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Multiple System Atrophy: Symptoms Management and Treatment

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Abstract

Multiple system atrophy (MSA) is a neurodegenerative synucleinopathy caused by the progressive loss of brain cells over time and the abnormal folding and accumulation of the alpha-synuclein protein (α-Syn) inside brain cells. More generally, alpha-synucleinopathies refer to age-related neurodegenerative and dementing disorders characterized by the accumulation of α-Syn in neurons and/or glia. MSA remains a challenging neurodegenerative disorder with a difficult and often inaccurate early diagnosis.

It is accompanied by diverse, highly variable, rapidly progressive, and aggressive clinical course with clinical manifestations that may include parkinsonism, cerebellar syndrome, and autonomic failure. This article will first describe what is MSA (its clinical description, symptoms, presentation, and progression), its types and variants, the etiology/neuropathophysiology and potential causes of the disease including its genetics, and the difficulties in reaching a diagnosis (main differential diagnoses, and panoply of diagnostic tests). Against this background, the management of symptoms will be elaborated upon in terms of monitoring, management, pharmacological therapy, supervision, rehabilitation, and supportive care.

Lastly, the available treatment portfolio will be analyzed (pharmacological use including orphan, repurposed, off-label, and compassionate use medicines; use of experimental disease-modifying drugs/therapies; participation in clinical trials; and the newer modalities of growth hormone therapy, immunotherapy, gene therapy, and mesenchymal stem cell therapy).

Abbreviations

α-Syn: Alpha-synuclein protein; AD: Alzheimer's disease; ANS: Autonomic nervous system; ASON: Anti-sense oligonucleotide; ATMP: Advanced therapy medicinal products; BDNF: Brain-derived neurotrophic factor; BP: Blood pressure; CBD: Corticobasal

degeneration; CNS: Central nervous system; CT: Computerized tomography; CUP: Compassionate use program; DMD/T: Disease-modifying drugs/therapies; FTLD: Frontotemporal lobar degeneration; GCI: Glial cytoplasmic inclusions; GDNF: Glial-derived neurotropic factor; GHT: GHT: Growth hormone therapy; GT: Gene therapy; GWAS: Genome-wide association study; IGF: Insulin/insulin-like growth factor; IT: Immunotherapy; LB: Lewy bodies; LBD: Lewy body dementia; MOD: Multiple organ dysfunction; MOS: Multiple organ system; MRI: Magnetic resonance imaging; MS: Motor system; MSA: Multiple system atrophy; MSCT: Mesenchymal stem cell therapy; MSP: Multiple system proteinopathy; NDD: Neurodegenerative disease/disorder; NSAID: Non-steroidal anti-inflammatory drug; OPCA: Olivopontocerebellar atrophy; PD: Parkinson's disease; PET: Positron emission tomography; PSP: Progressive supranuclear palsy; REM/SBD: Rapid eye movement/sleep behavior disorder; ROS: Reactive oxygen species; SBOD: Steele-Richardson-Olszewski disease; SDS: Shy–Drager syndrome; SND: Striatonigral degeneration; SPECT: Single photon emission computerized tomography; TLR: Toll-like receptor; VD: Vascular dementia.

Keywords

Multiple system atrophy; alpha-synucleinopathy; autonomic failure; cerebellar syndrome; neurodegeneration; parkinsonism; growth hormone therapy; immunotherapy; gene therapy; mesenchymal stem cell therapy.

Introduction

With the increase in life expectancy due to advances in medical diagnoses and treatments, the incidence of age-dependent neurodegenerative diseases increased, including Alzheimer's disease (AD), parkinsonian syndromes, small vessel disease, and motor neuron disease. Despite knowing the pathogenesis of various neurodegenerative diseases at molecular and genetic levels, they are still very incompletely understood and often cause diagnostic and therapeutic challenges. Further, due to overlapping presentations and similar brain pathologies, especially in the early stages of the diseases, it is difficult to differentiate idiopathic Parkinson's disease from atypical parkinsonian syndromes such as MSA and progressive supranuclear palsy (PSP). Similarly, distinguishing Alzheimer bodies, corticobasal degeneration, (CBD) and vascular dementia (VD) can be difficult. Still further, co-morbidities are common in the elderly, further complicating the diagnosis. It is, therefore,necessary to develop accurate and comprehensive diagnostic tests to properly prognosticate the diseases, start treatments in the early stages of the diseases, and maximize the accuracy of drug trials for more effective preventive and therapeutic measures. The discussion to follow will be solely limited to that chronic, progressive, neurodegenerative synucleinopathic disease called MSA.

What is MSA?

Multiple system atrophy (MSA) is a sporadic, progressive, and fatal neurodegenerative disorder (NDD) characterized by autonomic failure (cardiovascular and/or urinary), parkinsonism, cerebellar impairment, and corticospinal signs with a median survival of 6-9 years. The combination of its symptoms shows that it affects both the (involuntary) autonomic nervous system (ANS) and the motor system (MS). ANS is that part of the nervous system that controls the body's automatic or regulating functions whereas, as its name implies, MS controls movement.

MSA causes the loss of nerve cells (neurons) in several parts of the brain, thus affecting the associated brain functions. It impacts the basal ganglia (Figure 1), the cerebellum which is involved in controlling movement and some emotions as well as certain types of learning and memory, and the inferior olivary nucleus.

MSA is distinct from multiple system proteinopathy (MSP), a more common muscle-wasting syndrome. It is also different from multiple organ dysfunction (MOD) syndrome, and from multiple organ system (MOS) failure, an often-fatal complication of septic shock and other severe illnesses.

Clinical Description

MSA is an adult-onset disorder (>30 years, mean age 55-60 years). Clinical manifestations include autonomic failure (orthostatic hypotension, syncope), respiratory disturbances (sleep apnea, stridor, and inspiratory sighs), constipation, bladder dysfunction (early urinary incontinence), erectile dysfunction in males, and Raynaud's syndrome. In some cases, pyramidal signs (generalized hyper-reflexia and positive Babinski sign) are observed.

Neuropsychiatric features, oculomotor dysfunction, and sleep disturbances are also observed. They include apathy, anxiety, depression, rapid eye movement/sleep behavior disorder (REM/SBD), and periodic limb movements in sleep.

