Review

Multiple system atrophy - a clinicopathological update

Kurt A. Jellinger

Institute of Clinical Neurobiology, Vienna, Austria

Corresponding author:
Kurt A. Jellinger · Institute of Clinical Neurobiology · Alberichgasse 5/13, A-1150 Vienna, Austria
kurt.jellinger@univie.ac.at

Submitted: 25 May 2020 · Accepted: 24 June 2020 · Copyedited by: Nicole Schwab · Published: 03 July 2020

Abstract

Multiple system atrophy (MSA) is a fatal, adult-onset neurodegenerative disorder of uncertain etiology, clinically characterized by various combinations of Levo-dopa-unresponsive parkinsonism, and cerebellar, motor, and autonomic dysfunctions. MSA is an α-synucleinopathy with specific glioneuronal degeneration involving striatonigral, olivopontocerebellar, autonomic and peripheral nervous systems. The pathologic hallmark of this unique proteinopathy is the deposition of aberrant α-synuclein (αSyn) in both glia (mainly oligodendroglia) and neurons forming pathological inclusions that cause cell dysfunction and demise. The major variants are striatonigral degeneration (MSA with predominant parkinsonism / MSA-P) and olivopontocerebellar atrophy (MSA with prominent cerebellar ataxia / MSA-C). However, the clinical and pathological features of MSA are broader than previously considered. Studies in various mouse models and human patients have helped to better understand the molecular mechanisms that underlie the progression of the disease. The pathogenesis of MSA is characterized by propagation of disease-specific strains of αSyn from neurons to oligodendroglia and cell-to-cell spreading in a "prion-like" manner, oxidative stress, proteasomal and mitochondrial dysfunctions, myelin dysregulation, neuroinflammation, decreased neurotrophic factors, and energy failure. The combination of these mechanisms results in neurodegeneration with widespread demyelination and a multisystem involvement that is specific for MSA. Clinical diagnostic accuracy and differential diagnosis of MSA have improved by using combined biomarkers. Cognitive impairment, which has been a non-supporting feature of MSA, is not uncommon, while severe dementia is rare. Despite several pharmacological approaches in MSA models, no effective disease-modifying therapeutic strategies are currently available, although many clinical trials targeting disease modification, including immunotherapy and combined approaches, are under way. Multidisciplinary research to elucidate the genetic and molecular background of the noxious processes as the basis for development of an effective treatment of the hitherto incurable disorder are urgently needed.

Keywords: Multiple system atrophy; α-synuclein; Glio-neuronal degeneration; Animal models; Etiopathogenesis; Prion-like seeding; Biomarkers; Experimental therapeutics

Abbreviations

αSyn - α-synuclein, **ADNC -** Alzheimer disease neuropathological changes, **BG -** basal ganglia, **CAA -** cerebral amyloid angiopathy, **CI -** cognitive impairment, **CN -** caudate nucleus, **CNS -** central nervous system, **CSF -** cerebrospinal fluid, **DAT -** dopamine transporter, **FTLD** - frontotemporal lobar degeneration, **GCI -** glial cytoplasmic inclusion, **GDNF -** glia-derived neurotrophic factors, **GP** - globus pallidus, **GWAS -** genome-wide association study, **HPR -** hyperintensive putaminal rim, **LBD -** Lewy body disease, **LBs -** Lewy bodies, **MBP -** myelin basic protein, **MCI -** mild cognitive impairment, **MSA -** multiple system atrophy, **MSA-C -** MSA with prominent cerebellar ataxia, **MSA-P -** MSA with predominant parkinsonism, **OPC -** olivopontocerebellar, **OPCA -** olivopontocerebellar atrophy, **OS -** oxidative stress, **PART -** primary age-related tauopathy, **PD -** Parkinson disease, **PET -** positron emission tomography, **PrPC -** cellular prion protein, **PSP -** progressive supranuclear palsy, **SN -** substantia nigra, **SND -** striatonigral degeneration, **tg -** transgenic, **TPPP -** tubulin polymerization-promoting protein, **wt -** wild type

Introduction

Multiple system atrophy (MSA) is a rare adult-onset and lethal neurodegenerative disorder clinically characterized by rapidly progressing autonomic and motor dysfunctions. The pathological hallmark of MSA, a specific form of α-synucleinopathy, is abnormal accumulation of fibrillar α-synuclein (αSyn) in oligodendrocytes as glial cytoplasmic inclusions (GCI) [1], which may represent a primary pathologic event [2]. Degeneration of many neuronal pathways causes multifaceted clinical phenotypes: a parkinsonian variant (MSA-P), associated with striatonigral degeneration (SND), and a cerebellar (MSA-C) variant with olivopontocerebellar atrophy (OPCA) [3]. In addition to combined or "mixed" MSA, there are several disease variants [4-6]. The underlying molecular mechanisms are poorly understood, but converging evidence suggests that a "prion-like" spreading of disease-specific αSyn strains is involved in the pathogenic cascade leading to a specific multisystem neurodegeneration in this (oligodendro)glioneuronal proteinopathy [4, 7-12]. The aim of the present review is to describe recent advances in MSA neuropathology, clinical diagnosis, neuroimaging, and candidate biomarkers. It further provides an overview of the mechanisms underlying MSA pathogenesis and of possible novel therapeutic targets that have emerged from animal studies and preclinical interventional trials [13-16].

Epidemiology

MSA is a rare disease with an estimated incidence of 0.6-0.7/100,000 person-years [17], although studies from Russia and Northern Sweden have reported incidences of 0.1 and 2.4/100,000 person-years, respectively [18, 19]. Prevalence estimates range from 1.9 to 4.9/100,000 [20] but may reach up to 7.8 after the age of 40 years [21], and up to 12/100,000 after the age of 70 [22]. MSA-P accounts for 70-80% of cases in the western world [23], whereas MSA-C is more frequent in Asian populations (67-84%) with rather frequent mixed phenotypes [24-27], probably due to genetic and environmental factors [5].

Etiology and genetics

MSA is generally considered a sporadic disease [17], but MSA pedigrees with both autosomal dominant and autosomal recessive inheritance patterns have been reported in Europe and Asia [28-33]. A genome-wide association study (GWAS) found an estimated heritability of 2-7% [34], but unlike Parkinson disease (PD), no single gene mutations linked to familial forms and no definite environmental risk factors have been identified [35]. Screening for PD causal genes (MAPT, PDYN, Parkin, PINK1, and several single nucleotide polymorphisms/SNPs) did not reveal any association with MSA [36-38], while LRRK2 exon variants may contribute to its susceptibility [39]. Glucocerebrosidase (GBA) variants were associated with autopsy-proven MSA [40, 41], particularly with MSA-C [42], while others have found no association [43]. Furthermore, C9ORF72 repeat expansions [44] and SNCA polymorphisms as risk factors of MSA [45, 46] have not been confirmed [47-49]. No significant associations of the APOE locus nor the prion PRNP with risk of MSA was observed [50, 51], and there is

no evidence of autosomal dominant MSA or of *de novo* mutations in this disorder [52]. A British family with SNCA mutation showed neuropathologic features of both PD and MSA [53], but they are distinct from PD patients carrying the H50Q or SNCA duplication [54]. None of the nucleotide polymorphisms (FBXO47, ELOVL7, EDN1, etc.) reached genome-wide significance [34], and polymorphisms of the LINGO1 and LINGO2 (nogo receptor interacting protein-1 and -2) do not decrease the risk of MSA [55]. The possible involvement of the SNCA, COQ2, MAPT, GBA1, LRRK2 and C9ORF72 genes in MSA pathogenesis was examined recently [56].

The link between V393A mutations and the COQ2 gene, encoding the coenzyme Q10 (COQ10), and familial or sporadic MSA in Japanese and other Asian populations [44, 57-61] has not been confirmed in other populations [34, 62-64]. Thus, COQ2 polymorphisms may be region-specific and may not represent common genetic factors for MSA. Decreased levels of COQ10 in cerebellum and plasma of MSA patients [65, 66] suggest that its deficiency may contribute to pathogenesis due to decreased electron transport in the mitochondria and increased vulnerability to oxidative stress (OS) [67].

RNA analyses of MSA brain tissue revealed alterations in α- and β-immunoglobuline [68], dysregulations of microRNAs that regulate gene expression in the pons and cerebellum [69, 70], and disruption of long intervening non-coding RNAs (lincRNA) in the frontal cortex along with protein coding genes related to iron metabolism and immune response regulation [71, 72]. Epidemiological studies suggested that epigenetic factors or environmental toxins may be associated with the risk for MSA [73], but there are no convincing data correlating increased risk of MSA with exposure to pesticides, solvents, other toxins, or alcohol consumption [74, 75].

