopathy in wild-type mice, pointing to specific changes in cell homoeostasis that are a prerequisite for seeding α-synuclein aggregates in multiple system atrophy. One reason for these results might be a too short observation period after inoculation to induce substantial glial α-synuclein pathology. In a mouse model, an increasing glial α-synuclein burden was noted 7 months after inoculation with mouse α-synuclein preformed fibrils; at the same time, neuronal inclusions were observed as early as 1 month after inoculation.[37] Additional support for extended observation periods necessary to induce glial pathology after inoculation with α-synuclein comes from a study in non-human primates.[38] In this study, subtle behavioural changes and moderate brain

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pathological alterations reminiscent of multiple system atrophy—such as the loss of nigral dopamine and striatal medium spiny neurons, demyelination, and loss of oligodendrocytes, inflammation, and a glial and neuronal synucleinopathy—were observed 2 years after injection of glial cytoplasmic inclusion-containing brain fractions derived from individuals with multiple system atrophy.[38] The neurodegenerative process might require several years after the initial pathological event before symptom onset in people with multiple system atrophy.

Prominent astrogliosis and microgliosis also occur in multiple system atrophy (figure 3). Both features are particularly observed in regions highly involved in the neurodegenerative process, and they correlate with glial cytoplasmic inclusion burden, but not neuronal loss.[39] Growing evidence further suggests that altered iron metabolism, mitochondrial dysfunction, reduced trophic support, impaired maturation of oligodendrocytes, and atypical brain insulin signalling might have roles in the neurodegenerative process. Several of these pathophysiological mechanisms are potential targets for disease-modifying therapies and are currently being pursued in clinical trials in people with multiple system atrophy.

Novel diagnostic and prognostic biomarkers

In the past 5 years, research efforts have intensified to develop diagnostic and prognostic biomarkers for multiple system atrophy,[40] which could even be used in individuals at risk of developing multiple system atrophy or at the earliest prodromal stages of the disease.[41] Furthermore, biomarkers could facilitate longitudinal monitoring of disease progression, potentially leading to development of more effective disease-modifying therapies. Nevertheless, careful clinical examination remains important for the diagnosis of multiple system atrophy and, despite their limitations, disease-specific rating scales—such as the Unified Multiple System Atrophy Rating Scale (UMSARS)—support the assessment of disease progression.[42]

Fluid biomarkers

The most promising molecular markers for multiple system atrophy are associated with the measurement of α-synuclein seeding and aggregation and the detection of increased amounts of neurofilament light chain in blood and CSF. Elevated neurofilament light chain in CSF is thought to reflect injury to myelinated axons, but because this marker can be elevated not only in multiple system atrophy, but also in other atypical parkinsonian disorders, its differential diagnostic yield is reduced when used alone.[43,44] However, in the initial stages of multiple system atrophy, amounts of neurofilament light chain increase over time, suggesting that this biomarker might serve as a useful marker of progression; high amounts of neurofilament light chain have been associated with a poor prognosis.[45]

α-Synuclein seed aggregation assays have high sensitivity and specificity for detecting pathological α-synuclein seeds in the CSF of people with Lewy body diseases, but results are inconsistent in people with multiple system atrophy.[20,46–48] However, this diagnostic inaccuracy might partly be explained by the use of different recombinant α-synuclein monomers as aggregation substrate and differences in incubation conditions.[46] Comprehensive characterisation of kinetic and ligand profiles of α-synuclein seeding aggregation assays are, therefore, crucial to appropriately discriminate synucleinopathies.[48,49] As well as using CSF to detect α-synuclein seeds, homogenates from skin biopsies, nasal swabs, saliva and (most recently) immunoprecipitated blood samples can be used.[40,50,51] α-Synuclein aggregation assays have also predicted the conversion from prodromal stages of synucleinopathies to manifest disease stages.[41,47]

At present, a combination of different biomarker candidates has the greatest potential to improve diagnostic accuracy. A 2020 clinical study using a combination of neurofilament light chain measurements and α-synuclein seeding aggregation assays in CSF showed excellent diagnostic accuracy, distinguishing all individuals with multiple system atrophy from those with Lewy body diseases.[52]

Few molecular biomarkers have been established that can reflect clinical progression in multiple system atrophy, with inconsistent results on longitudinal changes in neurofilament light chain measurements, and glial fibrillary acidic protein levels remaining unchanged over time.[53–55] Early results using kinetic profiling of α-synuclein seeding aggregation assays suggest that an increase in the amount of α-synuclein might be associated with worse clinical progression.[56] Future studies will require inclusion of individuals who have been thoroughly clinically assessed (using validated rating scales and questionnaires) and will need to relate the severity of clinical symptoms to imaging and fluid biomarker findings, if prognostic and surrogate markers of target engagement are to be identified for future disease-modifying clinical trials.