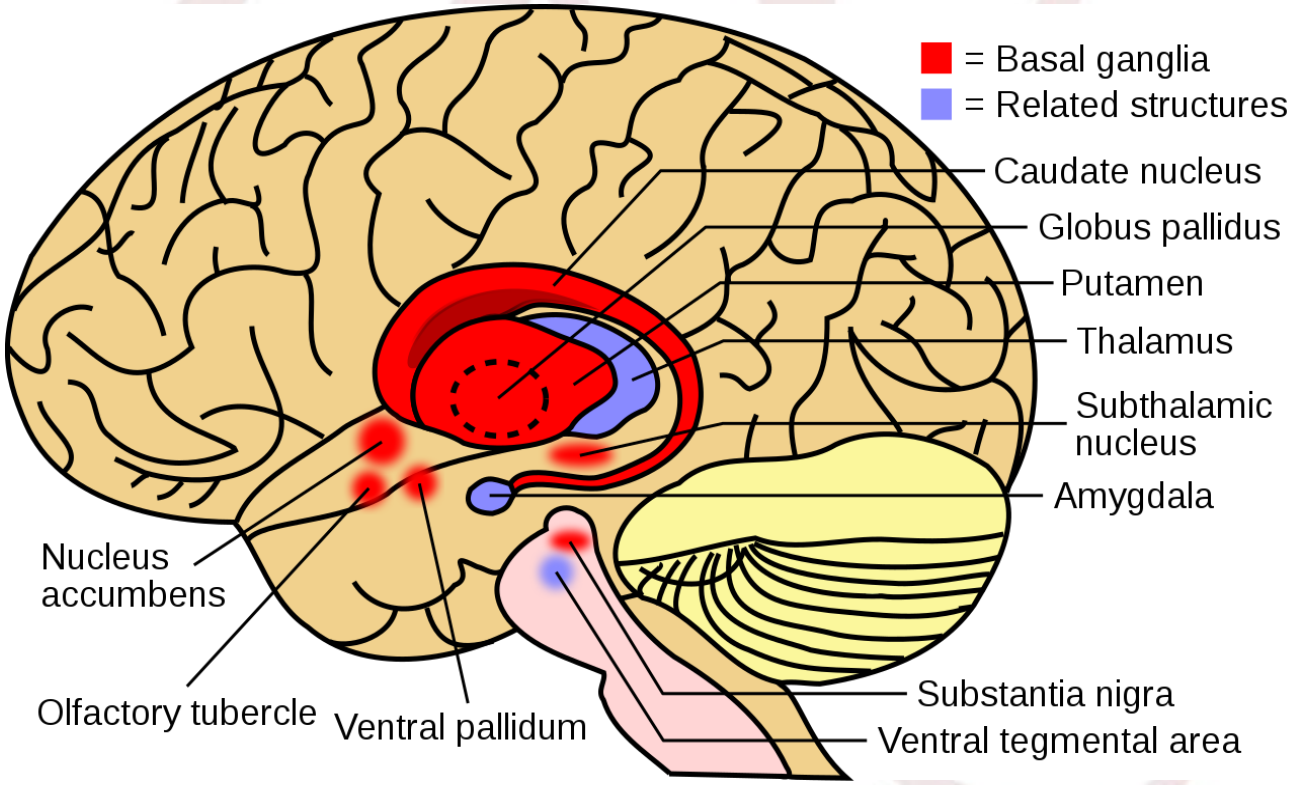

Figure 1: Brain structures affected by MSA: Basal ganglia and related structures

Source: BrainCaudatePutamen.svg

The disease was formerly called by such other names as:

- **Shy-Drager syndrome:** This term was used to describe MSA with predominant autonomic dysfunction. Now, it is no longer used as almost every patient is affected by autonomic or urinary dysfunction;

- **Olivopontocerebellar atrophy:** This atrophy relates to the olivary nucleus, the basis pontis, and the cerebellum; and

- **Striatonigral degeneration:** This degeneration refers to the efferent connection of the striatum with the substantia nigra.

Symptoms

The varied symptoms of MSA reflect the death of different types of nerve cells in the brain and spinal cord and the progressive loss of associated functions. The symptoms caused by dysfunction of the ANS include, e.g., bladder control, blood pressure, digestion, and temperature. On the other hand, the symptoms caused by the MS dysfunction cause motor control problems, rigidity of muscles, loss of coordination, and malfunction of internal body processes; which are commonly manifest as orthostatic hypotension, impotence, loss of sweating, dry mouth, and urinary retention and incontinence.

The initial symptoms are often difficult to distinguish from the symptoms of Parkinson's disease (PD). They may include: Slowness of movement, tremor or rigidity (stiffness), clumsiness or coordination problems, impaired speech, croaky quivering voice, fainting or light-headedness due to orthostatic hypotension, and bladder control problems.

Additional symptoms of MSA may include: Muscle contractures; Pisa syndrome; abnormal posture; antecollis; palsy of the vocal cords; involuntary, uncontrollable sighing or gasping; sleep disorders: and emotional problems: Such as feelings of anxiety or depression.

Presentation

The first symptoms are often autonomic and may predate recognition of motor manifestations (orthostatic hypotension and, in men, erectile failure). They start around age 50-60 and affect about twice as many men as women. They advance rapidly over the course of 5-10 years, with progressive loss of motor function and eventual confinement to bed. People with MSA often develop breathing problems while sleeping (sleep apnea), irregular heart rhythms, and pneumonia in later stages of the disease.

The most common first sign of MSA is the appearance of an "akinetic-rigid syndrome" (i.e. slowness of initiation of movement resembling Parkinson's disease) found in 62% at first presentation and problems with balance (cerebellar ataxia) found in 22% followed by genito-urinary symptoms (9%). Patients may also present with parkinsonian symptoms, often with a poor or temporary response to Levodopa therapy or cerebellar dysfunction, corticospinal tract dysfunction, non-autonomic features (imbalance caused by cerebellar or extrapyramidal abnormalities, and constipation. There may possibly be mild intellectual impairment (particularly so in older patients with greater physical disability) and other neuropsychiatric problems that may include depression, insomnia, daytime sleepiness, restless legs, hallucinations, and dementia.

Progression

MSA tends to progress more rapidly than PD and most people with MSA will require an aid for walking (cane, walker) within a few years after symptoms begin. As the disease progresses one of three groups of symptoms predominates. These are:

1. **Parkinsonism:** Slow and stiff movement; writing becomes small and spidery.
2. **Cerebellar dysfunction:** Difficulty coordinating

movement and balance.

3. **Autonomic nervous system dysfunction:** Impaired automatic body functions, including one, some, or all of the following: Postural or orthostatic hypotension, resulting in dizziness or fainting upon standing up; urinary incontinence or urinary retention; impotence; constipation; vocal cord paralysis; dry mouth and dry skin; trouble regulating body temperature due to sweating deficiency in all parts of the body; loud snoring, abnormal breathing or inspiratory stridor during sleep; other sleep disorders including sleep apnea and REM/SBD; double vision; muscle twitches; and cognitive impairment.

Types and variants of MSA

MSA is one of several neurodegenerative diseases known as synucleinopathies, which have in common an abnormal accumulation of the alpha-synuclein protein in various parts of the brain (Figure 2). Other synucleinopathies include Parkinson's disease (PD), the Lewy body dementia (LBD), and other rarer conditions.

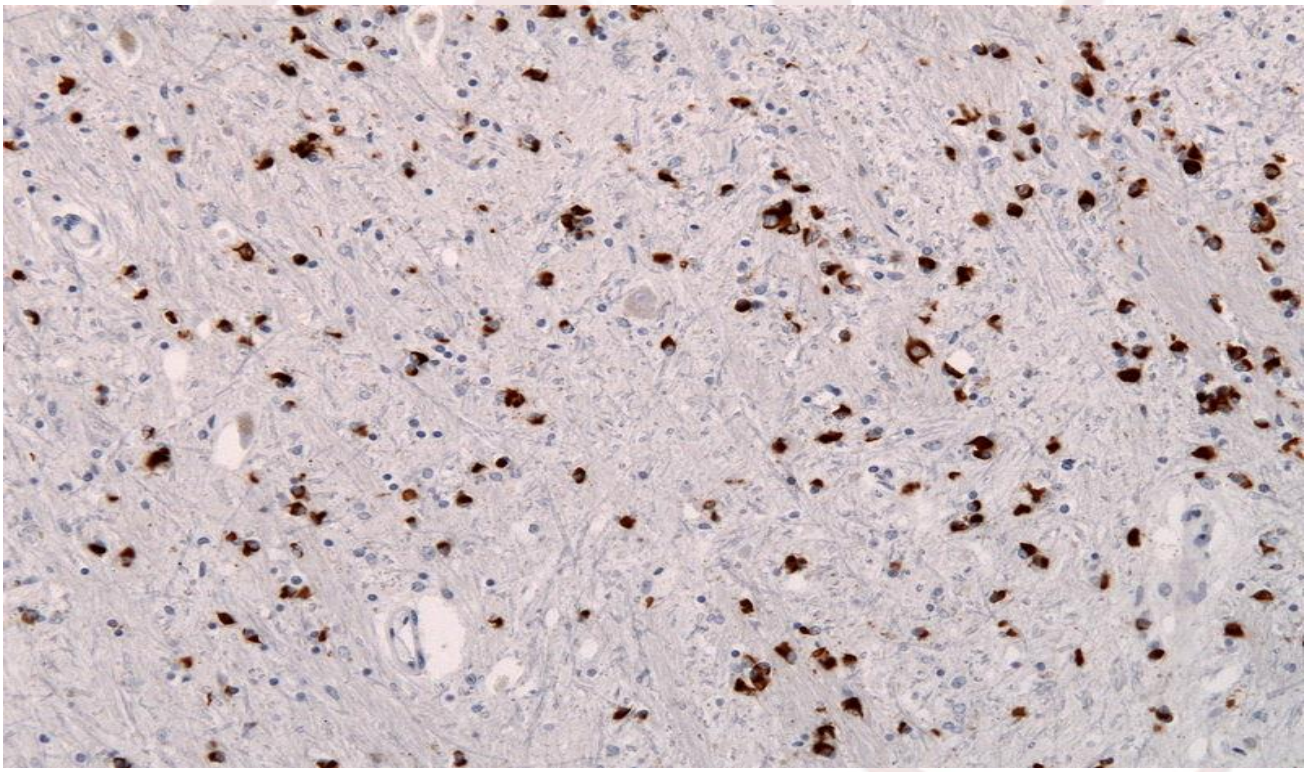

Figure 2: Alpha synuclein immunohistochemistry showing many glial inclusions seen in MSA

