What's New in Multiple System Atrophy.

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Abbreviations: Aβ-42: amyloid β-42; αSyn: α-synuclein; FTLD: frontotemporal lobe dementia; GCI: glial cytoplasmic inclusion; MSA: multiple system atrophy; MSA-C: multiple system atrophy cerebellar variant; MSA-P: multiple system atrophy parkinsonism variant; NI: neuronal inclusion; OPCA: olivoponto-cerebellar atrophy; PD: Parkinson's disease; PNS: peripheral nervous system; SND: striatonigral degeneration

Multiple system atrophy (MSA) is a rare, fatal, rapidly progressing neurodegenerative disorder of uncertain etiology that is clinically characterized by a variable combination of parkinsonism, cerebellar impairment, autonomic dysfunction and pyramidal tract signs. The mean age of disease onset is 56±9 years with poor prognosis and a mean survival of 9.5 years. The prevalence is 1.9 to 4.9 cases/100,000, increasing to 7.8/100,000 after age 50 and the incidence is 3 cases/100,000 [1]. Depending on the predominant initial motor presentation, MSA is classified into a parkinsonism variant (MSA-P) associated with striatonigral degeneration (SND) and a cerebellar variant (MSA-C) defined by olivoponto-cerebellar atrophy (OPCA) [2]. In the Western hemisphere, MSA-P involves 70% of the patients, while in Asian populations MSA-C predominates in two-thirds of patients [1].

Together with Parkinson's disease (PD) and Lewy body dementia, MSA belongs to the neurodegenerative group of α-synucleinopathies, which are characterized by abnormal accumulation of α-synuclein (αSyn) and are caused by toxic forms of α-synuclein (αSyn) [3]. The histological core features of MSA are glial cytoplasmic inclusions (GCI, Papp-Lantos bodies) in oligodendroglia [4]. αSyn, the main constituent of GCIs, also involves neurons and other cells in the nervous system, causing neuronal loss and demyelination [5]. Based on semiquantitative assessment, the striatonigral and olivoponto-cerebellar lesions into four degrees of severity [6], but there is an overlap between striatonigral and OPCA system degenerations [7]. In addition to the striatonigral and olivoponto-cerebellar systems, the lesions also involve many other parts of the nervous system, underpinning the multisystem character of MSA [3,5]. Significant neuronal loss involves substantia nigra, striatum and globus pallidus [8], and the frontal cortex of MSA patients with impaired executive function [9]. Gray matter atrophy in the MSA-P group in bilateral basal ganglia, cerebellum, frontal and temporal cortices, was correlated with cognitive dysfunction [10]. αSyn pathology in PD, DLB and MSA has recently been described in sacral spinal visceral sensory pathways, contributing to impaired micturition and constipation [11].

Recent consensus criteria differentiate possible, probable, and definite MSA, the latter confirmed by postmortem examination [2]. Red flag clinical categories had a specificity of 98.3% and a sensitivity of 84.2% [12]. Due to overlapping clinical presentations, it can be difficult to distinguish MSA from PD in early disease, and from other atypical parkinsonian disorders, e.g., progressive supranuclear palsy and corticobasal degeneration [10]. Prevalence of REM sleep behavior disorder in MSA is up to 88% [13].

No reliable fluid biomarkers are currently available to guide the clinical diagnosis and prognosis of MSA, although combining CSF biomarkers, e.g., DJ-1, phospho-tau, light chain neurofilament protein, and Aβ-42 may be successful in differentiating between MSA and other parkinsonian disorders [14]. Hypointensity of the dorsolateral putamen in T2-weighted MRI due to iron deposition, widespread volume loss throughout the brain and more severe white matter abnormalities differentiate MSA-P from PD [15-17]. Recently described rare cases of atypical MSA with clinical features consistent with frontotemporal lobe dementia (FTLD), have been suggested to represent a novel subtype of FTLD associated with αSyn [18,19].

Around 40% of MSA patients show peripheral nerve dysfunctions [20]. Skin biopsies revealed paSyn in Schwann cells in Schwann cells [21] and in unmylinated somatosensory dermal nerve fibers [22,23]. In the PLP-α-syn MSA mouse model, the peripheral nervous system is affected by αSyn deposits in Schwann cells, although there is no evidence for functional peripheral nervous system perturbances [20].

The causes of MSA are unknown. No environmental
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Factors have been recognized. MSA is generally considered
a sporadic disease, but there are familial cases, and in
some pedigrees it has been transmitted in an autosomal
dominant or recessive inheritance pattern. Mutations of
Coenzyme Q10 (COQ2) [24], SNCA (encoding αSyn),
and other genetic loci have been investigated, but no clear
association has been identified [25-27]. A G51D SNCA
mutation was reported in British families with autosomal
dominant parkinsonism and neuropathological findings
comparable with both PD and MSA [28], while MSA is
not related to C9orf72 [27].