Imaging markers

A large body of evidence suggests that neuroimaging is crucial to distinguish different neurodegenerative movement disorders.[57] MRI is currently the modality that is most broadly available and capable of substantially enhancing diagnostic accuracy,[16] minimising misdiagnosis rates, facilitating early detection, and tracking disease progression. Brain atrophy patterns that are specific to multiple system atrophy can be detected by visual inspection of structural MRI. Commonly reported irregularities in the putamen include a flattened lateral border and T1-weighted and T2-weighted signal intensity changes. Infratentorial changes include atrophy and signal intensity changes in the pons, the middle cerebellar peduncle, and cerebellar hemispheres.[58] Rater-dependent assessments

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are highly variable with respect to sensitivity and specificity in distinguishing multiple system atrophy from Parkinson's disease. A consistent finding, however, is an increased diffusivity in the posterior putamen of individuals with multiple system atrophy, irrespective of the method of diffusivity evaluation (ie, visual inspection *vs* quantification).[58] A common underlying theme in all parkinsonian disorders is the degeneration of the substantia nigra, which can be detected on neuromelanin-sensitive and on susceptibility-weighted MRI images.[59] Although substantia nigra irregularities on iron-sensitive MRI images are similar in Parkinson's disease and multiple system atrophy, hypointensity on susceptibility-weighted or T2* in the posterior putamen suggests aberrant iron deposition and is a valuable additional finding that suggests a diagnosis of multiple system atrophy. Similar to fluid biomarkers, a combination of imaging signs—preferably including quantifiable readouts, such as the degree of atrophy, changes in diffusivity, and iron-sensitive sequences—further improve the discrimination of multiple system atrophy and Parkinson's disease.[16]

Machine learning-supported image quantification has not yet become clinically routine in neurological assessment. Between-scanner and sequence differences,[60] a paucity of harmonisation, and incomplete validation of proposed algorithms are the main reasons for the current disregard of this scientific process. Nevertheless, machine learning-supported quantification of brain atrophy has shown distinct patterns in individuals with multiple system atrophy, and automated post-processing of multimodal imaging (diffusion-weighted and iron-sensitive imaging) has increased the diagnostic accuracy of MRI.[61] The largest multicentre study to date[62] introduced a machine learning-supported imaging score, which yielded high diagnostic accuracy in classifying parkinsonism. The results were robust across different MRI machines and sequence properties.[62]

Previous longitudinal MRI studies in multiple system atrophy revealed progressive atrophy in different brain areas. The rate of progression was more than three-fold higher than control populations that included healthy volunteers and people with Parkinson's disease.[63–65] The brain regions primarily affected by progressive atrophy in multiple system atrophy individuals were the pons, the cerebellar white and grey matter, and the putamen. In some of the studies, these volume changes were accompanied by changes in iron content and diffusivity.[65]

Apart from MRI, radio-tracer imaging has been extensively studied, with several clinical studies suggesting that [^{18}F]fluorodeoxyglucose-PET is particularly useful for differential diagnosis.[58] Metabolic patterns detected by independent observers discriminated different parkinsonian disorders, such as Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy, with high diagnostic accuracy.[66] ^{123}I-metaiodobenzylguanidine—an inactive radiopharmaceutical sympathomimetic—can be used to examine postganglionic cardiac sympathetic innervation, with a reduced radiotracer uptake being a characteristic finding in people with Parkinson's disease, contrasting the findings in individuals with multiple system atrophy.[58] In line with marked neuroinflammation, radioligands binding to the translocator protein of glia showed elevated tracer uptake in brain regions known to be affected by multiple system atrophy, with one clinical study suggesting so-called hotspots of neuroinflammation in the cerebellar white matter and the lentiform nucleus.[22] Despite advances in the past 2 years in the development of α-synuclein binding PET tracers,[23,67] establishing a broadly available, fluorinated α-synuclein PET tracer with an excellent signal-to-noise ratio remains a major unmet need in the field.

Symptomatic management

A multidisciplinary approach to care, with treatment individualised to optimally manage various symptoms of multiple system atrophy, is recommended.[68] Both non-pharmacological and pharmacological treatments can offer symptomatic benefits when implemented stepwise and tailored to the needs of the individual (table 1).