Reference: Jensflorian

Historical descriptions

Based on the predominant symptoms presented, many terms were used to refer to this disorder including striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA), and Shy–Drager syndrome (SDS). These terms were discontinued by consensus in 1996 and replaced with MSA and its subtypes. Awareness of these older terms and their definitions is nonetheless helpful to understanding the relevant literature prior to 1996.

Current terminology

The current terminology and diagnostic criteria for the

disease were established at the 2007 Second Consensus Statement, which defined two categories of MSA based on the predominant symptoms at the time of evaluation. Although the disease begins as one of these types, symptoms of the other type eventually develop. After about 5 years, symptoms tend to be similar regardless of which disorder developed first. They are:

1. MSA-P

MSA is referred to as of the MSA-P type if extrapyramidal parkinsonian features predominate. It is a rare condition characterized by a number of the following symptoms:

• **Parkinsonism** (bradykinesia, rigidity, irregular jerky tremor and postural instability).
• **Autonomic failure** (bladder dysfunction and/or orthostatic hypotension. The presence of autonomic failure is mandatory for the diagnosis of MSA-P).
• **Other autonomic features** (dysphonia, dysphagia, respiratory disturbances such as sleep apnea, stridor and inspiratory sighs, as well as constipation and sexual dysfunction).
• **Some cerebellar signs** (gait and limb ataxia, oculomotor dysfunction, dysarthria).
• **Abnormal postures** (camptocormia, Pisa syndrome, and disproportionate antecollis).
• **Neuropsychiatric features** (REM/SBD, periodic limb movements in sleep, depression, apathy and anxiety).
• **Pyramidal signs** (generalized hyper-reflexia with a positive Babinski sign).
• **Early-onset Levodopa-induced effects** (orofacial and craniocervical dystonia).

2. MSA-C

MSA is referred to as of the MSA-C type (indicated by the 'C') if features of cerebellar dysfunction (such as gait and limb ataxia, oculomotor dysfunction, and dysarthria) predominate. It used to be known as olivopontocerebellar atrophy (OPCA). It is a rare disease that causes areas deep in the brain, just above the spinal cord, to shrink. MSA-C features primary symptoms like:

• **Gait ataxia** (the most typical early symptom; problems with balance and coordination).
• **Autonomic dysfunction** (bladder dysfunction including early urinary incontinence, orthostatic hypotension, and constipation. Raynaud's syndrome occurs early and is mandatory for the diagnosis of MSA-C).
• **Additional features** (dysphonia, dysphagia, and other cerebellar features including limb ataxia and occulomotor dysfunction).
• **Parkinsonism:** All patients develop at least some parkinsonian signs in the course of the disease).
• **Pyramidal signs** (generalized hyper-reflexia and, in some cases, positive Babinski sign; respiratory disturbances).

The predominant motor feature can change with time and patients with cerebellar ataxia can develop increasingly severe parkinsonian features which dominate the clinical presentation.

3. Other variants

MSA-P and MSA-C can be present in any combination. A variant with combined features of MSA and Lewy bodies dementia (LBD) may also exist. There have been occasional instances of frontotemporal lobar degeneration (FTLD) associated with MSA.

There may also be other autonomic dysfunctions, particularly urogenital, and corticospinal features along the axis connecting the cortex and the spine.

Historical name	Characteristics	Modern name

Striatonigral degeneration	Predominating Parkinson's-like symptoms	MSA-P "P" = Parkinsonian subtype
Sporadic olivopontocerebellar atrophy	o Progressive ataxia of the gait and arms o Dysarthria	MSA-C "C" = Cerebellar dysfunction type
Shy-Drager syndrome	o Parkinsonism o More pronounced failure of the autonomic nervous system	No modern equivalent Before 1998, consensus referred to it as MSA-A "A" = Autonomic dysfunction subtype

Table 1: Characteristics and modern names of synucleinopathies

Etiology, Neuropathophysiology, and Potential Causes of MSA

MSA autopsy studies show olivopontecerebellar atrophy and degeneration of the striatum with typical inclusions in the cytoplasm of oligodendrocytes (Papp-Lantos bodies) that consist of misfolded α -Syn proteins. These proteins are a vital chemical for how the body operates, assisting with communication between different body systems, carrying different chemical compounds throughout the body, and more. But when proteins build up in the wrong places, they can cause damage. Damage is the culprit for the progressive deterioration of brain tissue with MSA.

Etiology

The exact etiology of MSA-P is still unknown but the presence of cytoplasmic aggregates of α-Syn, primarily in oligodendroglia, in combination with predominant neurodegeneration of the striatonigral pathway are the pathological hallmark features of MSA-P.

Likewise, the exact etiology of MSC-C is unknown while the presence of cytoplasmic aggregates of α-Syn, primarily in the oligodendroglia, in combination with predominant neurodegeneration of the olivopontocerebellar structures are pathological hallmark features of MSA-C.

Neuropathophysiology

MSA is characterized by widespread glial cytoplasmic inclusions (GCI), which are the hallmark of the disease (see Figure 2). Their main component has more recently been identified as misfolded, hyperphosphorylated, fibrillary α-Syn protein – the same protein that is involved in Parkinson's disease (PD). The presence of GCIs is associated with neuronal loss in the basal ganglia, cerebellum, pons, inferior olivary nuclei and the spinal cord, hence giving rise to the spectrum of symptoms and clinical findings.

Whereas the disease is often defined at the time of initial manifestation of any motor or autonomic features, subclinical neuropathology is likely to have started several years before overt disease. The density of GCI containing α-synuclein also correlates significantly with neuronal deterioration and disease duration. Another important protein, p25α has been found to stimulate α-Syn in vitro.

MSA can be explained as cell loss and gliosis or a proliferation of astrocytes in damaged areas of the central nervous system, forming a scar termed a glial scar. The presence of the Papp-Lantos inclusion bodies in the movement, balance, and autonomic control centers of the brain are the defining histopathologic hallmark of MSA. Their major filamentous component - the glial and neuronal cytoplasmic inclusions, is α-Syn.

Mutations in this substance may play a role in the disease. The conformation of the α-Syn is different from that of α-Syn in Lewy bodies. The disease starts with an oligodendrogliopathy. Also, tau proteins have been found in some GCI bodies.

Causes of MSA

MSA results from degeneration of several parts of the brain and spinal cord (Figure 1). The cause of the degeneration is unknown, but probably results when α-Syn changes shape (misfolds) and accumulates in support cells in the brain. Synuclein is a protein in the brain that helps nerve cells communicate, but whose function is not yet fully understood. Abnormal α-Syn can also accumulate in people with pure autonomic failure, PD or dementia with Lewy bodies (DLB). A modified form of the α-Syn within affected neurons may cause MSA.

The causes of MSA are unknown, although genetics, environmental processes (toxins), and lifestyle factors (trauma) may contribute to the underlying pathological processes. Most cases occur at random, without any other cases in the family.

