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Mini Review

Multiple System Atrophy - A Synucleinopathy with Specific Glioneuronal Degeneration

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Abstract

Multiple system atrophy (MSA) is a rare, largely sporadic, adult-onset neurodegenerative disorder of uncertain etiology, clinically manifesting with Parkinsonism, cerebellar impairment, autonomic dysfunction, and pyramidal signs. The pathological process affects striatonigral, olivopontocerebellar, and autonomic nervous systems. The major clinical variants correlate to the morphologic phenotypes of striatonigral degeneration (MSA-P) and olivopontocerebellar atrophy (MSA-C). Pathologically, MSA is characterized by glial cytoplasmic inclusions (GCIs) and neuronal inclusions (NIs) containing abnormal filamentous α-synuclein that involve many areas of the nervous system. Recent advances have increased our knowledge of the molecular pathogenesis of this devastating disease; updated consensus criteria and combined fluid and imaging biomarkers have increased the diagnostic accuracy and sensitivity versus other parkinsonian syndromes considerably. The pathology of this unique proteinopathy, in addition to ectopic deposition of misformed α-synuclein in glia and neurons, its cell-to-cell spreading in a prion-like matter, oxidative stress, proteasomal and mitochondrial dysfunction, dysregulation of myelin lipids, decreased expression of neurotropic factors, neuro inflammation, and energy failure, contributes to system-specific neuro degeneration. Despite several pharmacological approaches in MSA models, addressing these pathogenic mechanisms, no disease-modifying treatment for MSA is currently available.

Keywords: Multiple system atrophy; Diagnostic criteria; Pathogenesis; α-synuclein; Prion-like seeding; Glio-neuronal degeneration; Candidate biomarkers; New therapeutic approaches

Abbreviations

αSyn: α-Synuclein; CBD: Corticobasal Degeneration; FTLD: Frontolemporal Lobe Dementia; GCIs: Glial Cytoplasmic Inclusions; LBD: Lewy Body Dementia; MSA: Multiple System Atrophy; MSA-C: MSA Cerebellar phenotype; MSA-P: MSA with Predominant Parkinsonism; NCIs: Neuronal Cytoplasmic Inclusions; NFL: Light Chain Neurofilament Protein; NIs: Neuronal Inclusions; PD: Parkinson Disease; PSP: Progressive Supra nuclear Palsy

Introduction

Multiple system atrophy (MSA) is a rare, largely spontaneous, 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. Its estimated main incidence is 0.6 to 0.7 cases/ 100,000 populations; the estimated point prevalence is 1.9 to 5 cases/ 100,000 increasing to 7.8/100,000 after age 40 years. The pathological process predominantly affects the striatonigral and olivopontocerebellar systems, which underlies the stratification of the heterogeneous disorder into a clinical phenotype with predominant Parkinsonism (MSA-P) and a cerebellar phenotype (MSA-C). In the Western hemisphere, MSA-P involves 70% of the patients, while in Asian populations MSA-C predominates in two-thirds of patients. MSA is a late-onset disorder (mean age at onset 56±9 years) with poor functional prognosis and a median survival from onset of 9.5 years [1,2]. Shorter symptom duration at baseline and absent L-dopa response predicted rapid UMSARS (unified MSA rating scale) progression [3]. MSA-P with slow progression and prolonged survival is an uncommon "benign" subgroup [4], while "minimal change" MSA is considered an aggressive variant [5].

Clinical Diagnosis

Recent consensus criteria differentiate possible, probable, and definite MSA, the latter confirmed by postmortem examination [6]. Red flag clinical categories had a specificity of 98.3% and a sensitivity of 84.2% [7]. Due to overlapping clinical presentations, it can be difficult to distinguish MSA from Parkinson disease (PD) in early disease, and from other atypical parkinsonian disorders, eg., progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [8]. Prevalence of REM sleep behavior disorder in MSA is up to 88% [9].

