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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

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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 olivopontocerebellar 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 histolological 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 olivopontocerebellar lesions into four degrees of severity [6], but there is an overlap between striatonigral and OPCA system degenerations [7]. In addition to the striatonigal and olivopontocerebellar 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 pαSyn 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

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 parkinsonsm 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 pαSyn 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 syuncleinopathy 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 neurosin (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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