1. MSA-P: The cause of MSA-P is unknown. The affected areas of the brain overlap with areas affected by PD, with similar symptoms. Evidence that it is passed within families has not been found.

2. MSA-C: The cause of MSA-C in people with the sporadic form is also not known. The disease slowly gets worse (it is progressive) and can be passed down through families (inherited form). It can also affect people without a known family history (sporadic form).

Genetics

Researchers have identified certain genes that are involved in the inherited form of this condition. The gene mutations (COQ2, SHC2, and SNCA1) may be involved. Mutations in the COQ2 gene (4q21.23) (encoding an enzyme involved in the biosynthesis of coenzyme Q10) have been shown in multiplex families with MSA, while some variants were associated with an increased risk for sporadic MSA.

One study, involving a group of Japanese patients, found a correlation between the deletion of genes in a specific genetic region and the development of MSA. The region in question includes the SHC2 gene which, in mice and rats, appears to have some function in the nervous system. The authors of this study hypothesized that there may be a link between the deletion of SHC2 and the development of MSA. Heterogeneity of the disease may be reflected in different genetic backgrounds.

The presence of mutations, duplications, and triplications of the SNCA gene encoding α-Syn in familial cases showing features of MSA or Parkinson's disease (PD) gave rise to the question whether SNCA was associated with MSA.

A genome-wide association study (GWAS) reported in 2016 no association of COQ2 and SNCA with MSA, but several potential interesting candidates were identified, highlighting the need for further genome studies with larger and well-characterized MSA samples to understand the genetics of this disorder (Sailer et al. 2016). Recently, a GWAS summary statistics study of MSA and seven autoimmune diseases identified a shared genetic etiology between MSA and inflammatory bowel disease (Shadrin et al., 2020). These findings reinforced the role of neuroinflammation and the gut-brain axis in association with a possible polygenic predisposition in the pathophysiology MSA.

Diagnosis of MSA

The diagnosis of MSA is clinically based on the combination of signs and symptoms, medical history, physical examination, laboratory test results, various autonomic insufficiency tests, neuroradiological

imaging studies, and response to certain treatments. The tests can help determine whether the diagnosis is 'probable MSA' or 'possible MSA'. "Probable" MSA requires the presence of parkinsonism with poor Levodopa response or cerebellar signs together with severe autonomic failure (otherwise unexplained urinary incontinence or an orthostatic decrease of blood pressure within 3 min of standing-up by at least 30 mm Hg systolic or 15 mm Hg diastolic). MRI findings include atrophy of putamen and middle cerebellar peduncles, as well as putaminal and cerebellar hypometabolism on [18F]-fluorodeoxyglucose positron emission tomography (PET). 'Definite" MSA requires post-mortem demonstration of α-Syn positive GCIs with neurodegeneration of striatonigral and olivopontocerebellar structures.

However, reaching a diagnosis can be challenging and difficult, particularly in the early stages, in part because many of its features are similar to those observed in PD, parkinsonism, and a number of other confounding diseases. Because of this difficulty, some people are actually never properly diagnosed. It must be noted that no laboratory or imaging studies are able to definitively confirm the diagnosis. Further, it is necessarily differential as MSA may be confused with other diseases. In addition, the histologic proof can only be obtained post mortem as it is impossible to identify a buildup of α-synuclein in areas of the brain (a hallmark of the disease) while the person is alive. The diagnosis, therefore, remains essentially clinical and differential.

It is common for healthcare providers to initially diagnose a person as having PD or another form of parkinsonism, and then to revise the diagnosis when other symptoms appear or when certain treatments do not work.

Main differential diagnoses

In addition to pure autonomic failure, autonomic neuropathies, multiple cerebral infarcts, drug-induced parkinsonism, cerebellar symptoms, and response to certain medications, the main differential diagnoses seek to rule-out any one or more of the following diseases:

- **Alzheimer 's disease (AD).**
- **Corticobasal degeneration (CBD)** manifested by obvious signs of cortical dysfunction (e.g., apraxia, dementia, and aphasia).
- **Creutzfeldt-Jakob disease (CJD)** where dementia is usually apparent with myoclonic jerking, ataxia, and common pyramidal signs.
- **Dementias** including **Lewy bodies dementia (LBD)**, which **o**ften mimics parkinsonian features and **multi-infarct dementia (MID)** characterized by cognitive impairment, spasticity, and extrapyramidal signs.
- **Frontotemporal degeneration (FTD)**, including **Pick's disease (PD),** which affects the frontal and/or temporal lobes. Here, the level of consciousness is not affected (unlike in AD) and Parkinsonism is usually mild.
- **Guam disease (GD)** or **Lytico-Bodig syndrome (LBS)**.
- **Huntington's disease (HD)** which can present earlier with rigidity instead of chorea when parkinsonism is not expected. Normally, there is family history.
- **Parkinson's disease** (PD): MSA may also present with parkinsonian symptoms, often with a poor or temporary response to Levodopa therapy.
- **Parkinsonism** with atypical syndromes in which a group looks like PD but is much more severe. Median survival is only seven years compared with the normal lifespan in PD.
- **Progressive supranuclear palsy (PSP)** or **Steele-Richardson-Olszewski disease (SROD):** It is characterized by paresis of conjugate gaze with initially problems looking up and down on request, advancing to difficulty in following objects up and down.
- **Tremors:** The variety of confounding tremors

includes benign essential tremor, cerebellar tremor, drug- or toxin-induced tremor, and pyschogenic tremor.

- **Wilson's disease (WD)** with an earlier onset with characteristic Kayser-Fleischer rings and hepatitis.

Differential diagnosis between PD and MSA

PD is the main differential; about 10% of patients diagnosed with PD are actually found to have MSA on autopsy. Features that suggest MSA over PD include: MSA progresses faster; its symptoms develop differently; and it responds poorly to Levodopa.

In 2020, researchers at The University of Texas Health Science Center at Houston concluded that protein misfolding cyclic amplification could be used to distinguish between PD and MSA, providing the first process to give an objective diagnosis of MSA instead of just a differential diagnosis.

Differences between MSA and parkinsonism

MSA is suspected if parkinsonian symptoms are rapidly worsening and Levodopa (used to treat PD) has little or no effect on symptoms.

Diagnostic tests

Clinical diagnostic criteria were defined in 1998 and updated in 2007. Certain signs and symptoms of MSA also occur with other disorders (as listed earlier in this article), making the diagnosis even more difficult. Diagnostic techniques include some or all of the following, as appropriate:

- **Autonomic function tests:** They assess autonomic (body's involuntary) functions that include: Blood pressure, thermoregulatory sweat, bladder function, bowel function, electrocardiogram, and sleep. Other autonomic abnormalities tests include: Diminished respiratory sinus arrhythmia, olfaction, skin biopsy, abnormal response to the Valsalva maneuver, diminished response to isometric exercise, and diminished response to cold pressor stimuli. Generalized failure of autonomic tests is helpful for the diagnosis.

- **Neuropathological tests** Pathological diagnosis can only be made at autopsy by finding abundant glial cytoplasmisc inclusions (GCI) on histological specimens of the central nervous system. Contrary to most other synucleinopathies, which develop α-Syn inclusions primarily in neuronal cell populations, MSA differs in its pathological presentations such as: Extensive pathological α-Syn inclusions, regional differences, and high density of GCIs - a hallmark of MSA.

- **Radiopharmaceutical imaging tests:** They include **DaTscanTM** to assess the dopamine transporter in a part of the brain called the striatum (however, this test cannot differentiate between MSA and PD), Iodine-123 (I-123) scintigraphy, **MIBG** scans to show intact innervation of the heart, which is thought to be useful for differentiation between PD and MSA early after onset of autonomic dysfunction and to show significantly lower cardiac uptake of I-123 in patients with PD have than patients with MSA.