Pathogenesis

Although our understanding of MSA remains incomplete, evidence from animal models and human post mortem studies indicates that the accumulation of misfolded αSyn, particularly in oligodendrocytes but also in neurons, plays an essential role in the disease process [10, 76-78]. The impact of the neuronal endosomal-lysosomal system in the processing of αSyn in PD is well established, while lysosomes contribute to the pathogenesis of MSA, enabling oligodendroglial and neuronal uptakt of αSyn [79]. Reduced oligodendrocyte-derived enriched microvesicles (OEMVs) could be an important mechanism related to pathological αSyn aggregation in oligodendrocytes [80]. Although it has been speculated that primary neuronal pathology leads to secondary oligodendroglial degeneration, as suggested by the widespread occurrence of NCIs even in areas lacking GCIs [77], the distribution and severity of neurodegeneration reflects subregional GCI density and supports the assumption that MSA is a primary oligodendrogliopathy [2, 81]. The role of oligodendroglia in introducing the neurodegenerative process was confirmed experimentally in transgenic (tg) mice overexpressing αSyn in oligodendrocytes [10, 13, 82-84]. These and other results highlight the role of endogenous αSyn and p25α in the formation of αSyn assemblies in oligodendrocytes and provide *in vivo* evidence of the role of oligodendroglial αSyn in the establishment of αSyn pathology in MSA [85]. Early events are an ectopic appearance of αSyn in oligodendrocytes, loss of the cAMP-regulated phosphoprotein of 32kDA (DARPP-32), and calbindin indicating calcium toxicity and disturbance of phosphorylated proteins [86]. Recent findings suggest the possibility of endogenous αSyn accumulation in oligodendrocyte precursor cells that contribute to GCI formation and perturbation of neuronal/glia support in MSA brain [86a]. Reduced OEMVs could be an important mechanism related to pathological αSyn aggregates in oligodendroglia, inducing dysfunction of the SNARE protein complex, which regulates membran fusion in eukaryotic cells. The concentrations of OEMVs in MSA were significantly reduced compared to those in PD [80]. Decreased expression of glia-derived neurotrophic factors (GDNF) in MSA brains [87] indicates that αSyn aggregation in oligodendrocytes impacts their trophic transport to neurons. Oligodendroglial changes are more widespread than αSyn positive GCIs, suggesting that oligodendroglial pathology induces degeneration of the oligodendroglia-myelin-axon-neuron complex [2, 26]. The selectivity of the neurodegeneration in MSA is determined by the interaction of multiple noxious factors. Some of these factors include:

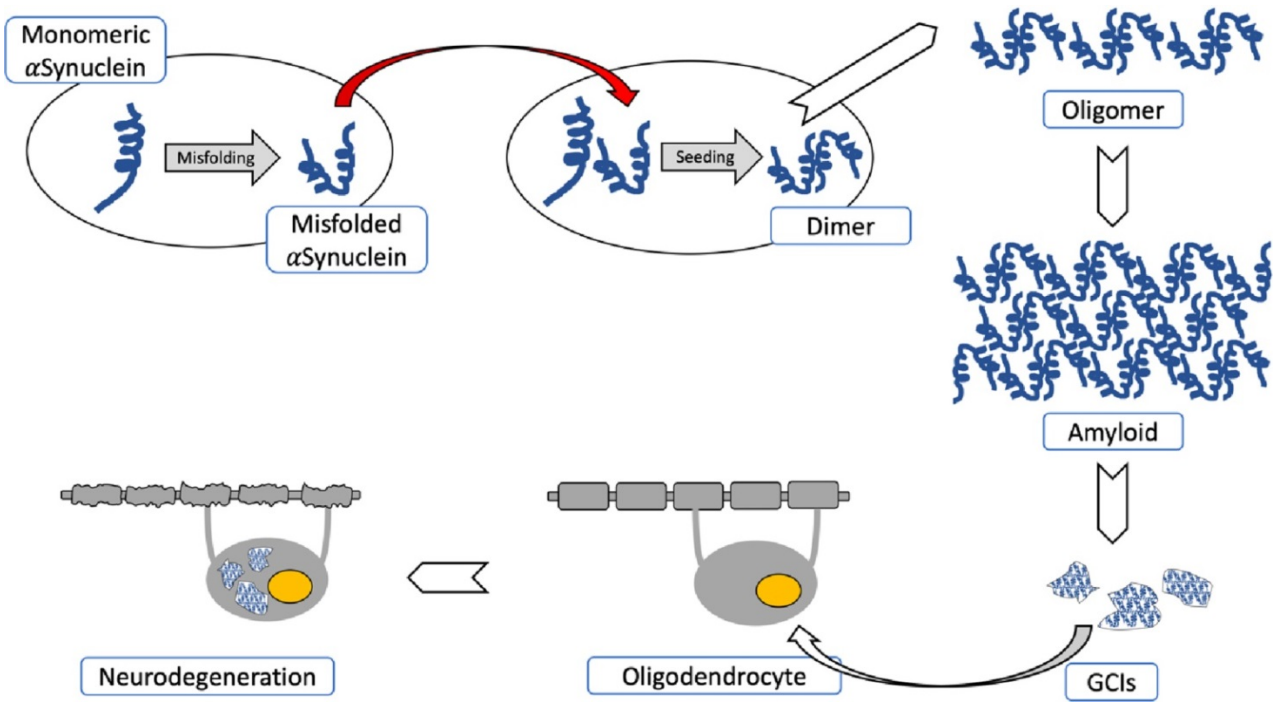

Fig. 1. Pathogenetical features of MSA causing neurodegeneration. Spontaneous misfolding of αSyn results in formation of abnormally folded dimers and further assembly results in oligomers and amyloid formations. αSyn-rich GCIs involving oligodendroglia result in demyelization and neurodegeneration. The red arrow shows the "prion-like" cell-to-cell transfer of misfolded αSyn.

Courtesy of Victoria Sidoroff, MD, Dept. of Neurology, Medical University of Innsbruck, Innsbruck, Austria

ectopic αSyn accumulation in oligodendrocytes and neurons, "prion-like" propagation of disease-specific strains of misfolded αSyn [88], targeting distinct brain regions and cell types [89, 90], impaired protein degradation, proteasomal and mitochondrial dysfunctions [91, 92], alterations of the autophagic pathway [91, 93, 94], perturbed iron homeostasis [95], lipid dysfunction involved in myelin synthesis [96-98], genetic polymorphism [55], microglial activation [97, 99], neuroinflammation [100], proteolytic disturbance, autophagy [101], and microRNA dysregulation [102] driving inflammation, disrupting myelin, and contributing αSyn accumulation via the dysregulation of autophagy and prion mechanisms [103]. These and other factors are contributing to OS, which is suggested to be a major pathogenic factor in MSA and related diseases [104]. These multiple mechanisms interact to result in the system-specific pattern of neurodegeneration in MSA (Fig. 1). TNFα-dependent neuroinflammation may play a key role in MSA pathogenesis, and its relevance has been underlined in various models of the disease [105]. αSyn, which shows specific conformational strains [88, 106] that are primarily generated by neurons, can be toxic once released to the extracellular environment [107] and can spread throughout the brain in a "prion-like" manner [9, 108-111]. Extracellular αSyn, interacting with neuronal and non-neuronal cell types, mediates neuroinflammation and cell-to-cell spread [112, 113]. Neuron-to-oligodendrocyte transport of misfolded αSyn plays a major role in the pathogenesis of MSA [114, 115]. MSA and PD show different phosphorylation signatures of αSyn and distinct seed characteristics, indicating that distinct strains underlie these diseases [90, 116, 117]. After propagation in TgM83 tg mice, strain-specific phenotypic differences are maintained after serial transmission, providing evidence that disease heterogeneity among the synucleinopathies is caused by distinct αSyn strains [89]. MSA strains show several similarities to PD strains, and less so with DLB strains, but more potently induce motor deficits, nigrostriatal degeneration, αSyn spreading, and inflammation, reflecting the aggressive nature of this disease [118].

Recent animal model studies that only partially replicate the human disorder have provided some progress in our understanding of MSA pathogenesis [13, 15, 84, 119, 120]. Early accumulation of p25α (TPPP), a potent stimulator of αSyn aggregation, may decrease myelin basic protein (MBP), favoring both the deposition and fibrillation of αSyn and changing myelin metabolism [121]. Relocation of p25α from the myelin sheaths to the oligodendroglial soma, due to mitochondrial dysfunction, and the formation of cytoplasmic p25α inclusions precedes the aggregation of transformed αSyn in oligodendrocytes. Endogenous αSyn and p25α induce the formation of pathological αSyn assemblies in oligodendrocytes and provide *in vivo* evidence of their contribution to the pathogenesis of MSA [85]. Although large inclusions appear in a later disease states, small, soluble assemblies of αSyn, promoted by p25α, are pathogenic [122]. The source of αSyn in oligodendroglia is unclear, but it contains αSyn mRNA expression and αSyn may be secreted by neurons and taken up by oligodendrocytes, which is facilitated by protein Cx32 via direct protein-protein interaction in both neurons and oligodendroglia [115]. 21% of proteins found consistently in GCIs and LBs are synaptic vesicle-related, suggesting that misfolded αSyn may be targeted via vesicle-mediated transport, and may explain the presence of this neuronal protein within GCIs [123]. Thus, MSA represents a specific form of oligodendroglial proteinopathies [124], while others suggest that it is a primary neuronal disease with secondary accumulation of αSyn in oligodendrocytes [77]. Induced pluripotent stem cell (iPSC) studies indicate a pathological phenotype of MSA neurons, independently from oligodendrocytes. These data together with findings in animal models suggest that both neurons and oligodendrocytes are affected in MSA [91]. The disease is currently viewed as a primary synucleinopathy with specific glio-neuronal degeneration developing via the oligo-myelin-axon-neuron complex [2, 4].