Motor symptoms

Pharmacological therapies primarily target parkinsonism. Natural history studies suggest a beneficial response to levodopa in approximately half of the individuals with multiple system atrophy.[69] However, the response to levodopa is often less robust than in Parkinson's disease, and the drug might induce early and severe dyskinesias and aggravate dystonia. Additionally, the blood pressure-lowering effect of levodopa requires monitoring. Neurorehabilitation therapies remain the mainstay of management in multiple system atrophy, which include physical, occupational, and speech therapy. Physiotherapy is recommended to maintain function and prevent falls; an intensive and supervised approach is beneficial for individuals with the parkinsonian subtype of multiple system atrophy.[70,71] Speech therapy not only improves intelligibility but also dysphagia.[72]

Autonomic symptoms

Neurogenic orthostatic hypotension can be present at the same time as supine hypertension, and individuals with multiple system atrophy and their caregivers should, therefore, be counselled on monitoring supine and standing blood pressure and in the use of non-pharmacological measures. Pharmacological agents to treat orthostatic hypotension include intravascular volume expanders (eg, fludrocortisone) and vasopressor agents (eg, midodrine and droxidopa).[73] Vasopressor agents have been shown in clinical trials to be beneficial and offer shorter responses compared with volume expanders, thus allowing them to be tailored to the individual's activities. In people with supine hypertension, a risk–benefit trade-off between orthostatic hypotension therapy and blood pressure-lowering agents must be applied.[74]

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	Non-pharmacological therapeutic options	Pharmacological therapeutic options (dose range; potential side-effects)
Motor symptoms		
Parkinsonism	Physiotherapy, occupational therapy, speech therapy	Levodopa (up to 1000 mg daily dose; hypotension, dyskinesia, dystonia); amantadine (100 mg three times daily; hallucinations, livedo reticularis, autonomic dysfunction, corneal oedema)
Cerebellar ataxia	Physiotherapy, occupational therapy, speech therapy	..
Dystonia	Physiotherapy, reduce medications that cause dystonia as an adverse drug reaction (eg, levodopa)	Botulinum toxin A injections (up to 300 units; weakness)
Myoclonus	Reduce or stop medications that might cause or aggravate myoclonus (eg, serotonergic and noradrenergic reuptake inhibitors, opiates)	Clonazepam (0·5–2 mg daily; somnolence, hypotension); levetiracetam (250–1000 mg twice daily; personality changes)
Dysarthria	Speech therapy, augmentative and alternative communication devices	..
Dysphagia	Postural changes, reduced meal volumes, slower eating, liquid thickeners, modification of meal consistencies, closed-lid cups, video-assisted swallow therapy; in case of weight loss, additional enteral sip feeding; consider gastrostomy feeding; speech therapy	..
Autonomic symptoms		
Orthostatic hypotension	Patient education, stop medications that cause or aggravate orthostatic hypotension (eg, antihypertensives, anticholinergics), lifestyle adjustments, physical counter manoeuvres, increase fluid and salt, cold water bolus, compression garments (abdominal binders, thigh or waist-high stockings), elevate head of bed	Midodrine (2·5–15 mg three times daily; paresthesias, urinary retention, hypertension); droxidopa (100–600 mg three times daily; dizziness, hypertension); fludrocortisone (0·05–0·2 mg daily; fluid retention, renal failure, hypertension); etilefrine (15–30 mg/day; tremor, urinary retention); pyridostigmine (30–60 mg three times daily; diarrhoea, salivation); atomoxetine (10–18 mg twice daily; nausea, reduced appetite)
Supine hypertension	Limit fluid intake after noon, avoid the supine position after pressor agent intake, elevate head of bed, snack before bedtime, application of heating pad to abdomen, night-time use of continuous positive airway pressure	Losartan (12·5–50·0 mg nightly; dizziness); clonidine (0·1–0·2 mg nightly; fatigue); eplerenon (25–50 mg nightly; arrhythmia); glyceryl trinitrate patch (0·025–0·2 mg/h; dizziness); nifedipine (10–30 mg nightly; swelling, arrhythmia); hydralazine (10–50 mg nightly; nausea, arrhythmia); captopril (6·25–25·00 mg nightly; cough)
Postprandial hypotension	Smaller and more frequent meals, lower carbohydrate meals, alcohol avoidance	Acarbose (50–150 mg three times daily before meals; nausea and vomiting); octreotide (12·5 µg subcutaneous three times daily before meals; urinary, vision symptoms); caffeine (up to 100 mg before meals; tachycardia)
Urinary urgency and urge incontinence	Lifestyle adjustments, biofeedback, pelvic floor training, timed voiding, bladder support appliances	Anticholinergics (urinary retention, hypotension, confusion*): trospium (10 mg twice daily), solifenacin (5–10 mg daily), oxybutynin (5–30 mg daily), tolterodine (1–2 mg twice daily); mirabegron (25–50 mg daily; headache, tachycardia); botulinum toxin A injections (50–300 units every 3 months; infection, dysuria)
Urinary retention	Timed voiding, clean intermittent catheterisation, suprapubic catheterisation	..
Nocturia	Limit fluid intake after noon, bedside commode or urinal, external urinary catheters, elevate head of bed	Desmopressin (27·7–55·3 µg 1 h before bedtime, nasal spray 30 min before bedtime; hyponatraemia)
Constipation	High-fibre diet, increase fluid intake, abdominal massage	Psyllium (3·3 g up to three times daily; bloating, diarrhoea); polyethylene glycol (17 g daily; flatulence, cramps, diarrhoea); bisacodyl (5–15 mg daily; cramps, diarrhoea)
Sexual dysfunction	Consider medications (eg, antidepressants, antihypertensives), address secondary causes (eg, incontinence, motor, psychiatric causes); vacuum pump devices; vaginal lubrication (women)	Phosphodiesterase 5 inhibitors (hypotension): sildenafil (50–100 mg), tadalafil (2·5–20 mg), vardenafil (5–20 mg); intracavernosal or intraurethral prostaglandine injections for men; hormonal therapies for women who are perimenopausal or postmenopausal
Anhidrosis	Use of cooling garments or devices in heat, ice-cold fluid intake	..
Sialorrhoea	Functional dysphagia therapy	Glycopyrrolate (1–3 mg daily; confusion, anhidrosis, hypotension); 1% sublingual atropine drops (1–2 drops up to four times daily; confusion, mydriasis); botulinum toxin injections (A: up to 100 units; B: up to 4000 units; dry mouth, injection pain, worsening dysphagia with transient need for nasogastric tube feeding)