- **Neuroradiological imaging tests** for signs that may suggest MSA and also help determine if there are other causes that may be contributing to the observed symptoms. Both **MRI** and **CT** scanning may show a decrease in the size of the cerebellum and pons in those with cerebellar features (MSA-C). CT or MRI brain scans can sometimes show deterioration in areas of the brain, which can help narrow

down the diagnosis, and are useful in diagnosing MSA-C, which can cause a part of the brain to show a criss-cross pattern (experts call this the “hot cross bun” sign). In particular, MRI scanning is needed to exclude rare secondary causes (e.g., supratensorial tumors and normal pressure hydrocephalus) and extensive subcortical vascular pathology. Functional MRI and CT imaging are useful research tools. Structural MRI may be considered in the differential diagnosis of other parkinsonian syndromes. MRI changes are not required to diagnose the disease as these features are often absent, especially early in the course of the disease. However, characteristic changes in the midbrain, pons, and cerebellum are helpful for the diagnosis. Positron emission tomography (**PET**) scanning with fluorodopa: PET scans may demonstrate if metabolic function is reduced in specific parts of the brain: 123I-FP-CIT single photon emission computerized tomography (**SPECT**) for people in whom essential tremor cannot be clinically differentiated from parkinsonism, and transcranial sonography. It is recommended for the early diagnosis of PD, for the detection of subjects at risk for PD, and for the differentiation of PD from atypical and secondary parkinsonian disorders, however, the technique is not universally available and requires some expertise.

- **Genetic testing** to see if a person has a mutation that changes how their body processes α-Syn. Genetic tests are more likely to identify mutations related to MSA-C in people of Asiatic descent although there are geographical variations. They may be required (e.g., Huntington's gene). Fewer than 5% of all PD cases are caused by known single-gene mutations.

- **Ceruloplasmin levels** may be needed for young-onset or atypical disease (e.g. Wilson's disease).

- **Syphilis serology**

Tables 2-4 respectively summarize the major features supporting the diagnosis of 'probable MSA', 'possible MSA', or an alternative diagnosis:

System	Features	Notes
Autonomic	o Severe (symptomatic or otherwise) orthostatic hypotension o Commonly associated symptoms include light-headedness, dizziness, weakness of legs, fatigue, and syncope. o Postprandial hypotension may be a major feature.	o Blood pressure fall by ≥30 mm Hg systolic and ≥15 mm Hg diastolic within 3-minutes of standing from a previous 3-minute supine position o Associated supine hyper-tension is common, and is aggravated by medication used to reduce orthostatic hypotension.
Urogenital	o Urinary incontinence or incomplete emptying o Erectile dysfunction	o Urinary dysfunction is the most frequent initial complaint in women o Erectile dysfunction is the most frequent initial complaint in men
Extrapyramidal tracts	o Tremor (but not classic pill-rolling) o Rigidity o Bradykinesia o Gait postural instability	o Check that postural instability is not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Cerebellar function	o Gait/limb ataxia o Ataxic dysarthria o Oculomotor dysfunction (sustained	

	gaze-evoked nystagmus)	

Table 2 - Major features supporting the diagnosis of 'probable' MSA

System	Features	Notes
Parkinsonism	Parkinsonism	
Cerebellar	Cerebellar signs	
Autonomic system	Autonomic dysfunction (at least one feature)	Features include: o Urinary symptoms o Erectile dysfunction o Orthostatic hypotension that does not meet the level required in 'probable MSA' (see Table above10.1)
MSA-P or MSA-C	o Babinski's sign with hyper-reflexia. o Stridor	
MSA-P	o Rapidly progressive Parkinsonism with poor response to Levodopa o Postural instability within 3 years of motor onset o Gait ataxia o Cerebellar dysarthria o Limb ataxia o Cerebellar oculomotor dysfunction. o Dysphagia within 5 years of motor onset.	
MSA-C	o Parkinsonism (bradykinesia and rigidity). o Atrophy on MRI of putamen, middle cerebellar peduncle, or pons.	

Table 3: Additional features supporting the diagnosis of 'possible' MSA

Assessment	Feature
History	o Symptomatic onset at <30 years or >75 years o Family history of ataxia or Parkinsonism o Known co-morbidity featuring symptoms and signs listed in Tables 10.1-2 o Hallucinations unrelated to medication o Dementia
Examination	o Classical parkinsonian pill-rolling rest tremor o Clinically significant neuropathy o Prominent slowing of vertical saccades or vertical supranuclear gaze palsy o Evidence of focal cortical dysfunction such as dysphasia, alien limb syndrome, and parietal dysfunction

Table 4: Features suggesting an alternative diagnosis

Other diagnoses

Other diagnoses to consider include: Pure autonomic

failure, progressive supranuclear palsy (Steele - Richardson-Olszewski disease), multi-infarct dementia, multiple sclerosis, neuroacanthocytosis, eurosarcoidosis, and neurosyphilis.

Symptoms Management

Monitoring

Regulatory agencies have approved a few devices to help monitor symptoms. Kinesia 360, KinesiaU, PDMonitor, Personal KinetiGraph (PKG), STAT-ON, and possibly others. They are only conditionally recommended as options for the remote monitoring of PD.

Relief

At present, no available treatment can cure MSA. However, a combination of simple measures and drugs may help relieve symptoms, including for: Parkinsonism (daily activities for muscle strength and flexibility; regular stretching and exercising); orthostatic hypotension (increasing blood pressure by consumption of more salt and water; preventing blood pressure from increasing (raising the head of the bed by about 4 inches=10 centimeters); maintaining blood pressure (standing up slowly; wearing an abdominal binder or compression stockings); non-drug treatments (avoiding triggers of low blood pressure, such as hot weather, alcohol, and dehydration); b**o**dy fluids production (decreasing production); and other measures such as avoiding warm environments to prevent overheating the body, good dental care, use of artificial tears, self-inserted devices (urethra catheters) for urinary retention or incontinence, and regular check-ups.

Management

Currently, no specific treatment can reverse or halt the progression of the disease, but symptoms can be managed in case of orthostatic hypotension, movement disorders, and functional capacity. For instance, recombinant erythropoietin has been shown to correct anemia and improve standing blood pressure.

Pharmacological therapy

Patients require pharmacological therapy because the disorder is progressive and fatal. The therapy targets PD, parkinsonism and autonomic failure. The extrapyramidal and cerebellar aspects of the disease are debilitating and difficult to treat. (Note: The drug Tiluzole is ineffective in treating MSA or PSP.) Thus, for:

- **Autonomic failure:** Increasing blood pressure (using drugs such as Fluorocortisone Midodrine or Droxidopa,).

- **Orthostatic hypotension:** Treatment includes intravascular volume expansion with salt and water supplementation. Sometimes, Fluorocortisone (0.1 to 0.4 mg, orally, once a day) or alpha-adrenoreceptor stimulation with Midodrine (10 mg, orally, 3 times a day) may help. However, Midodrine also increases peripheral vascular resistance and supine blood pressure (BP), which may be problematic. Alternatively, Droxidopa may be used; its action is similar to that of Midodrine, but duration of action is longer.

- **Urinary retention**: Bethanechol (10-50 mg, orally, 3 or 4 times a day) is used to stimulate contractions of the bladder and, thus, help the bladder empty.
- **Urinary incontinence:** Certain drugs such as Oxybutynin chloride (5 mg, orally, 3 times a day), Mirabegron (25-50 mg, once a day), Tamsulosin (0.4-0.8 mg, once a day), or Tolterodine (2 mg, taken by mouth, 2 times a day), may be used to relax the muscles of an overactive bladder. Tamsulosin may be effective for urinary urgency. Unlike Tamsulosin, the beta-3 adrenergic agonist Mirabegron does not worsen orthostatic

hypotension.