Histopathology and molecular pathology

The histological core features of MSA encompass the following types of different severity: (1)specific αSyn-immunoreactive inclusion pathology with five types of inclusions: GCIs within oligodendrocytes (also referred to as Papp-Lantos bodies [125], the presence of which is mandatory for the *post mortem* diagnosis of definite MSA [1]) and less frequently glial nuclear inclusions, neuronal nuclear inclusions, astroglial cytoplasmic inclusions, and neuronal threads, also composed of αSyn [126]; (2) selective neuronal loss and axonal degeneration involving multiple regions of the nervous system; (3) extensive myelin degeneration with pallor and reduction in MBP with astrogliosis; and (4) widespread microglial activation [127] and neuroinflammation [128, 129], with extensive CD4 and CD8 T-cell infiltration [130]. GCIs and the resulting neurodegeneration show a characteristic distribution, involving not only the striatonigral and OPC systems, but also cortical regions, autonomic and motor nuclei in the brainstem, spinal cord, preganglionic autonomic nerve structures [131-134], and the peripheral nervous system [135-138], characterizing MSA as a multi-system/-organ disorder [2, 77, 139]. Phosphorylated αSyn is accumulated in subpial and periventricular astrocytes after long disease duration [140]. However, αSyn-positive astrocytes in subpial and perivascular regions are seen in both MSA and Lewy body disease (LBD), suggesting that this pathology is not a specific feature of MSA [141].

Inclusion pathology

GCIs are argyrophilic, triangular, sickle-/half moon-shaped or oval cytoplasmic aggregations, composed of fibrillar αSyn, ubiquitin and various multifunctional proteins, including 14-3-3 protein, LRRK2, aggressomal proteins, etc. [125] (Fig. 2). They form a meshwork of loosely packed filaments or tubules 15-30 nm in diameter with a periodicity of 70-90 nm and straight filaments, both composed of polymerized αSyn granular material and other filaments. The central core contains phosphorylated (ser129) αSyn Cryo-EM showed that αSyn inclusions from MSA are made of two types of filaments, each of which consists of two different protofilaments. Each type contains non-proteinaceous molecules at the interface of the two proteofilaments. Thus, they differ from those in DLB brain, which suggests that distinct conformations/strains are characteristic for specific synucleinopathies. In addition, αSyn filament extracts from MSA tissue

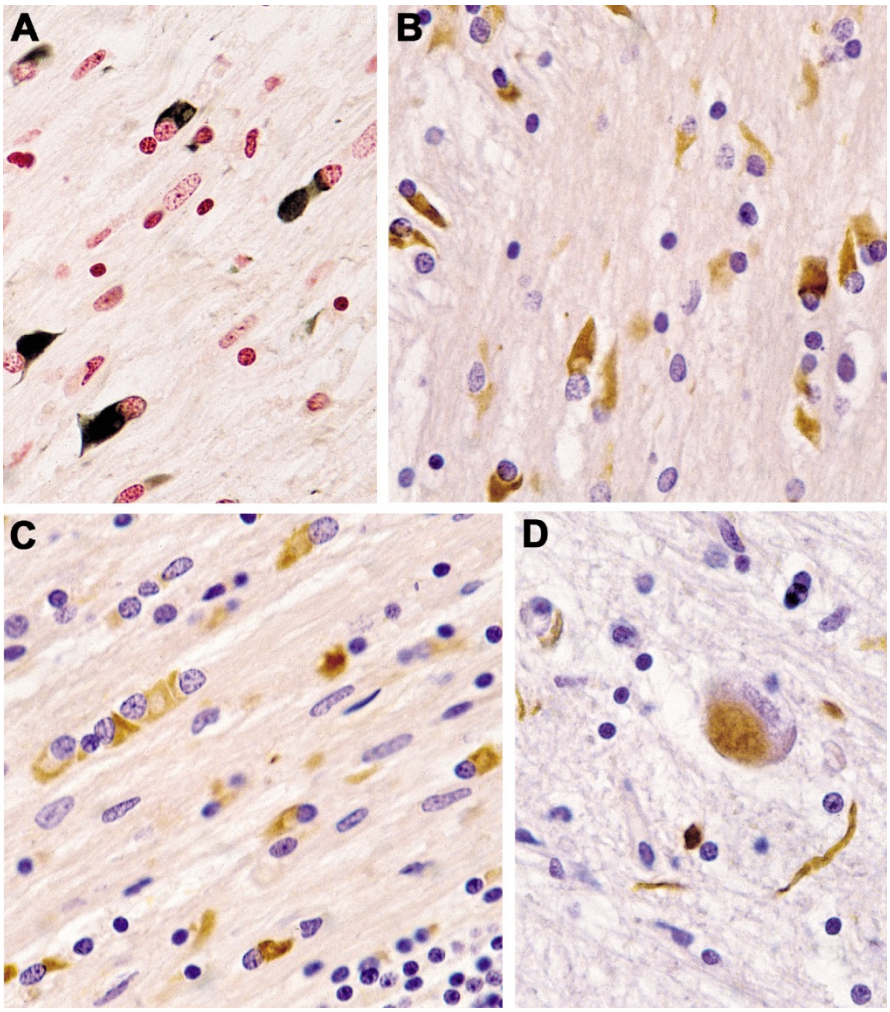

Fig. 2. (A–C) Glial cytoplamic inclusions in MSA: (A) in globus pallidus (Gallyas silver impregnation), (B) in pontine basis (α-Synuclein) and (C) in frontal white matter, anti-ubiquitin. (D) Neuronal cytoplasmic inclusion and neurites in pontine basis (α-Synuclein). (A–D) original magnification 34,000.

From [126].

differ from those formed in vitro using recombinant proteins, which may have implications for the mechanisms of protein aggregation and neurodegeneration [142]. Soluble αSyn in GCIs differs from the insoluble form in Lewy bodies (LBs) [143]. Purification of αSyn containing GCIs revealed 11.9% αSyn, 2.8% α-β-crystallin, and 1.7% 14-3-3 protein compared to 8.5%, 2.0% and 1.5% in LBs [144]. In the MSA brain, αSyn 140 and 122 isoform levels are increased, whereas αSyn 126 is decreased, in the substantia nigra (SN), striatum, and cerebellum. In early disease states, diffuse αSyn staining in neuronal nuclei and cytoplasm occurs in many gray matter areas, indicating that aggregation of non-fibrillary αSyn occurs early in neurons [26]. Recent studies using a proximity ligation assay revealed a wide distribution of αSyn oligomers not only in oligodendrocytes but also in neocortical neurons and Purkinje cells, suggesting that αSyn oligomer-mediated toxicity is an early event in MSA, inducing neuronal loss in MSA [145].

On the other side, interactions exist between extracellular αSyn and each of the major central nervous system (CNS) cell types. This has thepotential to contribute to secondary disease processes such as neuroinflammation, synaptic dysfunc-tion, and cell-to-cell spread, with vehicles such as microglia and exosomes that mediate spread of αSyn pathology to peripheral brain regions [113]. Cathepsin-D, calpain-1 and kallikrein-6 are elevated in the putamen, pontine basis, and cerebellar white

matter, indicating that αSyn accumulation is not due to reduced activity of these proteases, but rather that their upregulation is compensatory to increased αSyn [146]. Iron levels in basal ganglia (BG) and SN are higher in MSA than in PD and controls, indicating perturbed iron homeostasis as a potential pathogenic factor in MSA neurodegeneration [95].

Quantitative analyses of neuronal death and GCI density showed a positive correlation with each other, indicating the pivotal role of GCIs in neuronal death [81, 147], and additionally, both lesions increase with disease duration [148-150]. In the SN, severe neuronal loss is accompanied by low GCI density, indicating that this and other areas affected in early disease have been burned out [139].

Glial nuclear inclusions show a distinct distribution from GCIs (Fig. 2D), and similarly the density of neuronal cytoplasmic inclusions (NCIs) and neuronal nuclear inclusions are unrelated to that of GCIs [151]. NCIs are more widespread and show a hierarchical pattern related to the duration of disease but are independent of neuronal destruction, suggesting that other factors may induce the subtype-dependent neuronal loss [77]. Region-specific astrogliosis is positively correlated with αSyn pathology in MSA, in contrast to PD [152], and in general parallels the severity of neurodegeneration [148]. Microglial activation in degenerated regions accompanies GCI pathology and is most abundant in white matter areas with mild to moderate demyelination [153]. In MSA-C, the cerebellar subcortical white matter and cerebellar brainstem projections are the earliest involved, followed by other CNS regions.