No reliable fluid biomarkers are currently available to guide the clinical diagnosis and prognosis, although many studies suggest that combining CSF biomarkers, e.g. DJ-1, phospho-tau, light chain neurofilament protein (NFL), and Aβ-42 may be more successful in the differential diagnosis between MSA and other parkinsonian disorders [10]. Hypo intensity of the dorsolateral put amen in T2-weighted MRI due to iron deposition differentiates MSA-P from PD

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with high sensitivity [11-13]. There is recent evidence that functional MRI activation is abnormal in the basal ganglia, cerebellum, and cerebrum in MSA-P, and that another key distinguishing feature between MSA-P and PD is the extensive and widespread volume loss throughout the brain in MSA-P [14]. 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 [15].

Neuropathology

Together with PD and Lewy body dementia (LBD), MSA belongs to a group of neurodegenerative disorders - the α-synucleinopathies - which are characterized by the abnormal accumulation of α-synuclein (αSyn). The histological core features are glial cytoplasmic inclusions (GCIs, Papp-Lantos bodies) in oligodendroglia, the demonstration of which is required for the diagnosis of definite MSA [16]. αSyn, together with other proteins, is the main constituent of GCIs that also involves neurons as neuronal inclusions (NIs) [17] and other cells in wide areas of the nervous system, causing neuronal loss and demyelination [18]. Based on semi quantitative assessment of neuronal loss, gliosis and GCIs in brain regions, grading of striatonigral and olivopontocerebellar lesions into four degrees of severity [19] was confirmed by postmortem MRI [20], while others showed an overlap between striatonigral and Olivopontocerebellar atrophy (OPCA) system degeneration [21]. Recent stereological studies have demonstrated significant neuronal loss in substantial nigra, striatum and globus pallidus in MSA [22], and a widespread involvement of the neocortex, in particular the frontal cortex of MSA patients with impaired executive function [23]. Voxel-based morphometry (VBM) demonstrated significant gray matter atrophy in the MSA-P group in bilateral basal ganglia, cerebellum, frontal and temporal cortices, which were significantly correlated with cognitive dysfunction in MSA [24].

The lesions are not limited to the striatonigal and olivopontocerebellar systems but also involve many other parts of the central, peripheral and autosomal nervous system, underpinning the multisystem character of MSA [18,25]. Recent studies of skin biopsies revealed phospho-αSyn in Schwann cells [26] and in unmyelinated somatosensory dermal nerve fibers, whereas deposits in autonomic fibers are mainly found in PD [27].

Concomintant pathologies in MSA include Lewy bodies, the hallmark of PD and DLB, in 11 to 25.7%, frequently associated with cognitive impairment [17,18], rare co-occurrence of MSA and PSP and other tauopathies, while Alzheimer-related and TDP-43 pathologies occur infrequently in MSA [18,28].

Etiopathogenesis

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 form or recessive inheritance pattern. Mutations of Coenzyme Q10 (COQ2), SNCA, encoding αSyn, glucocerebrosidase gene (GBA) variants and other genetic loci have been investigated, but their association is under discussion [29-35]. A G51D SNCA mutation was reported in a British family with autosomal dominant Parkinsonism and neuropathological findings comparable with both PD and MSA [36], while MSA is not a C9orf72-related disease [37].

Although the mechanisms of αSyn triggered neurodegeneration and the pathogenesis of MSA are not fully understood, evidence from animal models and postmortem studies suggested that it is a primary oligodendrogliopathy [38]. The origin of αSyn-positive GCIs found in oligodendrocytes in MSA is enigmatic since earlier studies did not find expression of the protein in MSA oligodendroglia, which recently has been challenged [39]. Oligomeric αSyn and small fibrils are probably the most toxic forms initiating the aggregation process and subsequent cell death [40,41], and impairs maturation of primary oligodendrocyte progenitor cells [42,43]. Recent studies showed that αSyn can be transferred to grafted oligodendroglial cells from host rat brain neurons over expressing αSyn, supporting its neuron-to-oligodendrocyte transfer [44], and suggest that – similar to preclinical models of PD – it is seeded through the brain in a "prion-like" manner in MSA [45,46].