- **Erectile dysfunction:** Sildenafil, Tadalafil (2.5-5 mg, daily), Vardenafil, or Avanafil, taken orally, as needed, can be used.
- **Functional capacity:** Recombinant erythropoietin increases the functional capacity of patients, particularly if there is associated mild anemia, which is common. It has been shown to correct anemia and improve standing blood pressure.
- M**ovement disorders:** Usually treated with Levodopa, dopaminergic agonists, anticholinergic agents, or Amantadine, but effectiveness may be limited.
- **PD:** Levodopa plus Carbidopa may be tried, but this combination usually has little effect or is effective for only a few years.
- Parkinsonism: Levodopa (L-Dopa) improves parkinsonian symptoms in a small percentage of MSA patients. Levodopa/Carbidopa (25-100 mg, taken orally at bedtime) may be tried to relieve rigidity and other parkinsonian symptoms, but this combination is usually ineffective or provides modest benefit. Other agents that are much less often used include NSAIDs (non-steroidal anti-inflammatory drugs), antihistamines, somatostatin analogues, caffeine, and Yohimbine.
- **Postural hypotension:** It often responds to Fluorocortisone, a synthetic mineralocorticoid. Another common drug treatment is the alpha-agonist Midodrine.

Supervision

Ongoing care from a neurologist specializing in movement disorders is recommended because the complex symptoms of MSA are often not familiar to less-specialized neurologists. Hospice/homecare services can be very useful as disability progresses.

Rehabilitation

Management by rehabilitation professionals including physiatrists, physiotherapists, occupational therapists, speech therapists, and others for difficulties with walking/movement, daily tasks, and speech problems is essential. Physiotherapists can help to maintain the patient's mobility and will help to prevent contractures. Instructing patients in gait training will help to improve their mobility and decrease their risk of falls. A physiotherapist may also prescribe mobility aids such as a cane or a walker to increase the patient's safety. Physical and occupational therapists can teach people ways to compensate when walking, doing daily activities, and speaking become difficult. Social workers can help people find support groups and, when symptoms become disabling, home health care or hospice services. Speech therapists may assist in assessing, treating, and supporting speech (dysarthria) and swallowing difficulties (dysphagia). Speech changes mean that alternative communication may be needed, for example, communication aids or word charts. Early intervention of swallowing difficulties is particularly useful to allow for discussion around tube feeding further in the disease progression. At some point in the progression of the disease, fluid and food modification may be implemented.

Supportive care

As the disease progresses, people may need a breathing tube and/or a feeding tube (usually surgically inserted), or both. Clinicians should advise patients to prepare advance directives soon after MSA is diagnosed.

Treatment of MSA

Pharmacological

The disease etiology not being fully understood, there are currently no treatments to delay or arrest the progressive neurodegeneration of MSA, and there is no cure. The condition progresses gradually and eventually leads to death. However, there are alleviating treatments

to help people cope with the symptoms of MSA. Management options remain very limited and novel treatment options are continuously being investigated. The following are the treatments usually prescribed for the conditions indicated:

- **Bladder control problems:** T**hey** are treated according to the nature of the problem. Anticholinergic drugs, such as Oxybutynin or Tolteridine, may help reduce the sudden urge to urinate.
- **Dystonia:** Fixed abnormal muscle postures (dystonia) may be controlled with injections of botulinum toxin.
- **Mobility issues:** Physical therapy helps maintain mobility, reduce contractures (chronic shortening of muscles or tendons around joints, which prevents the joints from moving freely), and decrease muscle spasms and abnormal posture.
- **Motor function:** For some individuals, those in the variation MSA-P, the Parkinson's drug Levodopa may improve motor function, but the benefit may not continue as the disease progresses.
- **Orthostatic hypotension:** The fainting and lightheadedness from orthostatic hypotension may be treated with interventions such as wearing compression stockings, adding extra salt and/or water to the diet, and avoiding heavy meals. The drugs fluorocortisone and Midodrine are usually prescribed. In the U.S., the Food and Drug Administration (FDA) approved the medication Droxidopa for the treatment of orthostatic hypotension seen in MSA. Dihydroxyphenylserine helps replace chemical signals called neurotransmitters which are decreased in the autonomic nervous system in MSA.
- **Sleep problems:** Sleep problems such as rapid eye movement/sleep behavior disorder (REM/SBD) can be treated with medicines including Clonazepam, Melatonin, or some antidepressants.
- **Swallowing difficulties:** Some individuals with MSA may have significant difficulties with swallowing and may need a feeding tube or nutritional support. Speech therapy may be helpful in identifying strategies to address swallowing difficulties.
- **Complications:** The progression of MSA varies, but the condition does not go into remission. As the disorder progresses, daily activities become more difficult. Possible complications include:

1. **Motor complications:** They are usually related to the use of anti-parkinsonian medication, and include: Deteriorating function; loss of ability to care for oneself in day-to-day activities; loss of drug effect; motor fluctuations; dyskinesia; freezing of gait; falls and resultant injuries caused by poor balance or fainting; and progressive immobility that can lead to secondary problems such as a breakdown of skin.

2. **Non-motor complications:** These include: Mental health conditions (anxiety; apathy; depression; and psychotic symptoms of delusions and hallucinations); dementia; cognitive impairment; and impulse control disorders.

3. **Autonomic dysfunctions:** These include: Breathing problems during sleep; constipation; orthostatic hypotension; dysphagia; weight loss; excessive salivation and sweating; vocal cord paralysis; increased difficulty swallowing; bladder issues; and sexual problems.

4. **Other complications:** Nausea and vomiting; pain; sleep disturbance and daytime sleepiness; aspiration pneumonia; and pressure sores.

Use of orphan, repurposed, off-label, and compassionate use medicines

- **Orphan medicines:** They are intended for the diagnosis, prevention or treatment of rare diseases in general. They may also be pediatric medicines for the treatment of rare diseases in children or for advanced therapies. These medicines were called "orphan" because under normal market conditions (i.e. in the absence of an orphan regulation), the pharmaceutical industry has little interest in developing and marketing products intended for only a small number of patients, when the high cost of bringing a medicinal product to market may not be recovered by the expected sales of the product:
  - **Advanced therapy medicinal products:** They are medicines for human use that are based on genes, tissues or cells. They are highly relevant for the treatment of rare diseases as they might, for example, target the genetic cause of a rare disease. Research to develop ATMPs for rare diseases creates a pool of knowledge that can be highly valuable for the development of medicinal products for more common diseases.
  - **Other treatment forms available for rare diseases:** Assistive technologies and digital devices, medical devices, physiotherapy, radiotherapy, and surgery may also be used in the treatment of rare diseases.

- **Repurposed medicines:** A repurposed medicine is a medicine already approved for human use in a certain indication and for which researchers or clinicians identify new disease(s) that the medicine could treat (i.e. a new indication). Because the medicine is already in use, some data are already available, especially regarding the safety profile of the medicine. Additional data have to be collected through a clinical study to confirm the efficacy of the medicine in the new patient population. However, the repurposing approach brings advantages for a rare disease as it saves money and time as a new compound does not have to be found and developed from scratch.
- **Off-label use medicines:** When doctors prescribe a medicine for a use different from what is authorized on the label, this is called "off label" use, for example, when the drug is prescribed for a different disease or when the dosage differs from the one stated on the label. Patients with rare diseases and their families are often familiar with this practice, or may not even realize that they are taking products that are prescribed "off-label".
- **Compassionate use medicines:** A compassionate use program (CUP) consists of making a medicinal product available for compassionate reasons to a group of patients (or sometimes individual patients on a case-by-case basis) with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product.