Distribution of lesions

A grading system for SND was proposed based on semiquantitative assessment of atrophy, neuronal loss, and the presence of GCIs [154]: Neuronal loss in the SN pars compacta is grade 1; extension to the putamen is grade 2; further involvement of the caudate and globus pallidus (GP) is grade 3. Subsequently, the grading system was extended for both SND and OPCA [155]. Of 42 patients, 22 were assigned as MSA-P and 20 as MSA-C, but none displayed "pure" OPCA pathology or more severe OPCA pathology than SND (i.e., OPCA III+SND I/II). These clinicopathological subtypes correlated with initial symptoms and clinical features of both types. *Post mortem* MRI changes in the putamen (type 1, mild atrophy and isointensity; type 2, atrophy and diffuse hypointensity with a hyperintensive putaminal rim/HPR; type 3, putaminal atrophy and iso- or hypointensity with HPR) reflect various degrees of brain damage [156]. In two large series from the UK and Japan, another grading system for MSA was proposed [148]: each case of SND and OPCA was divided into three grades based on semiquantitative assessment of neuronal loss in regions of interest: for SND, the putamen, GP and SN; and for OPCA the pontine nucleus, cerebellar hemisphere and vermis, inferior olivary nucleus and SN. This classification showed significant clinicopathological correlations. SND phenotypes showed more severe bradykinesia, and the OPCA phenotype more frequently showed cerebellar signs. No patients showed "pure" SND or "pure" OPCA. However, there is an increasing overlap of αSyn pathology with increased duration of the disease the extent of αSyn pathology [157]. Damage to the striatonigral system is most severe in the dorsolateral caudal putamen and lateral SN, suggesting transsynaptic degeneration of the striatonigral fibers.

Consistently and severely affected areas are the putamen, CN, SN, pontine and medullary tegmental nuclei, inferior olives, and cerebellar white matter; moderately affected areas are the motor cortex and GP, and mild lesions involve the cingular cortex, hypothalamus, nucleus basalis of Meynert, thalamus, subthalamus, and pontine tegmentum [158]. Degeneration of the GP and SN leads to dysfunction of these inhibitory nuclei projecting to the motor thalamus, but the SN loss is of dopamine, not GABA (gamma aminobutyric acid), neurons. Stereological studies of the BG revealed a substantial loss of neurons in the SN, putamen, and GP, whereas astrocytes were more frequent in the putamen and caudate nucleus (CN). Microglia were found in all CNS regions with greatest frequency in the, otherwise unaffected, red nucleus. These data support the region-specific pattern of pathological changes in MSA [159]. Another neuropathological study showed that the striatonigral region was most severely affected in 34% of SND and in 17% in OPCA cases, while in almost half of them both re-

gions were equally affected [133]. In view of the frequent overlap and mixed forms, the value of grading systems for evaluation of MSA is under discussion [139].

There is widespread involvement of the neocortex with significant loss of neurons and increase of astrocytes and microglia in the frontal and parietal areas, but no change in the total number of oligodendrocytes [160]. Early degeneration of the BG drives late onset cortical atrophy due to frontostriatal degeneration [161, 162]. Reduced neuronal numbers in the anterior olfactory nucleus and intrabulbar part of the primary olfactory (pyriform) cortex may underlie olfactory dysfunction in MSA [163]. Limbic TDP-43 pathology is rare in MSA, but co-localization with αSyn suggests an interaction between the two molecules [164-167]; TDP-43 positive cases showed significantly older age at death than negative ones, suggesting that TDP-43 pathology in MSA is an age-related phenomenon rather than a disease-specific change [141].

Demyelination of variable intensity affecting all parts of the nervous system [168] is associated with reduction of MBP by about 50% [96]. GCIs and microglial burden are greatest in mild to moderate white matter lesions and decrease with progression of myelin damage that increases with disease duration [169]. The regional vulnerability of the white matter to MSA pathology is poorly understood, but recent GWASs revealed dysregulation of various methylated loci, including HIP1, LMAN2, MOBP, and others, giving the first evidence that DNA methylation changes contribute to the molecular processes altered in MSA [170]. Early MSA stages show increased microglia (about 100%) in the white matter [127], without concomitant astrogliosis or oligodendroglial degeneration [171]. Both microglial activation and αSyn-containing oligodendrocytes trigger neuroinflammation in the white matter [128].

The loss of tubulin polymerization-promoting protein (TPPP)/p25α immunoreactivity correlated significantly with the degree of microglial reaction and loss of MBP density as a marker of tract degeneration [124]. White matter degeneration causes degeneration of neuronal loops, leading to dysfunction of cerebral autoregulation [172]. Gliosis in the degenerated areas of the MSA brain usually correlates with αSyn pathology and the severity of neurodegeneration [153, 173], which is in contrast to PD [174]. Significant increase of monoaminoxidase B (MAO-B), a biomarker of astrogliosis, in the degenerated putamen (+83%) was associated with astrogliosis and showed a positive correlation with αSyn accumulation [175]. Microglial activation accompanying αSyn pathology and phagocytosing degenerating myelin is prominent in all degenerating regions [176], particularly in white matter input tracts to the extrapyramidal system and cerebellum [177]. Stereological studies revealed a significant increase of microglia in the white matter without concomitant astrogliosis and with absence of significant oligodendroglial degeneration [171], suggesting that microglia cells play an important role in the initiation and progression of neurodegeneration in MSA [100, 178]. This is supported by tg mouse models indicating an active contribution of microglial activation by triggering neuroinflammatory responses in the MSA brain [179].

In MSA-C, GCIs are most prominent in the cerebellum, pons, and medulla [169]. The cerebellar Purkinje cells are more severely affected in the vermis, with atrophy of olivary nucleus, cerebellopontine fibers, and pontine basis, causing interruption of specific cerebellocortical circuits [180]. The motor subnetwork in MSA-C is significantly altered in both BG and cerebellar connectivity [181], with hyperintensity of the middle cerebellar peduncle [182].

Involvement of autonomic and peripheral nervous systems

Degeneration of preganglionic autonomic neurons of the brain stem and spinal cord cause multidomain autonomic failures in MSA [133, 183, 184]. Supraspinal lesions involve cholinergic neurons of the ventrolateral nucleus ambiguous [185, 186], tegmental nuclei [187], ventral periaqueductal dopaminergic neurons [188], medullary and arcuate nucleus, noradrenergic locus ceruleus [134], serotonergic medullary groups, ventrolateral medulla [189], caudal raphe neurons [190, 191], catecholaminergic neurons of rostral ventral medulla, and noradrenergic neurons of the caudal ventrolateral medulla [185, 192]. The medullary serotonergic and catecholaminergic systems are

involved in early stages of MSA [193]. Other involved areas are the dorsal vagal nucleus [185], periaqueductal gray [132], the Westphal-Edinger nucleus and posterior hypothalamus, the tuberomamillary and suprachiasmatic nuclei [194], and the pontomedullary reticular formation [149]. The density of αSyn pathology did not correlate with neuronal loss, and there was no correlation between the αSyn burden and disease duration in these regions, indicating that the loss of monoaminergic neurons may progress independently from αSyn accumulation [195]. Sympathetic preganglionic neurons in the intermediolateral cell columns of the thoracolumbar spinal cord [26, 134, 196] and sympathetic ganglia and Schwann cells in autonomic nerves are involved [197]. Neuronal loss affects Onuf's nucleus in the sacral region [198], with minor loss of upper and lower motor neurons [26] and variable involvement of anterior horn cells [134]. Mild degeneration of cardiac sympathetic innervation has been reported in some cases of MSA [199, 200], which accounts for a mild to moderate decrease in the number of tyrosine hydroxylase, but not of neurofilament-immunoreactive nerve fibers in the epicardium. However, depletion of cardiac sympathetic nerves is closely related to the presence of αSyn pathology in the sympathetic ganglia of the CNS [200, 201]. The peripheral nervous system shows αSyn deposits in sympathetic ganglia, skin nerve fibers [138, 202, 203], and Schwann cells [204], but lack of αSyn immunoreactivity in dermal fibers in contrast to PD [203, 205]. Filamentous αSyn aggregates involve the cytoplasm of Schwann cells in cranial, spinal and autonomic nerves in MSA [141, 197, 206].

Clinical features

The onset of motor symptoms is 56±9 (mean ± SD) years, with both sexes equally affected [207], however 20-75% of MSA patients have a prodromal/preclinical phase with non-motor symptoms. This phase includes cardiovascular and other autonomic failures (urogenital and sexual dysfunctions, orthostatic hypotension, and REM sleep behavior disorder (RBD), which occurs in 88% or more [208, 209]), which may precede the motor presentation by months to years [210, 211] and indicates more rapid progression of the disease [212, 213]. Average age at disease onset is earlier in MSA-C compared to MSA-P, the latter leading to more severe disability [214-216]. Average duration after clinical diagnosis is 6-10 (mean 9.5) years [12, 23], with few patients surviving more than 15 years [217]. Others have reported a 5 year survival of 78% [218] and a 43% death rate during 3 years of follow-up [135]. A Pan-American multicenter study reported that 68% of the participants presenting as MSA-P showed an age at onset of 61.5 years, and those as MSA-C of 57.4 years [219], while a prospective cohort in the USA reported a median survival of 9.8 (95% CI 8.8-10.7) years [220]. Early autonomic dysfunctions and severity of orthostatic hypertension have negative impact on both disease progression and survival [221] and more than triples the risk of shorter survival [222, 223], and a meta-analysis identified severe dysautonomia, early combined autonomic and motor failure, and early falls as unfavorable predictors of survival, whereas MSA phenotype and sex did not predict survival [224].

Parkinsonism with rigidity, slowness of movements, postural instability, gait disability, and a tendency to fall, characterize the motor presentation of MSA-P [12]. Parkinsonism is rapidly progressing to wheelchair confinement within 5 to 10 years from symptom onset, poorly responsive to L-dopa, and is often associated with atypical features [17]. Unilateral parkinsonism occurs in 40% of MSA patients [220] and typical tremor in 4-10% [225]. Early postural instability and gait difficulties with recurrent falls are also seen in MSA [35]. Polyminimyoclonus, not included in the current diagnostic criteria of MSA, has now been recognized as a specific clinical feature of MSA.

