Multiple System Atrophy (MSA) Is a Progressive, Fatal, Rare, Neurodegenerative Disease Caused by Misfolding and Accumulation of α-Synuclein[1,2]

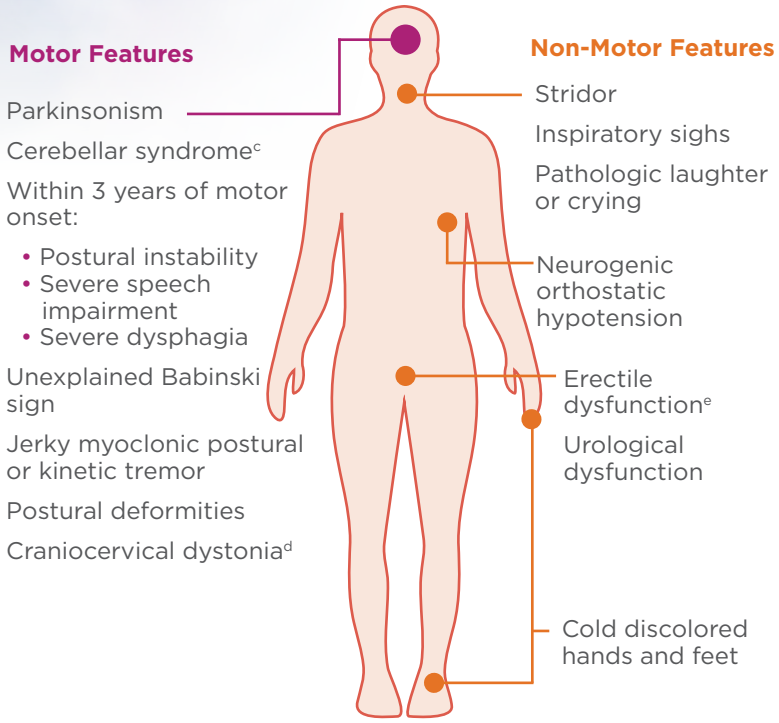
MSA is an adult-onset α-synucleinopathy with a diverse pathological spread of α-synuclein and varied clinical presentation.[2-4] Among synucleinopathies, MSA is associated with the lowest survival rate.[5,a]

MSA is characterized by and broadly sorted into two categories, parkinsonism (MSA-P) and cerebellar (MSA-C), although the majority of patients have a mixed/autonomic presentation.[2,6]

Diagnostic guidelines denote key "red-flag" symptoms of MSA for clinicians to be aware of that can help determine which α-synucleinopathy a patient has (**Figure 1**).[4]

MSA has an average age of onset of 63 years and a median survival of 9.8 years.[7]

Figure 1: "Red-Flag" Symptoms of MSA[4,b]



MSA Is Associated With "Prion-Like" α-Synuclein Accumulation and Propagation[3,4,8]

Figure 2: Pathological Spreading of α-Synuclein Neuronal Inclusions in MSA[9]

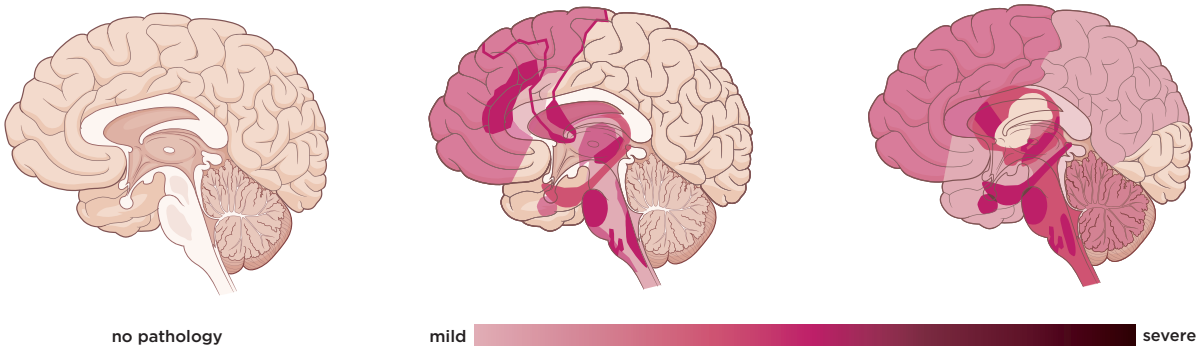


Figure Adapted from Halliday GM. *Brain.* 2015;138(Pt 8):2116-2119.

In MSA α-synuclein, encoded by *SNCA*, forms aggregates and glial cytoplasmic inclusions.[3,10,11]

Increased *SNCA* copy number variations lead to greater α-synuclein inclusions in MSA subjects that are correlated with earlier onset of disease.[11-13]

MSA is a progressive disease in which clinical symptoms and α-synuclein pathology both increase in severity as the disease progresses.[9,14]

[a]Among people with clinically diagnosed synucleinopathies with parkinsonism.[5] [b]Essential clinical features for all patients are a sporadic, progressive adult (>30 years) onset disease.[4] [c]Defined as at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features.[4] [d]Induced or exacerbated by L-dopa in the absence of limb dyskinesia.[4] [e]In males <60 years of age.[4]

SNCA, synuclein alpha.