(Table 1 continues on next page)

Non-pharmacological therapies, such as the use of continuous positive airway pressure and passive heat over the abdomen might be helpful to lower nocturnal blood pressure.[75,76]

Neurogenic bladder in multiple system atrophy typically causes urinary retention with overflow incontinence. However, if hyperactive bladder symptoms are prominent, anticholinergics or β3-receptor agonists

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	Non-pharmacological therapeutic options	Pharmacological therapeutic options (dose range; potential side-effects)
(Continued from previous page)		
Sleep and respiratory symptoms		
REM sleep behaviour disorder	Bedroom environmental precautions	Clonazepam (0·5mg daily; somnolence, hypotension, worsening of stridor and sleep disordered breathing); melatonin (5 mg daily; fatigue)
Sleep apnoea	Continuous positive airway pressure, non-invasive positive pressure ventilation, adaptive servoventilation	..
Stridor	Continuous positive airway pressure, tracheostomy for persistent or severe stridor	..
Neuropsychiatric symptoms		
Pseudobulbar affect	..	Serotonergic and noradrenergic reuptake inhibitors (tremulousness, dizziness), dextromethorphan (20 mg–40 mg daily; angioedema); quinidine (10 mg–20 mg daily; angioedema)
Depression and anxiety	Cognitive behavioural therapy	Serotonergic and noradrenergic reuptake inhibitors (tremulousness, dizziness, exacerbation of REM-sleep behaviour disorder), serotonergic and noradrenergic reuptake inhibitors (tremulousness, dizziness, supine hypertension, urinary retention)
Cognitive impairment	Mental exercises	Rivastigmine (1·5–6·0 mg oral twice daily; 4·6–9·5 mg per 24-h patch; nausea, diarrhoea); donepezil (5–10 mg daily; diarrohea, insomnia)

For pharmacological therapeutic options, recommendations reflect expert opinion with most of the listed options being off-label treatments commonly without validation in specific trials in multiple system atrophy. REM=rapid eye movement. *Trospium does not cause confusion.

Table 1: **Symptomatic therapeutic options for motor and non-motor symptoms in multiple system atrophy**

might be useful therapies. Timed voiding could reduce overflow incontinence in urinary retention, but if severe, catheterisation is often recommended by neuro-urologists or urologists to empty the bladder fully to avoid secondary consequences, such as renal failure and recurrent urinary tract infections.[77] Although sexual dysfunction in men can be treated pharmacologically, treatments for women remain scarce.