The earliest stages of MSA pathogenesis is currently unknown but is likely to involve a relocation of p25α (TPPP), an oligodendroglia-specific phosphoprotein, an important stabilizer of microtubules and myelin integrity [47], from the myelin sheaths into the oligodendroglial soma preceding the αSyn aggregation. Co expression of αSyn and p25α increases the expression of IκBα early and is dependent on aggregation and phosphorylation of αSyn. There is increased expression of IκBα and NF-κB in some oligodendrocytes containing GCIs, suggesting that both proteins are activate early in the course of MSA and their balance contributes to cellular demise [48]. These changes are followed by oligodendrocyte swelling and abnormal uptake or over expression of αSyn, which undergoes formation into insoluble oligomeres, followed by formation of GCIs [49]. Association with a significant decrease of p25α in oligodendroglia containing αSyn positive GCIs, implies that mitochondrial dysfunction can lead to secondary p25α relocation [50]. The ubiquitin-proteasomal pathway (UPS) and the autophagy-lysosomal pathway are tightly balanced and inhibition of the deubiquitinating enzyme carboxyl-terminal hydrolase L1 (UCH-L1) in oligodendrocytes results in microtubule stabilization and prevents αSyn aggregate formation by activating the autosomal pathway, thus playing a role in oligodendroglial degeneration [51].

Dysregulation of the specialized lipid metabolism involved in myelin synthesis is associated with these changes [52,53]. The decrease in lipid levels was concomitant with increased αSyn expression, indicating that levels and not distribution of myelin lipid are altered in MSA, triggering myelin instability [54]. The formation of GCIs interferes with oligodendroglial and neuronal trophic support leading to functional disorder and eventually death of these cells, and initiates neuroinflammation by activation of quiescent microglia [18]. Released misfolded αSyn into the extracellular space may be taken up by neighboring neurons to form neuronal cytoplasmic inclusions (NCIs); it is suggested to spread in a "prion-like" through functionally connected neuronal networks [55], resulting in a system-like pattern of neurodegeneration that is typical of MSA. Recent postmortem studies expanded the spectrum of neuronal pathology in MSA, describing increased frequencies of neuronal inclusions, both NIs and Lewy bodies across a wide spectrum of brain regions, not only in canonical disease-associated regions (striatum, substantia nigra), but

also in many other region, suggesting a hierarchy of region-specific susceptibility [17]. Disease duration is significantly correlated with the severity of neurodegeneration, suggesting that the progression of αSyn pathology is time-dependent [18]; NIs appears earlier than previously thought. A correlation between neuronal pathology and both GCIs and NIs in the most severely affected brain regions, suggesting a linked between these phenomena has been reported [56], 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 through mechanisms via the oligo-myelin-axon-neuron complex [38] Other authors have proposed that neuronal and glial inclusions may interact synergistically through unidentified mechanisms [57], disease progression resulting from the simultaneous degeneration of glia and myelin, due to GCIs, and aggregation of αSyn within neurons. On the other hand, MSA may be a primary neuronal disease and that the formation of GCIs results from secondary accumulation of pathologic αSyn that is neuronal in origin [58]. The influence of GCIs on the formation of NIs is unclear, but the burden of neuronal pathology appears to increase multifocally as an effect of disease duration associated with increasing overall αSyn load. Recent findings support the concept that neuronal pathology is an important if not primary component of MSA pathogenesis [17], which does not exclude the possibility of acceleration of neuronal pathology by accumulation of αSyn in glia as GCIs [38, 57]. Further research on the basic pathogenic mechanisms, the interplay of the disease process with various pathobiological changes, and the nature of possible genetic and environmental triggers that unmask its pathogenesis are 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 successful treatment of this hitherto incurable devastating disorder [59]. The advantages and limitations of MSA models and their application in preclinical target validation have been summarized critically [60].

Therapeutic Approaches in MSA

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 [61,62]. Symptomatic approaches include dopaminergic and anticholinergic agents, non-pharmacological treatment; options to treat orthostatic hypotension, urinary and erectile dysfunction as well as palliative care [63]. Active immunization against αSyn has been shown to ameliorate the degenerative pathology and to prevent demyelination in a mouse model of MSA [64]. Understanding the pathogenesis of MSA and the factors leading to αSyn accumulation is essential for the development of successful therapeutic options. Effective treatment may result from a multi-targeted approach addressing several pathophysiological mechanisms together and from multidisciplinary collaborative efforts to test promising new therapies in properly designed clinical trials.

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