Table 5 provides a list of all FDA-approved therapies and corresponding drugs:

Type of therapy	Drugs
Anti-inflammatory therapies	o Intravenous immunoglobulins (IVIg) o Lenalidomide o Rituximab
Alpha-synuclein targeted therapies	o Affitopac (R) PD01A o Belmacasan (VX-766) o FTY220 (Fingolimod) o Kalliterein-6 o Lu AF82422 (alpha-synuclein mAD) o MPLA o NBMI o Sirolinus o Synuclean-D o TAK-34
Neuroprotective therapies	o BNN-20 o Exonatide o Gene therapy (AAV 2-GDNF) o Inosine 5 – Monophosphate o Intranasal insulin (INI) o Stearoyl-coA desaterase inhibition o Stem cells o Ubiquinofi o Verdiperstat (BHV-3241)
Diagnosis & Biomarkers	o Alpha-synuclein o Alzheimer's disease biomarkers o Brain network activation o DaTscanTM Iofluopane (12) injection/ SPECT imaging o Digital speech analysis (Bvoice 4P D-MSA) o (18-F)F-Dopa imaging o Gait analysis o Magnetic Resonance Imaging (MRI) o Morphomer TM library PET tracer specific for alpha-synuclein o Transcranial magnetic stimulation (TMS) o Web-based automated imaging
Symptomatic treatments	o Abdominal binder o Ampreloxetine/TD-9855 o Atomoxetine o Botilunum A toxin o Continuous positive airway pressure (CPAP) o Deep brain stimulation (DBS) o Droxidopa o Expiratory muscle strength training (EMST) o Fipamezole (JP-1730) o Midodrine o Midodrine + Droxidopa o Nebivolol o NDMA modulator o Repetitive transcranial magnetic stimulation (rTMS) o Riluzole o Safinamide o Zoledronic acid

Source: (U.S.) FDA

Table 5: FDA-approved therapies and corresponding drugs

Use of experimental disease-modifying drugs/therapies

The treatment approaches discussed here are based on our current understanding of the pathogenesis of MSA and the results of preclinical and clinical therapeutic studies conducted over the last two decades. They point to putative targets for disease modification, including the leading disease-modifying drugs/therapies (DMD/T): Targeting α-Syn pathology, modulating neuroinflammation, and enhancing neuroprotection.

While the pathogenic mechanisms underlying MSA remain inconclusive, the evidence collected from *post-mortem* studies and preclinical models classifies MSA as a primary oligodendrogliopathy, included in the category of α--synucleinopathies together with PD and DLB The presence of α-Syn aggregates in the cytoplasm of oligodendrocytes defines MSA as a unique α--synucleinopathy. By contrast, in PD and DLB, α-Syn pathology occurs mostly in the cytoplasm of neurons. These observations result in several questions that we cannot completely answer so far. For instance, what is the source of α-Syn within oligodendrocytes? Are the α-Syn inclusions a disease trigger or an epiphenomenon? Where should we focus when defining therapeutic targets in MSA?

Targeting alpha-synuclein pathology: α-Syn is an intrinsically disordered protein widely distributed in the central nervous system (CNS), more precisely in the pre-synaptic terminals of neurons, with a suggested physiological role in synaptic homeostasis, vesicle recycling, and synaptic neurotransmission. Under pathological conditions, such as α-Syn mutations, multiplications, and post-translational modifications or stress-induced changes in the cellular environment, α-Syn becomes highly prone to aggregate into pathological oligomeric and large fibrillary structures such as GCIs and Lewy Bodies (LB). To date, the process of α-Syn accumulation and aggregation is considered to be one of the main pathological events underlying α-synucleinopathies, leading to neuronal dysfunction, neuroinflammation, and neurodegeneration. Specifically, pathological forms of α-Syn seem to interact with cellular components and pathways affecting the cellular homeostasis. Recently, it was observed that in the process of α-Syn aggregation, the formation of different fibrillary strains can arise in MSA as compared to PD or DLB.

Enhancing the degradation of α-Syn: It can be accomplished under one or more of the following processes:

Inducing α-Syn degradation by stimulating macroautophagy: Initial studies were conducted using Rapamycin, Lithium, and Nilotinib. Lithium was discarded due to severe adverse effects and Nilotinib did not show neuroprotective effects.

Promoting α-Syn degradation by microglial cells: It increases the extracellular a-Syn clearance.

Up-regulating Toll-like receptor 4 (TLR4) in microglia: TLR4 plays an important role in the microglial α-Syn clearance. It was tested experimentally using monophosphoryl lipid A (MPLA), a TLR4 selective agonist and vaccine component with lower pro-inflammatory toxicity. It showed that the administration of MPLA led to a significant motor improvement, preservation of nigral dopaminergic neurons, and decreased levels of GCIs.

Disrupting the oligomerization process of α-Syn: The small molecule ATH434 (formerly, PTB434) is a moderate iron chelator shown to reduce α-Syn accumulation by redistributing labile iron in the brain. It preserves dopaminergic neurons, lowers ferric iron in the brain and reduces α-Syn oligomerization, resulting in improvement of the motor deficits. In the preclinical stage, two more therapeutic candidates are being evaluated: the molecular tweezer CLR01 and the caspase-1 inhibitor VX-765. CLR01.

Using antisense oligonucleotides (ASON): They suppress the production of α-Syn, and therefore, reduce its intracellular toxic accumulation.

Targeting microglia activation and neuroinflammation:

Neuroinflammation is a crucial part of the neuropathological process in MSA and other α-synucleinopathies. It is mediated by the activation of quiescent microglia cells that respond to neuronal damage and pathological α-Syn by secreting pro- and anti-inflammatory cytokines, chemokines, and reactive oxygen species (ROS). Whether such inflammatory responses are directly associated with the pathogenesis of the disease or represent a downstream effect triggered by the pathological accumulation of α-Syn is still under debate. Although still not well understood, the processes of microglial activation and neuroinflammation have been getting increased attention and exploited for disease-modifying therapies in MSA. According to PET and neuropathological studies in MSA brains, the process of microglial activation and neuroinflammation can be already detected at early-disease stages. Such observations raise the possibility that reduction of microglial pro-inflammatory activity and anti-inflammatory strategies may represent a promising approach for disease modification in MSA.

- **Targeting cellular dysfunction and loss (neuroprotection):** The selective striatonigral degeneration observed in MSA-P patients can lead to the dysfunction of corticostriatal glutamatergic as well as striatal GABAergic projections. The impairment of such projections can result in neurotoxicity and add to the neurodegenerative cascade. On the other hand, the accumulation of α-Syn aggregates within oligodendrocytes leads to the dysfunction of these cells, hampering the neurotrophic support by brain-derived neurotrophic factor (BDNF) and glial-derived neurotropic factor (GDNF) and resulting in neuronal death.
- **Improving impaired growth factors:** Insulin/insulin-like growth factor-1 (IGF-1) signaling and insulin resistance in MSA patients, as well as increased IGF-1 brain levels in MSA mice appear to be involved in several cellular processes including the synthesis of the myelin sheaths and oligodendrocyte maturation as well as neuronal homeostasis. Thereafter ,their deficits lead to neurotoxicity and consequent neurodegeneration. This strategy aims to prevent oligodendroglial dysfunction and provides neuroprotection of the affected neuronal populations.
- **Use of small molecules:**
  - **Rasagiline:** It appears to induce neuroprotection and ameliorate motor deficits but in very high doses, which may not be appropriate in humans due to the associated side effects.
  - **Exendin-4 (Exenatide):** This anti-diabetic drug presents neuroprotective effects.
  - **Sodium phenylbutyrate:** This unspecific histone deacetylase inhibitor may be effective in reducing disease progression of MSA patients. It has not progressed to clinical trials because of its side effects.
  - **Benztropine:** An anti-cholinergic drug has likewise not progressed to clinical trials because, among other reasons, the contribution of the demyelination in early stages of the disease and its causative role for the neurodegeneration has remained uncertain.
  - **Supplementation of the co-enzyme Q10** (reduced form Ubiquinol): It is linked to the contribution of mutations in the COQ2 gene in rare familial MSA cases. It has been proposed as an individualized therapeutic approach for patients carrying the mutation/polymorphisms. At a high yet tolerable dose, it improves mitochondrial oxidative metabolism.
- **Major obstacles and open questions:** Despite the existence of prominent therapeutic strategies supported by extensive preclinical testing and target validation, a serious gap remains in their translation into successful clinical trials in MSA patients. The major difficulties are linked to the

following intertwined factors:

- Absence of useful biomarkers (early in the disease and as the disease progresses).
- Challenge in making an early diagnosis.
- Discrepancies in the design of preclinical and clinical studies.
- Failure of treatment outcome measurements in clinical trials.
- Limited knowledge about the root cause of the disease.
- Failure in defining the best therapeutic target(s) for disease modification.