Sleep and respiratory symptoms

REM-sleep behaviour disorder is frequent in multiple system atrophy and should be treated when symptoms cause potential injury or sleep disruption. Environmental precautions are important. Pharmacological therapies include clonazepam, melatonin, or both.[78] In people with sleep apnoea or nocturnal stridor, ventilation with continuous positive airway pressure is recommended. Persistent and severe stridor might require tracheostomy.[79]

Disease-modifying therapies

A characteristic of multiple system atrophy and other neurodegenerative diseases is the continuous spread of disease pathology, which corresponds clinically to the disease stage. Disease prevention, disease-modifying therapies, and restorative therapies remain a major unmet need in the management of the disease. At present, prevention of multiple system atrophy in particular appears to be unattainable, because of an absence of established risk factors or biomarkers that can reliably predict multiple system atrophy in healthy people or individuals in the prodromal stage of a synucleinopathy. However, disease-modifying therapies and restorative therapies have been trialled in the past two decades, with several randomised controlled trials attempting to modify the fatal course of multiple system atrophy. The largest clinical trial in multiple system atrophy, the M-STAR trial (NCT03952806) with verdiperstat has clearly shown that large-scale, phase 3 studies can be completed in multiple system atrophy in a reasonably short time (ie, 2 years from start of enrolment to the last participant's last visit).

Studies of therapies directed against α-synuclein and neuroinflammation have been a focal point of research efforts over the past 5 years, with anti-inflammatory agents and inhibitors of α-synuclein aggregation being studied in randomised controlled trials.[80,81] A restorative therapy entailing intrathecal delivery of mesenchymal stem cells was shown to be safe and well tolerated, except at high doses, in a proof-of-concept study.[82] Investigation into this approach is continuing, with the ultimate goal to conduct a phase 3 trial with the aim to slow disease progression.[82] Based on findings of reduced co-enzyme Q10 levels in individuals with multiple system atrophy,[83–85] a phase 2 randomised controlled trial of high-dose ubiquinol was conducted, showing a favourable safety and tolerability profile, as well as a statistically significant reduction in progression on the motor examination section of the UMSARS.[86] Although the clinical meaningfulness of the UMSARS difference between the treatment arms needs to be critically considered, these results encourage the further development of ubiquinol as a potential disease-modifying therapy in a larger phase 3 trial in individuals with multiple system atrophy.

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	Study type	Study duration	Key inclusion and exclusion criteria	Sample size	Treatment (target)	Study aims or outcomes
NCT05109091	Double-blind, placebo-controlled randomised controlled trial, phase 2	52 weeks	Inclusion criteria: clinical features of parkinsonism; orthostatic hypotension or bladder dysfunction; ataxia or pyramidal signs on neurological examination; participant is ambulatory; biomarker evidence of multiple system atrophy in biological fluid and on MRI; exclusion criteria: motor symptoms for more than 4 years, advanced disease, as indicated by frequent falls or choking	77	ATH434 (iron or α-synuclein)	Primary: iron content (brain MRI); secondary: α-synuclein levels, neurofilament light chain levels, change in UMSARS score, change in the Short Form-36 score
NCT05923866	Double-blind, placebo-controlled randomised controlled trial, phase 2	28 weeks	Inclusion criteria: clinically established or clinically probable multiple system atrophy according to Movement Disorders Society multiple system atrophy criteria; early stages less than 5 years since the onset of one of the following symptoms associated with multiple system atrophy: parkinsonism, ataxia, orthostatic hypotension, and urinary dysfunction; UMSARS I total score (excluding item 1.11 sexual function) of ≤17; anticipated survival of at least 3 years (investigator's opinion); ability to take at least ten steps and then to turn around and walk at least another ten steps, use of assistive devices (eg, walker or cane) is allowed; ability to swallow oral medication; exclusion criteria: documented liver diseases or cirrhosis; patients with suicide ideation	80	ONO-2808 (α-synuclein)	Primary: safety and tolerability; secondary: plasma concentration of ONO-2808, CSF concentration of ONO-2808
NCT04165486	Double-blind, placebo-controlled randomised controlled trial, phase 1	36 weeks (plus 96 weeks open-label extension)	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008); loss of dopamine nerve terminals on ioflupane [^{123}I] SPECT; ability to walk unassisted for at least 10 m; exclusion criteria: Montreal Cognitive Assessment score <25; family history of ataxia or parkinsonism and known genetic cause of ataxia or parkinsonism	40	ION464 (α-synuclein)	Primary: safety and tolerability; secondary: CSF levels of total α-synuclein, pharmacodynamics, pharmacokinetics
NCT04431713	Open-label study, phase 2	48 weeks	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008); participants who are less than 5 years from the time of documented multiple system atrophy diagnosis or from the time of documented parkinsonian or ataxic neurological condition; ability to walk at least 10 m with or without assistance; anticipated survival of at least 3 years (investigator opinion); exclusion criteria: any of the following criteria suggesting advanced disease: speech impairment (≥3 on UMSARS question 1); swallowing impairment (≥3 on UMSARS question 2); impairment in ambulation (≥3 on UMSARS question 7); falling more frequently than once per week (≥3 on UMSARS question 8); dementia (defined as <21 on the Montreal Cognitive Assessment score); severe depression (≥30 on the Beck Depression Inventory-II); participants with a BMI <18·5 kg/m^2	50	Exenatide	Primary: change in UMSARS (total); secondary: proportion of patients with loss of independent ambulation, multiple system atrophy quality of life, difference in anti-parkinsonian or anti-orthostatic hypotension drugs, number of falls, proportion of patients reaching a score of ≥3 on UMSARS I items 1 (speech), 2 (swallowing), and 8 (falling), change in Change in Clinical Global Impression, change in Montreal Cognitive Assessment scores
NCT05167721	Double-blind, placebo-controlled adaptive randomised controlled trial, phase 2	52 weeks	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008); UMSARS I score (omitting question 11) between 5 and 17, and able to walk unaided (ie, able to walk at least 50 yards without the use of a cane or walker, and without other support, such as holding on to an arm or touching walls); anticipated survival of ≥3 years (investigator opinion); normal cognition (Montreal Cognitive Assessment score ≥26); exclusion criteria: medications that could affect clinical evaluations are permitted, but need to be withdrawn at least four half-lives before study visits (including medications used to treat motor symptoms, such as levodopa and other anti-parkinsonian medications)	76	Mesenchymal stem cells (cell replacement therapy)	Primary: change in UMSARS total; secondary: change in UMSARS I, change in UMSARS II, change in modified UMSARS score, change in COMPASS select score, rate of atrophy of selected brain regions (MRI)