Although the mechanisms of αSyn-triggered
neurodegeneration and the pathogenesis of MSA are
not fully understood, evidence from animal models and
postmortem studies suggest that it is a synucleinopathy
with specific glioneuronal degeneration [29]. Oligomeric
αSyn is probably the most toxic form initiating the
aggregation process and subsequent cell death [30]. αSyn
can be transferred to grafted oligodendroglial cells from
host rat brain neurons overexpressing αSyn, supporting a
neuron-to-oligodendrocyte transfer of αSyn [31]. Recent
evidence suggests that -similar to the observations in
preclinical models of PD - αSyn spreads through the brain
in a “prion-like” manner in MSA to other functionally
connected neuronal networks [32], resulting in a system-
like pattern of neurodegeneration that is typical of MSA
[33,34]. Homogenates from MSA patients triggered
aggregates of αSyn and activated astrocytes in a
TgM83(+/-) mouse suggesting that this protein spreads
like a prion in mice, which has not been observed for αSyn
from PD patients [35].

The earliest stages of MSA pathogenesis are suggested
to involve a relocation of p25α (tubulin polymerization
promoting protein/TPPP), an oligodendroglia-specific
phosphoprotein and stabilizer of microtubules and
myelin integrity [36], from the myelin sheaths into the
oligodendroglial soma preceding αSyn aggregation.
Follows formation of insoluble αSyn oligomers and of
GCIs [37] and a decrease of p25α in oligodendroglia
containing αSyn-positive GCIs, implying that
mitochondrial dysfunction can lead to secondary p25α
relocation [38]. There is associated dysregulation of the
lipid metabolism involved in myelin synthesis [39].
Formation of GCIs interferes with oligodendroglial and
neuronal trophic support leading to death of these cells
and also initiates neuroinflammation by activation of
quiescent microglia [3]. Release of misfolded αSyn into
the extracellular space may be taken up by neighbouring
neurons to form neuronal cytoplasmic inclusions (NCIs).
In MSA brains some αSyn isoforms are increased, while
others are decreased [40].

Recent studies described increased frequencies of NIs that
together with Lewy bodies occur across a wide spectrum
of brain regions suggest a hierarchy of region-specific
susceptibility [41]. The burden of neuronal pathology
appears to increase multifocally as an effect of disease
duration associated with increasing overall αSyn burden
[3]. A correlation between neuronal pathology and both
GCIs and NIs in the most severely affected brain regions
suggests a link between these phenomena [42], although
the mechanisms underlying this remain to be elucidated.

In conclusion, the pathogenesis of MSA currently remains
unknown. The disease has been viewed as a primary
gliopathy-synucleinopathy with neuronal pathology
developing secondarily via the oligo-myelin-axon-neuron
complex [43]. MSA has also been suggested to be a
primary neuronal disease and that the formation of GCIs
resulting from secondary accumulation of pathologic αSyn
that is neuronal in origin [44]. However, strong evidence
against a primary neuronal pathology is the fact that there
are GCIs in MSA and not in PD, a disease with similar but
less extensive pattern of αSyn-immunoreactive neuronal
inclusions in many overlapping circuits but few GCIs, and
this differentiates these two disorders [45]. Recent findings
support the concept that MSA is a synucleinopathy with
specific glioneuronal degeneration [29]. In addition to a
‘prion-like’ spreading of α-synuclein, oxidative stress,
proteasomal and mitochondrial dysfunction, dysregulation
of myelin lipids, demyelination, neuroinflammation, and
energy failure contribute to the pathogenesis of system-
specific neurodegeneration in this unique proteinopathy.
The advantages and limitations of MSA models and their
application in preclinical target validation have been
summarized critically [46].

Currently, there is neither an effective neuroprotective nor
a disease-modifying therapy in MSA Although several
pharmacological approaches have been tried in transgenic
mouse or cellular models of MSA, including riluzole,
rasagilin, minocycline, stem cells, etc., treatments that can
halt or reverse the disease progression in humans have
not yet been identified [47,48]. Symptomatic approaches
include dopaminergic and anticholinergic agents, non-
pharmacological treatment, treatment of orthostatic
hypotension, urinary and erectile dysfunction as well as
palliative care. Active immunization against αSyn has
been shown to ameliorate the degenerative pathology and
to prevent demyelination in a mouse model of MSA [49],
while a modified brain-targeted neuroxin (kallikrein-6) that
reduces αSyn accumulation in an MSA mouse model may
warrant further investigations as potential therapy for MSA
[50]. Combination therapies, eg, immunotherapy against
αSyn + antiinflammatory agents or multi-target drugs may
be the next step for the treatment of synucleinopathies
[51]. Further research on the pathogenic mechanisms,
the interplay of the disease process with various
molecular changes, and the nature of possible genetic
and environmental triggers that unmask its pathogenesis
will be needed to develop optimal animal models, and
to clarify the relations between the development of
pathomorphology and clinical manifestations as a basis
for early diagnosis and a disease-modifying treatment of
this hitherto incurable devastating disorder.
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