Among motor and non-motor symptoms in early MSA, dysarthria was the most prevalent feature (98.4%), followed by sexual dysfunction (95%), RBD (90.2%), constipation (82%), snoring (70.5%), dysphagia (69%), and stridor (42.6%), which was more common in MSA-C than in MSA-P [226].

A resting tremor is rare, whereas irregular postural and action tremor may occur [227, 228]. Cerebellar ataxia, widespread gait, uncoordinated limb movements, action tremor, and spontaneous or gaze invoked nystagmus predominate MSA-C [35]. Hyperreflexia and a Babinski sign occur in 30-50% of patients, while abnormal postures, such as

bent spine, antecollis, and hand or foot dystonia are rare [229]. Early generalized and rapidly progressive autonomic failure is typical of MSA [230] and, in the absence of parkinsonism or cerebellar signs, indicating pure autonomic failure, which converts to MSA within a few years in about 28% [231-233]. Among non-motor symptoms observed in 75-95% of patients [234], urinary urgency and increased frequency are common in early disease stages [35]. In a subset of MSA patients with early urinary retention, the disease may begin in the sacral spinal cord and then spread to other regions [235].

Orthostatic hypotension with recurrent syncope, which occurs after the onset of urogenital symptoms, is a hallmark feature of MSA; less specific are dizziness and nausea. Other symptoms are anhydrosis, gastrointestinal dysfunction with early dysphagia and constipation [225], pupillary autonomic involvement with blurred vision and dry eyes. [236].

Dysproportional antecollis and Pisa syndrome are common postural deformities in MSA [35]. About 50% of patients with MSA-P develop cerebellar signs and even a higher proportion of MSA-C cases develop parkinsonian features [23, 220]. Dystonia, repeated falls, drooling, dysphagia, dysphonia, and pain occur in advanced stages of the disease [237]. Laryngeal stridor is rare [210]. Respiratory disturbances including diurnal or nocturnal inspiratory stridor and sleep apnea are frequent [238, 239].

Diagnostic biomarkers

Despite numerous studies, to date there are no reliable diagnostic and prognostic biomarkers available. While multimodal imaging of structural and functional brain changes gave insight into the pathophysiology and may evaluate disease progression, recent studies suggest that the combination of neuroimaging and fluid biomarkers may be more successful than using single markers to increase the accuracy of the clinical (differential) diagnosis of MSA [240].

Fluid and tissue biomarkers

Studies of αSyn levels in cerebrospinal fluid (CSF) and plasma have been shown to not be useful in the discrimination between MSA and PD or PSP [5, 241, 242]. A recent meta-analysis of available CSF data showed that reduction of p-tau, αSyn, Aβ-42 and total tau and elevated NFL are indicators for MSA [243]. Currently, the most promising approach is a combination of CSF DJ-1, phospho-tau, light chain neurofilament protein (NFL) and Aβ-42 that may be helpful in the differential diagnosis between MSA and other parkinsonian disorders [5, 240, 243, 244] (Fig. 3). Other studies have shown increased CSF levels of cytokines such as MCP-3, MDC, fractalkine, and MIP-1β [246]. Phosphorylated αSyn in red blood cells may be a potential diagnostic biomarker for MSA [247]. The results of proteomics for biomarker discovery and mRNA expression need further elucidation [248].

Molecular and functional imaging

A cardiac sympathetic postganglionic denervation distinguishes PD from MSA, showing intact innervation. I-123 MIBG (metaiodobenzylguanidine) scintigraphy can help differentiate the two diseases with a pooled specificity of 77% (95% CI: 68-84%) [199]. Recent meta-analyses suggest that MIBG imaging is useful to discriminate PD from MSA in moderate to advanced disease stages, but unreliable in early stages [199, 249]. However, interactions with many drugs limit the value of this method [250]. The anteroposterior diameter of the medulla oblongata is a potential imaging marker of parasympathetic dysfunction in MSA [251].

In recent years, several brain magnetic resonance imaging (MRI) features have been described as helpful in the differential diagnosis of parkinsonian syndromes. They include atrophy of the putamen, pons, cerebellum, and middle cerebellar peduncle, a dilated fourth ventricle, and various signal intensity variations on MRI [252]. MRI abnormalities including the "hot-cross bun" sign, a cruciform hyperintensity in the pons [253], and the "putaminal rim sign", which marks hyperintensive bordering of the dorsolateral margins of the puta men in T2-weighted MRI reflecting degeneration and iron deposition, may differentiate MSA-P from PD [254-258]. They are, however, non-specific signs and therefore not included in the recent consensus criteria [3], in contrast to putaminal atrophy which shows 92.3% specificity but low sensitivity (44.4%)

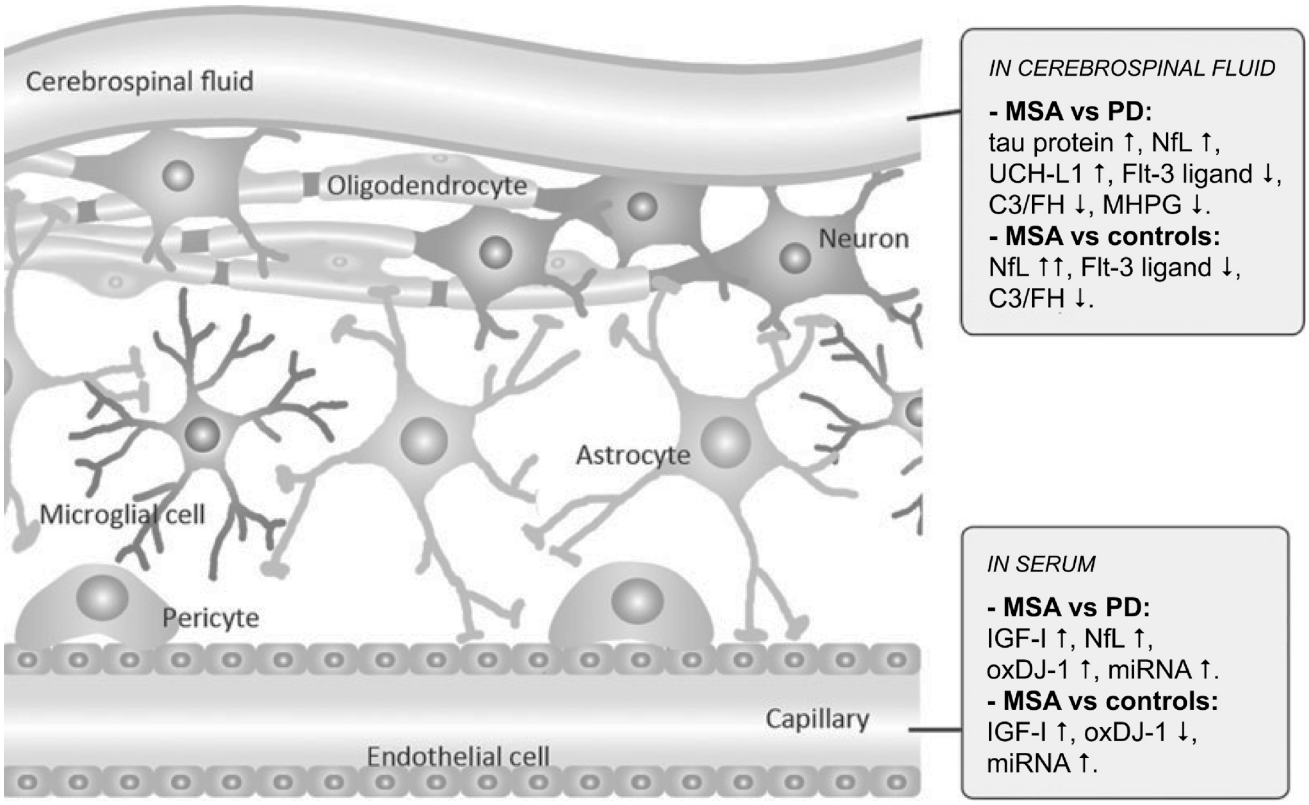

Fig. 3. Candidate biomarkers of multiple system atrophy compared to Parkinson's disease and controls.

MSA: multiple system atrophy; PD: Parkinson's disease; NfL: neurofilament light chain; FH: complement factor H; C3: complement 3; MHPG: 3-methoxy-4-hydroxyphenylethyleneglycol; IGF-I: insulin-like growth factor I; UCH-L1: ubiquitin carboxy-terminal hydrolase L1; oxDJ: oxidized DJ-1 protein; miRNA: microRNA.

Modified from [245].