(Table 2 continues on next page)

Other developments in disease-modifying therapies are focused on α-synuclein as the most obvious therapeutic target, and treatment strategies aim to address the aggregation, spreading, and clearance of (misfolded) α-synuclein. Despite two negative studies of monoclonal antibodies targeting α-synuclein in people with Parkinson's disease,[87,88] phase 2 studies with monoclonal antibodies have recently been completed or have entered phase 2 clinical development in multiple system atrophy (table 2). A phase 1 trial of active immunisation against α-synuclein

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	Study type	Study duration	Key inclusion and exclusion criteria	Sample size	Treatment (target)	Study aims or outcomes
(Continued from previous page)						
NCT05695378	Double-blind, placebo-controlled, phase 2	40 weeks	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008); BMI range of 18·5–30 kg/m^2; cognitive ability (possible to make self-decision, understand, and follow the instruction); if no ability to walk, patients must be accompanied by caregiver by wheelchair at all visits; exclusion criteria: history of suicide attempt; any recent suicidal ideation (a level of 4 or 5) within the past 3 months before day 1 (ie, initial check-in), or has a positive response (ie, "yes") to either question 4 or 5 of the Columbia Suicide Severity Rating Scale at day 1, or who is at substantial risk of committing suicide, as judged by the investigator using the Columbia Suicide Severity Rating Scale at screening	78	KM-819 (cell death)	Primary: change in putaminal dopamine transporter binding; secondary: change in UMSARS total score, change in UMSARS I score, change in UMSARS II score, change in putaminal glucose metabolism ([^{18}F]fluorodeoxyglucose-PET)
NCT05526391	Double-blind, placebo-controlled randomised controlled trial, phase 2	52 weeks	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008); first multiple system atrophy symptoms occurred ≤4 years from symptom onset; evidence of multiple system atrophy specific symptoms and deficits as measured by the UMSARS scale; exclusion criteria: participant has participated in another study investigating active or passive immunisation against α-synuclein within 6 months before screening	138	Tak-341 (α-synuclein)	Primary: change in modified UMSARS score; secondary: serum concentration for TAK-341, CSF concentration of TAK-341, change in 11-item UMSARS score, change in UMSARS total, change in UMSARS I, change in UMSARS II, change in Clinical Global Impression–Severity of Illness score, change in Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction, survival, pharmacokinetics and pharmacodynamics, safety and tolerability
NCT04680065	Double-blind, placebo-controlled randomised controlled trial	156 weeks	Inclusion criteria: clinical diagnosis of multiple system atrophy, parkinsonian type; aged >30 years; <5 years from multiple system atrophy diagnosis with expected survival >3 years; ability to walk 25 feet with or without an assistive device; exclusion criteria: none (other than exclusion of relevant other neurological, medical, or surgical condition)	9	AAV2-GDNF (trophic support)	Primary: safety and tolerability; secondary: change in UMSARS score, change in multiple system atrophy quality of life; change in striatal dopamine transporter binding
NCT05104476	Double-blind, placebo-controlled, randomised controlled trial	48–72 weeks	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008); onset of motor or autonomic (orthostatic or urinary) multiple system atrophy symptoms within 5 years of symptom onset; UMSARS part I score ≤16 (omitting item 11 on sexual function); Montreal Cognitive Assessment score score ≥22; exclusion criteria: the participant has been treated with an anti-α-synuclein monoclonal antibody, mesenchymal stem cells, or an inhibitor of α-synuclein aggregation within the past 12 months; the participant has any past or current treatment with an active vaccine targeting α-synuclein; two or more blood relatives with a history of multiple system atrophy	64	Lu AF82422 (α-synuclein)	Primary: change in UMSARS total score; secondary: change in modified UMSARS I; change in Schwab and England Activities of Daily Living; change in Clinical Global Impression–Severity of Illness score; Change in Patient Global Impression–Severity of Illness; Change in Observer-Reported Global Impression–Severity of Illness; change in Composite Autonomic Symptom Score Select; change in UMSARS IV; change in speech, swallowing, falls, and walking, as assessed by the UMSARS I items; change in frequency, cause, and consequence of falls; change in EuroQol 5-Dimension, 5-Level; percent change in brain volume (MRI); change in neurofilament light chain; change in Lu AF82422 plasma and CSF concentrations
NCT05698017	Double-blind, sham-controlled randomised controlled trial, phase 1/2	72 weeks	Inclusion criteria: probable or possible multiple system atrophy according to the revised consensus criteria (2008) within 60 months of symptom onset (excluding impotence); ability to take at least 10 steps; use of assistive devices is allowed; Montreal Cognitive Assessment score ≥24; exclusion criteria: patients who fulfill the criteria of Parkinson's disease; history of electroconvulsive therapy	18	Allogenic human oral mucosa stem cells (cell replacement therapy)	Primary: safety and tolerability; secondary: "clinically significant motor and behavioral change from baseline" (without further definition)