1. Koga S, et al. *Mol Neurodegener*. 2021;16(1):83. 2. Wenning GK, et al. *Lancet Neurol.* 2013;12(3):264-274. 3. Chelban V, et al. *J Neurol.* 2020;267(9):2754-2770. 4. Wenning GK, et al. *Mov Disord*. 2022;37(6):1131-1148. 5. Savica R, et al. *JAMA Neurol.* 2017;74(7):839-846. 6. Figueroa JJ, et al. *Mov Disord.* 2014;29(9):1151-1157. 7. Low PA, et al. *Lancet Neurol*. 2015;14(7):710-719. 8. Woerman AL, et al. *Cold Spring Harb Perspect Med*. 2018;8(7):a024588. 9. Halliday GM. *Brain.* 2015;138(Pt 8):2116-2119. 10. Yamasaki TR, et al. *J Biol Chem.* 2019;294(3):1045-1058. 11. Perez-Rodriguez D, et al. *Acta Neuropathol Commun.* 2019;7(1):219. 12. Tseng FS, et al. *J Transl Med.* 2023;21(1):104. 13. Garcia-Segura ME, et al. *Mov Disord.* 2023;38(2):338-342. 14. Reddy K, Dieriks BV. *Mol Neurodegener*. 2022;17(1):77.

Prompt Diagnosis and Treatments That Target the Underlying Pathophysiology Are Critical Unmet Needs in Multiple System Atrophy (MSA)[1-3]

MSA is frequently misdiagnosed due to its varied clinical manifestation, notably at the onset of disease with up to 38% of patients not receiving an accurate diagnosis of MSA.[2,4]

Diagnosis of MSA is delayed on average of 3.7 years.[5]

Premortem diagnosis of MSA is classified into three broad types with varied diagnostic certainty: clinically established, clinically probable, and possible prodromal (**Figure 3**).[1]

Figure 3: Clinical Characteristics of Premortem Diagnosis of MSA[1,6,a]

	Core Clinical Features		MRI	Supportive Clinical Features
Clinically Established	**Autonomic dysfunction (defined as at least one of):** • Unexplained voiding difficulties with post-void urinary residual volume ≥100 mL • Unexplained urinary urge incontinence • Neurogenic OH[b] within 3 minutes of standing or head-up tilt test	**AND at least one:** • Poorly L-dopa responsive parkinsonism • Cerebellar syndrome[c]	Yes	≥2
Clinically Probable	**At least two of:** **1.** Autonomic dysfunction defined as (more than one is required): • Unexplained voiding difficulties with post-void urinary residual volume • Unexplained urinary urge incontinence • Neurogenic OH[b] within 10 minutes of standing or head-up tilt test	**2.** Parkinsonism **3.** Cerebellar syndrome[c]	Not Required	≥1[d]
Possible Prodromal	**At least one of the following:** • Rapid eye movement sleep behavior disorder • Neurogenic OH[b] within 10 minutes of standing or head-up tilt test • Urogenital failure	**AND at least one:** • Subtle parkinsonian signs • Subtle cerebellar signs	N/A	N/A

Current Standard-of-Care Treatment for MSA Is to Minimize Symptoms[2]

As MSA progresses, patients are at an increased risk for falls, wheelchair dependency, loss of coherent speech, and feeding by nasogastric tube or gastrostomy.[7]

Medications to manage MSA are focused on controlling symptoms, including for parkinsonism, autonomic lability, bladder and bowel dysfunction, and mood problems.[2,3]

Current options do not prevent or reduce disease progression, presenting a need for effective therapeutic agents.[3]

[a]Essential clinical features for all patients are a sporadic, progressive adult (>30 years) onset disease.[1] [b]≥20/10 mmHg blood pressure drop.[1] [c]Defined as at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features.[1] [d]Excluding erectile dysfunction as an isolated feature.[1]
MRI, magnetic resonance imaging; N/A, not applicable; OH, orthostatic hypotension.

1. Wenning GK, et al. *Mov Disord.* 2022;37(6):1131-1148. 2. Chelban V, et al. *J Neurol.* 2020;267(9):2754-2770. 3. Reddy K, Dieriks BV. *Mol Neurodegener.* 2022;17(1):77. 4. Koga S, et al. *Neurology.* 2015;85(5):404-412. 5. Foubert-Samier A, et al. *Neurobiol Dis.* 2020;139:104813. 6. Goh YY, et al. *Pract Neurol.* 2023;23(3):208-221. 7. Wenning GK, et al. *Lancet Neurol.* 2013;12(3):264-274.