[259, 260]. Putaminal atrophy together with hypointense putaminal signal changes on iron-sensitive routine sequences seem to be specific for MSA-P [252]. Others showed significantly increased putaminal diffusivity volumes in the small anterior region of interest in MSA-P versus PD [261]. Another distinguishing feature is the extensive and widespread volume loss across the entire brain in MSA-P [262]. In quantitative MRI studies, the bilateral R2* increase in the putamen best separated MSA-P from PD [263]. Putaminal and infratentorial volume information classified 96.8% of MSA cases [260]. Diffusion tensor imaging permits differentiation between PD and MSA-P, the latter showing higher values of the diffusion coefficient in the inner capsule, corona radiata, and lateral periputaminal white matter [264], while a meta-analysis of putaminal diffusivity measurements showed sensitivity of 90% and specificity of 93% in distinguishing MSA-P from PD based on putaminal diffusivity [265]. Combined use of diffusion ratios and magnetic susceptibility values/quantitative susceptibility mapping allowed differentiation of MSA-P and MSA-C from other parkinsonian syndromes with sensitivities and specificities of 81-100% [266]. Hyperintensity of the middle cerebellar peduncle and hot cross bun sign should be added into the list of additional neuroimaging features of possible MSA-C [182]. Several studies assessed the diagnostic potential of multimodal MRI [267-270]. In conclusion, the sensitivity of conventional MRI findings in MSA compared to PD and healthy controls is inconsistent (36-83%), the specificity of MRI abnormalities differentiating MSA from PD is high (88-100%). Automated imaging differentiation in parkinsonism (AID-P) and magnetic resonance Parkinsonism index (MRPI) are robust biomarkers for PD and MSA [271]. Diffusion weighted images, T2* weighted images and proton density weighted images are useful for diagnosis MSA-P in early stages [272].

Fluorodeoxyglucose-positron emission tomography (FDG-PET) can distinguish MSA-P from PD, showing different patterns of decreased glucose metabolism with a positive predictive value of 97% [273, 274]. Targeting postsynaptic dopaminergic functions using 123FβCIT SPECT differentiates PD (normal or increased signal) from MSA (normal or increased signal) [275]. Dopamine transporter (DAT) imaging showed more prominent and earlier DAT loss in the anterior caudate and ventral putamen in MSA than in PD [276], although normal DAT imaging does not exclude MSA [277]. In autopsy-confirmed cases a greater asymmetry of striatal binding was seen in MSA than in PD [278], but it is highly correlated with SN cell loss [279]. 18F-Dopa-PET showed more widespread BG dysfunction in MSA than in PD without evidence of early compensatory increase in Dopa uptake [280]. Future studies will be needed to determine the usefulness of tau-PET imaging for the characterization of αSyn filaments and the differential diagnosis of atypical parkisonian disorders.

Interpretation of tau-PET should be done cautiously, since some MSA cases with severe GCI pathology may be false-positive [281, 282], even though the affinity of PBB3 is 10 to 50 times less than αSyn [283]. 1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide (PK11195) for imaging microglia-mediated processes showed elevated tracer binding in many areas of the MSA brain, consistent with the known neuropathologic distribution [284].

Diagnostic accuracy and differential diagnosis

Revised consensus guidelines define 3 degrees of certainty of clinical diagnosis of MSA: definite, probable and possible [3] (Table 1, Fig. 4).

Definite MSA requires post mortem evidence of widespread αSyn inclusions with concomitant SND or OPCA [1]. *Probable MSA* is defined as a sporadic, progressive disorder in adults, clinically characterized by severe autonomic failure, urinary dys-

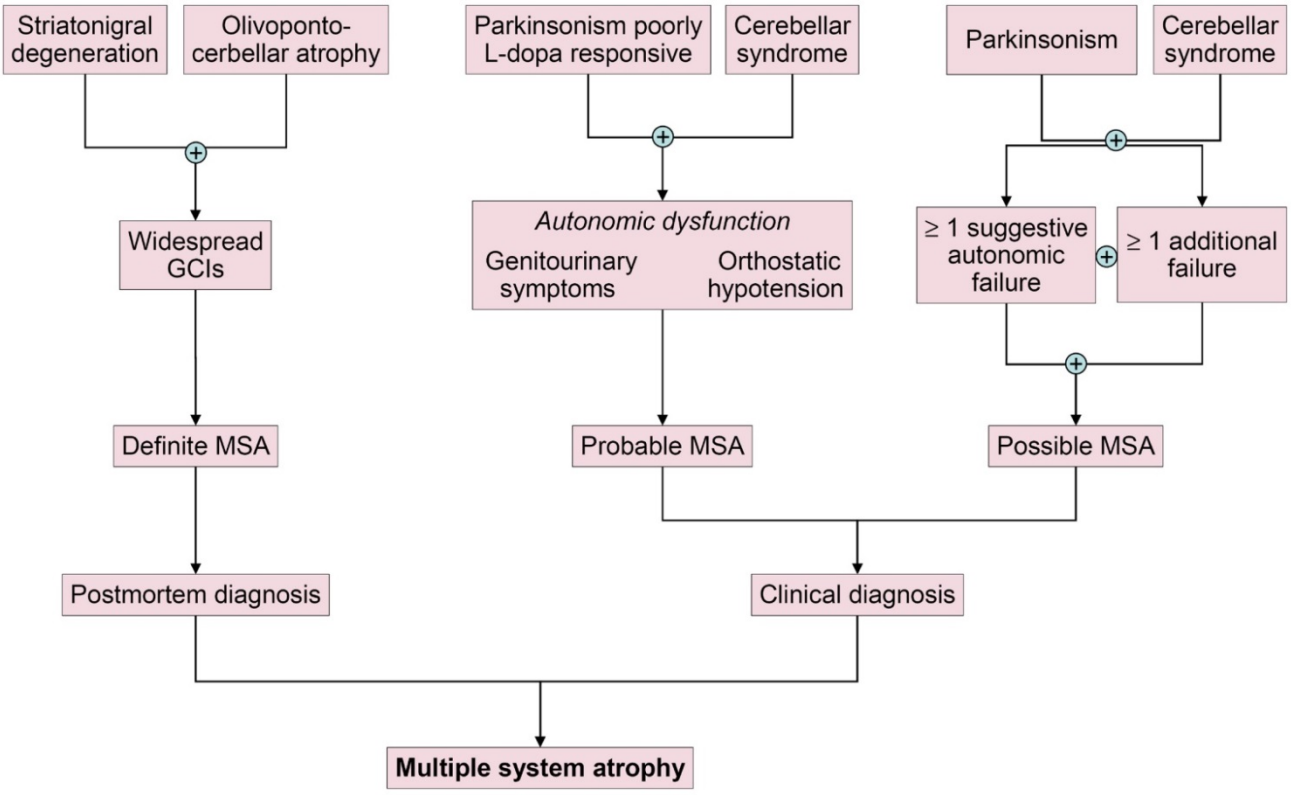

Fig. 4. Diagnostic scheme for MSA according to the current consensus diagnostic criteria.

Features suggesting autonomic failure	Additional clinical features suggesting possible MSA
• Urinary urgency (otherwise unexplained) • Increased urinary frequency (otherwise unexplained) • Incomplete bladder emptying (otherwise unexplained) • Erectile dysfunction in males • Significant orthostatic blood pressure decline	• Possible MSA • Babinski sign with hyperreflexia • Stridor *Possible MSA-P:* • Rapidly progressive parkinsonism (bradykinesia and rigidity) • Poor response to levodopa • Gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor dysfunction • Dysphagia within 5 years of motor onset *Possible MSA-C:* • Parkinsonism (bradykinesia and rigidity) • Atrophy of putamen, middle cerebellar peduncle, or pons on MRI • Hypometabolism in putamen on 18F-FDG–PET • Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

Table 1. Diagnostic clinical markers for MSA. Modified from [240].

MSA, multiple system atrophy; MSA-C, MSA with cerebellar features; MSA-P, MSA with predominant parkinsonism.

function and poor L-dopa-responsive parkinsonism or cerebellar ataxia. A diagnosis of probable MSA is based on clinical features and ancillary diagnostic tests. *Possible MSA* can be diagnosed when a sporadic progressive adult-onset disorder with parkinsonism or cerebellar ataxia is accompanied by at least one of the following additional features within 3 years of motor onset: dysphagia, gait ataxia and other cerebellar symptoms (Table 1).

"Red flag" diagnostic features

The presence of "red flag" (warning sign) features highly specific for MSA may provide important clues for a correct and early diagnosis. They include orofacial dystonia; inspiratory signs, contractures of hands and feet, jerky myoclonic postural/action tremor, polyminimyoclonus, severe dysphonia and dysarthria, pathological laughter and crying, snoring, disproportional antecollis, camptocormia and/or Pisa syndrome, and cold hands and feet [225, 229] (Table 2). In addition, severe disability milestones include: frequent falls, use of urinary catheters, wheelchair dependence, unintelligible speech, cognitive impairment, severe dysphagia, and residential care. In a recent clinicopathological study of 203 clinically diagnosed MSA patients, a lifetime recorded number of red flags in

both MSA-P and MSA-C was compared to LBD and PSP [225]. Recognition of patients with early or possible MSA may be supported by one or more red flags, and two or more out of six had a specificity of 98.3% and a sensitivity of 84.2% [228, 229], while no differences were found in the frequencies of red flags within 3 years from disease onset between MSA and MSA look-alikes [225]. Recent studies confirmed the validity of an eight-item pilot scale for the assessment of early MSA [285].