Only selected key inclusion criteria and exclusion criteria are shown and other criteria might apply. For example, contraindications to study procedures, such as MRI and lumbar puncture, hypersensitivities against the investigational product, history of medical, surgical (including brain surgery), and neurological conditions have been omitted. UMSARS=Unified Multiple System Atrophy Rating Scale.

Table 2: **Ongoing studies of disease-modifying interventions in clinical development for multiple system atrophy**

in people with multiple system atrophy revealed that one of the two tested α-synuclein-directed short-peptide vaccines induced a statistically significant and sustained immune response against α-synuclein, proving the concept of active immunisation to be successful. However, the putative neuroprotective benefits of this approach need to be established in future interventional studies.[89]

Other approaches entering early-phase clinical development target inhibition of α-synuclein aggregation through small molecules and reduction of endogenous α-synuclein production, using antisense oligonucleotide therapies, which partly inhibit intracellular production of α-synuclein by targeting the pre-mRNA of the *SNCA* gene (table 2). Some concerns regarding antisense

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	Milestones	Unmet needs and future priorities
Pathophysiology	Essential role of oligodendrocytes has been established; multiple system atrophy-specific α-synuclein strains were identified as a key protein in multiple system atrophy pathogenesis; mitochondrial dysfunction is a major contributor to the pathophysiological cascade; neuroinflammation contributes to the neurodegeneration	Initial triggers of pathology, causative mechanisms, and sequence of events need to be established
Clinical	Novel diagnostic criteria were developed; symptoms of prodromal multiple system atrophy are increasingly recognised	More comprehensive disease-specific scales to assess motor and non-motor symptoms are required
Biomarker	Identification of α-synuclein-based diagnostic biomarkers in CSF (seeding aggregation assays); neurofilament light chain measurements in blood and CSF recognised as a diagnostic, as well as a surrogate, marker of disease progression in multiple system atrophy; quantitative, multimodal MRI was established as a diagnostic tool and surrogate measure of disease progression; development of α-synuclein-labelling PET tracers detecting aberrant α-synuclein inclusions	Independent validation is not available for most of the proposed biomarkers, emphasising the need to harmonise sampling and study protocols and perform multicentre validation studies to offer broadly available biomarker-supported diagnostic algorithms; quality control programmes for biomarkers (defined sampling and analytical standard operating procedures, site training, and inter-laboratory comparisons) should be implemented to ensure the integrity of the biomarkers
Therapeutic	Several large-scale and high-quality randomised controlled trials were conducted; early efficacy signals in randomised controlled trials; droxidopa has been established as an effective and safe treatment of neurogenic orthostatic hypotension in multiple system atrophy	Improvements in clinical trial methodology with improved clinical outcome assessments and validated surrogate markers of progressive brain damage are required; further improvements of preclinical models, which currently only partly recapitulate the human disease, are needed; additional studies needed to establish symptomatic therapeutic options for multiple system atrophy; evaluation of long-term efficacy of non-pharmacological treatments are needed; health-care models with a holistic treatment approach integrating advanced care planning, telemedicine tools, and mobile palliative care should be studied

Table 3: **Milestones from the past decade and future priorities in multiple system atrophy research**

oligonucleotide therapies have emerged because of findings from animal studies, indicating that complete α-synuclein knock-out could have detrimental effects.[90,91] Therefore, selecting the appropriate degree of treatment-induced interference with α-synuclein translation is crucial. Furthermore, experimental studies and clinical data from related synucleinopathies[92–95] suggest that the Abelson tyrosine kinase and GLP-1 receptor agonists are promising therapeutic targets for multiple system atrophy, and these therapies are currently being tested in early clinical trials.