Participation in clinical trials

Clinical trials are prospective biomedical or biobehavioral research studies on human participants designed to answer specific questions about biomedical or biobehavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. They generate data on dosage, safety, and efficacy and look at new ways to prevent, detect, or treat diseases. Treatments might be new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. They can also look at other aspects of care, such as improving the quality of life for people with chronic illnesses. Their overriding goal is to determine if a new test or treatment works and is safe.

MSA patients can participate in a clinical trial. This is encouraged for those eligible participants. The best way to find out about drug trials and to express interest in participating in one of them is to be referred by one's own neuroradiologist or physician. That healthcare professional will be able to identify possible suitable trials for the existing medical condition, make a referral, and facilitate the enrollment process, as appropriate.

The list of clinical trials available and can be found on-line at www.clinicaltrials.gov. This site lists all registered trials across the world and their status (recruiting, not recruiting, completed, or suspended). The latest information on current drugs in the pipeline and clinical trials is posted at: at: hps://defeatmsa.org/msa-research/pipelines/. The number of clinical trials that are currently recruiting may vary depending on the particular date at which the website is searched. At the date of the preparation of this article, there were 58 such trials.

Growth hormone therapy

Experimentally, growth hormone therapy (GHT) appears to slow the progression of the disease but not significantly. Drugs employed include:

Minocycline: A tetracycline with neuroprotective efficacy in transgenic MSA mice, which has shown some promise in the early stages of the disease in laboratory studies.

Rasagiline: A monoamine-oxidase-B inhibitor which appears to have disease-modifying effects and is soon expected to enter phase 3 trials.

Rifampicin: It has been shown to have the property of preventing α-synuclein aggregation and so is also being considered as a therapeutic candidate.

Immunotherapy

Immunotherapy or biological therapy is “the treatment of disease by activating or suppressing the immune system”. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies. Immunotherapy is under preliminary research for its potential to treat MSA: The use of immunotherapy for the treatment of neurodegenerative disorders consists in the development of anti-α-Syn immunotherapies to enhance the degradation and

clearance of α-Syn.

- **Principle and use;** The principle of immunotherapy (passive or active) is based on the specific binding of the antigen α-Syn and its respective antibody, followed by clearance of the complexes.
- **Activation immunotherapy:** It employs the following antibodies:
  - **Affitope®:** Activation immunization for targeting the α-Syn pathology has been carried out with short synthetic peptide fragments (AFFITOPEs®), mimicking parts of the native sequence and structure of the human α-Syn protein. An 'epitope', also known as 'antigenic determinant', is the part of an antigen that is recognized by the immune system, specifically by antibodies, B-cells, or T-cells. The part of an antibody that binds to the epitope is called a 'paratope'. Although epitopes are usually non-self proteins, sequences derived from the host that can be recognized (as in the case of autoimmune diseases) are also epitopes. The immunogenic peptide, i.e., AFFITOPE, operates a B-cell epitope and is responsible for the specificity of the immune response. Initial studies in PD, DLB, and MSA mouse models demonstrated the efficacy of the AFFITOPE® PD01 and PD03. It triggered specific antibody generation with CNS penetration and lowered α-Syn aggregates and oligomers, leading to neuroprotection and improvement of locomotor behavior in PD and MSA mice, respectively.
  - **PD01 and PD03:** The first phase I clinical trial with PD patients using PD01 suggested good immunogenicity, safety, and tolerability.
  - **Anle138b:** This small molecule modulates the oligomerization of α-Syn. It can be delivered orally and crosses the blood–brain barrier (BBB).It supports the hypothesis that the plasma levels of anti-α-Syn antibodies may reflect not simply the immunogenicity of the used vaccine, but also the level of selective binding to a specific α-Syn conformation.
- **Suppression immunotherapy:** Approaches of suppression immunotherapy target α-Syn pathology using antibodies targeting different α-Syn species. They have been extensively tested pre-clinically in PD models. Several clinical trials testing passive immunization in PD have been launched. First preclinical data supporting the efficacy of passive immunization approach in MSA were also reported and the clinical application in MSA is currently being discussed.

Gene therapy

Gene therapy is the insertion of genes into an individual's cells and tissues to treat hereditary diseases where deleterious mutant alleles can be replaced with functional ones. The genes are usually placed within a non-pathogenic virus, which serves as the vector to penetrate the cells. It can also be used to correct non-genetic deficiencies such as the loss of dopamine in MSA, to modify the function of a group of cells (e.g. convert an excitatory structure to one that is inhibitory) or to provide a source of growth factors.

Fewer than 10% of rare diseases have FDA-approved treatments. About 80% of rare diseases are caused by known alterations in a single gene. This common feature makes these diseases potential candidates for gene therapy, which entails replacing or correcting a defective gene. Developing gene therapies for rare diseases, however, is complex, time consuming, and expensive. The gene therapy development process is hampered by a lack of access to proprietary tools and methods, a dearth of standards, and a one-disease-at-a-time approach. As of December 2021, only two rare diseases have an FDA-approved gene therapy. Currently, a phase I clinical trial with AAV2-GDNF gene therapy in MSA patients is in progress (NCT04680065).

Mesenchymal stem cell therapy

Cell therapies have been of interest in MSA for a long time. Initial efforts in toxin SND models have aimed at restoration of the dopaminergic response. Applied

intravenously, mesenchymal stem cells therapy (MSCT) was found to suppress the exacerbated neuroinflammatory cellular environment by producing anti-inflammatory cytokines and neurotrophic factors and exert neuroprotection in a transgenic MSA mouse model. It may delay the progression of neurological deficits in patients with MSA-cerebellar type.

The treatment with autologous MSCs has been attempted in MSA patients indicating some positive trends. However, due to some insufficiencies in the designs of these clinical trials, further studies are required and currently performed (e.g., NCT02795052, NCT02315027, NCT04876326, NCT04495582) to better evaluate the therapeutic potential of MSCs in MSA patients.

Summary and conclusions

Since it became widely accepted that α-Syn accumulation, spreading, and aggregation constitute major driving forces leading to neurodegeneration, promising therapeutic approaches for the modification of MSA and other α-synucleinopathies have been focused on enhancing α-Syn degradation and preventing or disrupting its aggregation. However, while a considerable amount of preclinical evidence supports this approach, successful clinical trials to prove efficacy in patients are currently awaited. Further, since MSA is a multifactorial disease, multi-target individualized therapies might be necessary to unravel the root cause of the disease and arrive at a cure. In the meantime, tentative and limited symptomatic therapies might continue to be prescribed.

Because of our incomplete understanding of the disease, there are currently no treatments to delay or arrest the progressive neurodegeneration of MSA, and there is no cure. There are alleviating symptomatic treatments that include medications and lifestyle changes. Management options are very limited and offered for issues of motor function, orthostatic hypotension, mobility issues, dystonia, bladder control problems, sleep problems, and swallowing difficulties. Potential drug candidates include Minocycline, Rasagiline, and Rifampicin. Alternatives include orphan, repurposed, off-label, and compassionate use medicines. As appropriate and convenient, patients are encouraged to volunteer for participation in clinical trials for prospective biomedical or biobehavioral research studies, including new treatments and known interventions that warrant further study. Treatments might be new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. However, despite the existence of prominent therapeutic strategies, major obstacles and open questions remain including the absence of useful biomarkers, the challenge in making an early diagnosis, the discrepancies in the design of preclinical and clinical studies, the failure of treatment outcome measurements in clinical trials, the limited knowledge about the root cause of the disease, and the failure in defining the best therapeutic target(s) for disease modification.

Newer therapies include growth hormone therapy, immunotherapy (active, passive), gene therapy, and mesenchymal stem cell therapy. Unfortunately, no reliable approach has been identified yet, despite the extensive preclinical evidence. Nonetheless, there is still hope as our understanding of the biology underlying the rare diseases processes is increasing and significant progress continues to be made.

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