Due to the heterogeneity of clinical phenotypes and lack of specific biomarkers, it is a challenge to make a correct *antemortem* diagnosis of MSA [286]. The sensitivity of the second consensus criteria was 41% for possible and 18% for probable MSA at first clinical visit and 92% and 63% at last clinical visit, respectively [287]. In two recent brain bank studies, among patients diagnosed with MSA during life, only 62% and 79% met the pathological criteria [225, 286], while 25% of patients with the diagnosis of "possible" MSA had different pathological diagnoses, including PD and PSP [225]. The most common misdiagnoses were DLB (13 and 14%, respectively), PSP (6 and 11%) and PD (6%). Autonomic failure was the leading cause of misdiagnosis in PD and DLB, and cerebellar ataxia that of misdiagnosis in PSP [286]. Sporadic spinocerebellar ataxia (SCA) with autonomic failure can masquerade as MSA-C. A study reported that 7% of patients with clinically diagnosed MSA had mutations in SCA genes [288]. Fragile X tremor-ataxia syndrome and X-linked adrenoleukodystrophy can also be misdiagnosed as MSA-C [61]. The possible explanations for the suboptimal diagnostic accuracy of the current consensus criteria for MSA that saw a positive predictive diagnosis even in later disease stages from 60 to 90% [286, 287] have been recently discussed [289].

Supporting clinical features (red flags)	Non-supporting features
• Orofacial dystonia • Disproportionate antecollis • Camptocormia (severe anterior flexion of the spine) with or without Pisa syndrome (severe lateral flexion of the spine) • Contractures of hands or feet • Inspiratory sighs • Dysphonia • Dysarthria • New or increased snoring • Cold hands and feet • Pathological laughter or crying • Jerky, myoclonic postural or action tremor	• Pill-rolling rest tremor • Clinically significant neuropathy • Onset after age 75 years • Family history of ataxia or parkinsonism • Dementia (on DSM-V) • Hallucinations not induced by drugs • Loss of smell

Table 2. Clinical features supporting and non-supporting a diagnosis of multiple system atrophy. Modified from [240].

Atypical MSA

Almost all cases of MSA display neuronal loss in both striatonigral and OPC structures [24, 148], with only 11 of 42 cases assigned to the category of "pure" SND [155]. However, MSA has a wider range of presentations, which expands the list of differential diagnoses. Several subtypes of MSA do not fit into the current classification [290]. *"Minimal change" MSA* is a rare aggressive form with GCIs and neurodegeneration almost restricted to the SN, putamen, and locus coeruleus, thus representing "pure" SND [291-294], suggesting that GCI formation is an early event and may precede neuronal loss. One patient with "minimal" MSA-C showed abundant GCIs in pontine nuclei, middle cerebellar peduncle and cerebellar white matter, with NCIs and neuronal nuclear inclusions restricted to the pontine basis, cerebellar vermis, and inferior olivary nuclei, which were associated with neuronal loss indicating a link between both lesions in early disease [295]. Neurologically normal individuals are rarely found to have GCIs at autopsy as coincidental or incidental findings limited to the pons and inferior olivary nuclei with mild neuronal loss restricted to the SN, suggesting that these regions may be afflicted first in MSA-P [296, 297]. The presence of GCIs may represent an age-related phenomenon not necessarily progressing to overt clinical disease, classifying these cases as "incidental" or "prodromal/preclinical" MSA, similar to incidental LBD [298]. Young-onset MSA with a mean age of 36.4 years shows more L-dopa-induced dyskinesia but less common myoclonus and pyramidal signs compared to late-onset cases. On *post mortem* analysis, the "minimal change" variant was more common in young-onset MSA [299].

The other extreme are "benign" MSA cases with prolonged survival up to 15 years in about 2-3% of patients [217, 300]. Most of them showed slowly progressing parkinsonism with subsequent rapid deterioration after development of autonomic failure [301]. Many of them developed motor fluctuation and L-dopa-induced choreiform dyskinesias [302, 303]. Other cases of survival up to 18 years revealed extensive distribution of GCIs in the CNS [304]. Another variant of pathological confirmed MSA showed neither parkinsonism nor cerebellar symptoms [305]. An atypical case of frontotemporal lobar degeneration (FTLD)-TDP type A with MSA phenocopy syndrome showed severe striatal degeneration and cerebellar involvement [306], while four cases with clinical features of FTLD, but without autonomic dysfunction, showed frontotemporal atrophy and severe limbic αSyn neuronal pathology with Pick body-like, but tau-negative, inclusions. These cases were suggested to represent a novel subtype of FTLD associated with αSyn (FTLD-αSyn) [307]. Rare cases in a family with pathologic hexanucleotide repeat expansions in C9ORF72, a gene linked to amyotrophic lateral sclerosis, demonstrated clinical and neuroimaging features indistinguishable from MSA [308], and a cerebello-brainstem dominant form of X-linked adrenoleukodystrophy presented as MSA [61]. Recently, rare cases of MSA with transitional or diffuse DLB developing clinical features of PDD or DLB have been reported. Those with neuronal loss in SN but not in striatal or OPC systems with widespread GCIs were considered "minimal change" MSA, in which LBD was considered the primary pathology and MSA as coincidental. APOE allele frequency was not different between these forms [309]. These and other subtypes should be considered in establishing a correct diagnosis of MSA.

Cognitive impairment in MSA

Unlike other synucleinopathies, MSA has not been associated with significant cognitive impairment (CI), which has been considered an exclusion criterion for the diagnosis of MSA [3]. However, a recent position statement by the Neuropathology Task Force of the Movement Disorder Society indicated that CI may be an under recognized feature in MSA occurring in 17-47% of MSA patients, while severe dementia is rare [310]. Because CI has been underestimated in MSA, not all patients have undergone formal cognitive assessments and, therefore, the frequency could be higher than reported in several studies. The degree of CI in MSA patients ranges from mild to moderate decline and affect executive, attentional and visuospatial functions, while memory is less often impaired [197, 310-312]. CI may occur in early stages of MSA, but it is generally common in advanced cases [313] and often correlates with disease duration [314]. Mild

cognitive impairment (MCI) has been reported in up to 40% of MSA-P patients, mainly characterized by frontal dysfunction [310, 315]. Mild or moderate CI has been reported in 14-37% of pathologically proven MSA cases [134, 286, 302, 316]. More severe and widespread cognitive dysfunction was seen in MSA-P than in MSA-C patients [317], probably due to prefrontal impairment [315], whereas others saw no differences in cognitive variables between the two groups [318] or more severe cognitive dysfunctions in MSA-C [319]. CI has been regarded as a result of cortical and subcortical structural changes [320], frontal lobe dysfunction [321, 322], cortical dysfunction driven by focal frontostriatal degeneration [162], alterations in the corpus callosum [323], the dorsolateral prefrontal cortex network [324], or neocortical neuronal loss [159], while others have not found any differences in the severity of pathological findings between cases with and without CI [325].

Recent studies indicated that NCI burden in the hippocampus and parahippocampal gyrus is associated with memory impairment in MSA [326]. Alzheimer's disease neuropathological changes (ADNC), cerebral amyloid angiopathy (CAA), and cerebrovascular lesions did not differ between cases with and without CI [325], whereas others showed a greater burden of NCIs in medial temporal regions, the hippocampus or perirhinal regions [77, 197, 316, 326, 327]. ADNC has been reported in only 2/35 (7%) autopsy-proven cases of MSA [134], whereas two cases of combined MSA and AD (Braak stages III and VI) have been reported, in which only a few neurons shared αSyn and tau [328]. A recent retrospective clinicopathological study of 48 MSA patients (33 MSA-P and 15 MSA-C) with a mean age at death of 60.5±7.8 (range 46-82) years, reported MCI in 10 cases (20.8%), in which three had associated moderate cortical tau pathology (Braak I-II), and moderate CI in seven patients (14.5%), for which six had associated cortical amyloid plaques and moderate cortical tau pathology (Braak II-III), one had probable primary age-related tauopathy (PART), and one female aged 82 years with severe dementia showed fully developed AD. Cortical Lewy pathology, observed in four cases, was not associated with clinical CI. 77.1% of the MSA cases were free of ADNC, compared to 42% in controls, while Lewy pathology was higher than in the control groups (8.4%) [329]. In view of the limited data on the molecular basis of CI (and other neuropsychiatric symptoms) in MSA, further studies on the pathological basis of CI in MSA are needed.

MSA - a prion-like or prion disease?

The spread of αSyn pathology from one cell to another and even from one nervous structure to another has been demonstrated *in vivo* [11, 330-335]. This pattern, resembling prion spreading, has led to the concept of prion-like propagation of αSyn and tau [110]. Self-propagation of αSyn oligomers, however, is not sufficient to declare them as prions, because they show "seeding" activity rather than infectivity of αSyn [336]. However, the applicability of the prion hypothesis in α-synucleinopathies and, in particular, MSA remains controversial, since injections of brain lysated from MSA patients failed to replicate the oligodendroglial αSyn pathology that is typical for MSA. While studies in wild type (wt) mice provided insights into the mechanisms of oligodendroglial αSyn aggregations in MSA, intracerebral inoculation studies in non-human primates to the best of our knowledge have not been performed yet.

There are other challenges to the hypothesis that MSA is a prion disease. First, endogenous wt αSyn is insufficient to propagate αSyn pathology; mutant αSyn is needed as a template. The transmission of αSyn "prions" to a second synucleinopathy model and their ability to propagate between two distinct mouse cell lines while retaining strain-specific properties was suggested to provide evidence that MSA is a prion disease [337]. However, these and other mouse experiments have not yet explained why in MSA αSyn pathology predominantly accumulates in oligodendroglia, as MSA-derived αSyn does not appear to have the ability to induce strain-like cell-specific aggregates. This demonstrates that the intrinsic properties of A53T αSyn in the M83 mouse model dominate over any strain features harbored by misfolded αSyn in MSA brains [9].