In general, therapies that inhibit α-synuclein aggregation are often not specific for pathological strains; thus, unintended long-term effects could arise, affecting normal protein functions. Furthermore, immunotherapies designed to enhance α-synuclein clearance have the potential to elicit detrimental immune responses, analogous to the observed complications associated with early antibody treatments for Alzheimer's disease. A further limitation of α-synuclein-directed strategies is that α-synuclein is primarily an intracellular protein, and current treatment approaches are largely unable to cross cell barriers, thereby only addressing the extracellular compartment. This aspect of α-synuclein treatment strategies requires detailed investigation in future studies. Finally, it is unlikely that a single therapeutic approach will be sufficient to halt the neurodegeneration that has already occurred in a disease as complex as multiple system atrophy. A multifaceted approach that combines different treatment strategies might, therefore, offer a more promising avenue for intervention.

Conclusions and future directions

In the past 5 years, major achievements have been made in the understanding of pathophysiological processes in multiple system atrophy,[39,85,96,97] in the recognition of a prodromal stage of the disease,[4] in the development of biomarkers for diagnosis and for disease progression, and in clinical trial efforts (table 3). Despite these achievements,[39] the exact causative mechanisms underlying multiple system atrophy pathology still remain elusive and require further investigation.

In the field of diagnostic biomarkers, α-synuclein-based biomarkers in CSF, neurofilament light chain measurements in blood and CSF, and machine learning-supported imaging techniques are of particular interest.[16,40,47,52,54,56,62,98] Two research groups have recently reported encouraging results regarding an α-synuclein seed aggregation assay in blood samples.[50,51] Regarding imaging biomarkers, there is a paucity of broadly available and validated α-synuclein labelling PET tracers that can detect aberrant α-synuclein inclusions. Despite success in the biomarker field, the availability of biomarkers is often restricted to highly specialised research centres in high-income countries. Moreover, there are insufficient independent validation and quality control programmes for most proposed biomarkers, outlining an urgent future research need. Although advances in fluid and imaging biomarkers provide valuable insights, no definitive biomarker for multiple system atrophy yet exists, and all candidate biomarkers still require further prospective validation in large patient cohorts with long-term follow-up. Nevertheless, with the advent of biomarkers allowing accurate detection of pathologically misfolded α-synuclein in CSF and the emergence of imaging modalities capable of discerning multiple system atrophy-specific imaging patterns, efforts should be intensified to integrate multiple system atrophy into the most recent biological classifications of α-synucleinopathies[99,100] and a biomarker-supported diagnostic category could be considered in the future.

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Search strategy and selection criteria

We searched PubMed, MEDLINE, and the Clarivate Web of Science Core collection for peer-reviewed papers in English published from Oct 1, 2018, to June 10, 2024, using the key words "Multiple System Atrophy"[Mesh], "multiple system atrophy", "striatonigral degeneration", "olivopontocerebellar atrophy", "Shy-Drager syndrome", "atypical parkinson*", or "synucleinopathies". ClinicalTrials.gov was searched for randomised controlled trials; the term "multiple system atrophy" was used for the search with no additional restrictions on search records. We also screened the authors' own files and recent high-impact expert reviews on multiple system atrophy for additional references and seminal works published before the start date of the search period. Resulting articles were assessed for relevance to the topic and methodological rigour. We focus on seminal work, clinical trials, and systematic reviews.

Finally, drug discovery programmes for multiple system atrophy have made good progress in the past 5 years. Numerous large-scale clinical trials, including phase 3 trials attempting to modify the disease course, have been conducted in multiple system atrophy, demonstrating that academic research networks—supported by patient trusts and support groups—are in place to facilitate interventional studies of candidate drugs and research in holistic health-care models. Continuous efforts to raise awareness and advocate for individuals who have this fatal and orphan disease are crucial to foster research and collaboration.

Contributors

FK and GKW formulated the overarching Review goals and aims. The Review concept was critically revised by all other authors. All authors contributed to the writing of the initial draft and critically revised the manuscript.

Declaration of interests

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