Furthermore, GCIs have never been identified in wt mouse brains inoculated with MSA-derived αSyn [338]. Hence, αSyn aggregates ("prionoids")

derived from MSA patients created a neurodegenerative pattern that is atypical for MSA [336]. Moreover, αSyn aggregates, the morphological hallmarks of MSA, were not detected in MSA-inoculated TgM83+/- mice [339, 340], and no study has definitely propagated patient-derived seeds from cell-to-cell or mouse-to-mouse, or fully characterized αSyn strains from MSA vs. PD [117]. The variety of seeds, animal models, and methodologies currently prevents clear conclusions regarding αSyn-related spreading and toxicity, as well as translation of preclinical findings to human disease [341]. A recent study found no evidence of binding between cellular prion protein (PrPC) and αSyn oligomers, while PrPC neither binds to αSyn oligomers nor mediates their detrimental effects [342]. However, there may be different species of αSyn oligomers, which have different binding capacity with PrPC, and it remains possible that future studies could demonstrate that both PrPC-dependent and -independent pathways could play a role in the pathogenesis of synucleinopathies [343]. Accordingly, it could be possible that aggregated αSyn is potent in cross-seeding of prion protein misfolding and aggregation *in vitro*, producing self-propagating states that can lead to prion diseases upon serial passing in wt animals [344]. However, recent studies showed that abnormal misfolded cellular prion protein was able to efficiently propagate in the brain of animals even in the absence of αSyn, suggesting that this protein may *not* act as a key modulator of prion propagation. Thus, αSyn may take part in this process of self-propagation but is not specifically required for sustaining prion conversion and propagation [345]. Finally, gene analyses have shown that the homozygous state of positions 129 in the PRNP gene is not a risk factor for MSA and no variants of the PRNP gene were associated with increased risk for MSA [50]. Review of clinical notes from patients who had died of MSA showed no evidence of neurosurgical transmission [346], and studies of couples whose spouses had autopsy-confirmed PD, PSP, or MSA, did not suggest an increased risk of synucleinopathy development in the other spouses [347, 348]. Although there is no evidence of iatrogenic or direct transmission in autopsy-confirmed MSA cases, this is no evidence of absence of human transmission or misfolded proteins other than prions and β-amyloid, and further research is necessary before any conclusion can be drawn [349]. In conclusion, it seems reasonable to postulate that even if prion-like spreading in experimental systems may justify the view that the progression of neurodegeneration in MSA reflects a cell-to-cell spread of pathological αSyn, this is not sufficient to define MSA as classical prion disease [336].

New therapies

So far there are no causative or disease-modifying treatments available for MSA and symptomatic therapies are limited [35, 350]. The first-line treatment of a hypokinetic-rigid syndrome is dopaminergic treatment with L-dopa, the initial responsiveness to which has been reported in 83% of MSA patients [228], but its effect is usually transient, and only 31% showed a response for a period of 3.5 years [23]. L-Dopa response was observed in 42-57% of MSA-P and in 13-25% of MSA-C patients [220]. Recent animal studies suggest that L-dopa failure can be induced by restricted lateral striatal lesions combined with dopaminergic denervation [351]. In some patients, motor fluctuations with wearing-off phenomena or off-bound dystonia were observed [352]. L-dopa-induced dyskinesias were reported in 24.7% of definite MSA patients [23]. Dopamine agonists are not considered a therapeutic option, as they show poor efficacy and may involve severe side effects, particularly the worsening of orthostatic hypotension [353]. For cerebellar symptoms, no efficient drug treatments are available. Deep brain stimulation in MSA patients showed only transient improvement of motor symptoms, but was rapidly counteracted by the occurrence of disabling symptoms [303]. Non-pharmacological treatment options such as physiotherapy and occupational therapy play an important role in improving symptoms and patients' quality of life, and should be integrated into the therapeutic concept [354].

Translational and novel therapeutic approaches

Based on the current knowledge about the pathogenesis of MSA and the different findings in animal models, a number of therapeutic strategies have been proposed to target disease progression in MSA [5, 15, 16]. Based on the ability of αSyn to be transferred from cell to cell and to spread

through the brain in a prion-like manner, inhibition of αSyn oligomerization and aggregation may constitute a promising therapeutic strategy for disease modification, and interesting efforts have been made in this direction. These include (1) αSyn inhibition, (2) αSyn degradation enhancement, (3) intervening neuroinflammation, and (4) neuronal loss.

Numerous randomized, placebo-controlled trials of putative disease-modifying agents have been performed including riluzole, minocyline, lithium, rifampicin, fluoxetine, rasagilin, neuroprotective mesenchymal stem cells, epigallocatechin gallate, intravenous immunoglobulins and others. Although most of these treatments were efficient in cellular or animal models of MSA, in human patients they showed no clinical effects [16, 341].

Among drugs targeting αSyn aggregation, PROMESA studies on the effect of epigallocatechin gallate, a polyphenol found in green tea which reduces aggregation and toxicity of αSyn oligomers [329], did not modify disease progression [355]. Among αSyn degradation enhancing compounds, rapamycin, an autophagy enhancer, showed a reduction of αSyn aggregates in some brain areas [356] in preclinical studies, and is now under clinical trial [357]. Another approach concerns the possible involvement of toll-like receptor 4 (TLR4) and its selective antagonist monophosphoryl lipid A (MPLA) that reduced GCIs and motor deficits in mice [358]. Targeting neuroinflammation, the inhibition of myeloperoxidase as well as the reduction of TNFα-dependent reactions are promising disease-modifying targets and are being clinically tested in MSA patients [16]. The use of microglia inhibitors, such as minocycline, that rescues dopaminergic neurons in MSA mice, and the anti-inflammatory substance fluoxetine, however, fail to change disease progression. An alternative approach was used in MSA patients to target neuroinflammation by delivering intravenous immunoglobulin, but the results were inconclusive [359]. The compound FTY720-Mitoxy, an FDA-approved immunosuppressive for multiple sclerosis, reduced parkinsonism by increasing brain-derived neurotrophic factor (BDNF), and protected movement and mitochondria in wt and CNP-αSyn mice [360]. Numerous efforts have been undertaken to address neuronal loss, including bone marrow-derived mesenchymal stem cells [361, 362] and the antioxidant target of rapamycin (mTOR) receptor [363], however all of these efforts have failed to slow or halt disease progression [16].

Several studies have successfully proven the therapeutic potential of anti-αSyn immunotherapy by preventing αSyn spreading [5, 15]. Based on the fact that active immunization of MBP mice reduced αSyn accumulation and neurodegeneration [364], two αSyn vaccines (PD03A, PD01A) were evaluated in phase I studies with MSA and PD patients and showed good safety and tolerability [365, 366]. Active immunization against αSyn and combination with anti-inflammatory treatment may also be promising therapeutic strategies [367, 368].

Gene therapy may constitute another feasible approach to diminish OS excitotoxicity and subsequent neuronal loss, but none of the used compounds demonstrated effects on disease progression and the underlying neurodegeneration [16].

New strategies targeting αSyn are in progress [16, 280, 369], based on completed or ongoing interventional trials by the MSA coalition [12]. Therefore, there is a strong need to clarify the pathogenic mechanisms of MSA in order to develop new therapeutic strategy options, including combined approaches by targeting different MSA-specific pathogenetic effects.

Conclusions and further outlook

Current evidence supports the hypothesis that misfolded αSyn contributes to OS that induces a cascade of deleterious events, including proteasomal and mitochondrial dysfunctions, neuroinflammation, and energy failure that is associated with deposition of aberrant αSyn in both glia (mainly oligodendroglia) and neurons resulting in neurodegeneration and demyelination. Currently, the cascade of events that underlies the pathogenesis of MSA is not completely understood. Recent studies using animal models that only partially replicate human pathology and the molecular dynamics of the neurodegenerative process have provided progress in our understanding of MSA pathogenesis. The disease is viewed as a primary synucleinopathy with specific (oligodendro)glial-neuronal degenera-

tion developing secondarily via the oligo-myelin-axon-neuron complex [2, 4, 370]. Strong evidence against a primary neuronal pathology with the formation of GCIs, resulting from secondary accumulation of pathological αSyn that may be of neuronal origin [371], is the fact that GCIs are the hallmark of MSA and not of PD, a disease with similar patterns of αSyn inclusions (LBs) but resulting from different strains of αSyn, differentiating the two disorders [88, 89, 106, 372]. The source of αSyn in MSA and the pathogenic cascade leading to "prion-like" spreading of its strains contributing to progression of the disease need further elucidation, and there is no convincing evidence for the suggestion that MSA is a prion disease. Although disease-modifying treatments are currently not available, better knowledge about the molecular pathogenesis of MSA derived from animal models and human post mortem experience have contributed to the development of future therapeutic strategies to target disease progression in MSA.

Acknowledgements

The author thanks Mr. E. Mitter-Ferstl, PhD, for secretarial and editorial work.

Funding

The study was partially funded by the Society for the Promotion of Research in Experimental Neurology, Vienna, Austria.

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