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Pathogenesis of Multiple System Atrophy - Recent Developments

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Abstract

Multiple System Atrophy (MSA) is a rare 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. In addition to extopic deposition of modified α-synuclein in oligodendroglia and neurons, 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.

Keywords

Multiple system atrophy, Pathogenesis, α-Synuclein, Neuron-oligodendroglia transfer, Glial neuronal inclusions

Abbreviations

αSyn: α-synuclein, GCI: Glial Cytoplasmic Inclusion, MSA: Multiple System Atrophy, NI: Neuronal Inclusion, NCI: Neuronal Cytoplasmic Inclusion, PD: Parkinson's Disease

Introduction

Multiple system atrophy (MSA) is a rare 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 population; the estimated point prevalence is 3.4-5 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 heterogenous 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 has poor functional prognosis and survival [1].

Together with Parkinson's disease (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 histolological core features are glial cytoplasmic inclusions (GCI, Papp-Lantos bodies) in oligodendroglia, the demonstration of which is required for the diagnosis of definite MSA [2]. αSyn, together with other proteins, is the main constituent of GCIs that also involves neurons (neuronal inclusions/NIs) and other cells in wide areas of the nervous system, causing neuronal loss and demyelination. The lesions are not limited to the striatonigral and olivopontocerebellar systems but also involve many other parts of the central, peripheral and autosomal nervous system, underpinning the multisystem character of MSA [3,4].

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 transmission or recessive inheritance pattern. Mutations of Coenzyme Q10 (COQ2), SNCA, encoding αSyn, and other genetic loci have been investigated, but no clear association has been identified [5-7]. A G51D SNCA mutation was reported in a British family with autosomal dominant parkinsonsm and neuropathological findings comparable with both PD and MSA [8].

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 [9]. 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 [10]. Oligomeric αSyn and small fibrils are probably the most toxic forms initiating the aggregation process and subsequent cell death [11,12]. Recent studies showed that αSyn can be transferred to grafted oligodendroglial cells from host rat brain neurons overexpressing αSyn, supporting a neuron-to-oligodendrocyte transfer of αSyn [13], and recent evidence suggests that-similar to the observations in preclinical models of PD- αSyn may propagate through the brain in a "prion-like" manner in MSA [14,15].

The earliest stages of MSA pathogenesis are currently unknown but are likely to involve a relocation of p25α (tubulin polymerization promoting protein/TPPP), an oligodendroglia-specific phosphoprotein

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and important stabilizer of microtubules and myelin integrity [16], from the myelin sheaths into the oligodendroglial soma preceding the αSyn aggregation. This is followed by oligodendrocyte swelling and abnormal uptake or overexpression of αSyn, which undergoes formation of insoluble oligomers, followed by formation of GCIs [17]. This is associated with a significant decrease of p25α in oligodendroglia containing αSyn-positive GCIs, implying that mitochondrial dysfunction can lead to secondary p25α relocation [18]. Dysregulation of the specialized lipid metabolism involved in myelin synthesis is associated with these changes [19]. The formation of GCIs interferes with oligodendroglial and neuronal trophic support leading to functional disorder and eventually death of these cells, and also initiates neuroinflammation by activation of quiescent microglia [4]. Release of misfolded αSyn into the extracellular space may be taken up by neighbouring neurons to form neuronal cytoplasmic inclusions (NCIs). It is suggested to spread in a "prion-like" form to other functionally connected neuronal networks [20], 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 NIs. Both NIs and Lewy bodies occur across a wide spectrum of brain regions, not only in canonical disease-associated regions (striatum, substantia nigra), but also in many other regions, suggesting a hierarchy of region-specific susceptibility [21]. Disease duration is significantly correlated with the severity of neurodegeneration, suggesting that the progression of αSyn pathology is time-dependent [4,22]. However, according to these new data, the appearance of 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 link between these phenomena has been reported [22], 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 [9]. Other authors have proposed that neuronal and glial inclusions may interact synergistically in the neurodegenerative process through unidentified mechanisms [23], disease progression resulting from the simultaneous degeneration of glia and myelin, due to GCIs, and aggregation of αSyn within neurons. Another possibility is that MSA is a primary neuronal disease and that the formation of GCIs results from secondary accumulation of pathologic αSyn that is neuronal in origin [24]. The influence of GCIs on the formation of NIs is unclear. Nonetheless, the burden neuronal pathology appears to increase multifocally as an effect of disease duration associated with increasing overall αSyn burden [25]. Recent findings support the concept that neuronal pathology is an important if not primary component of MSA pathogenesis, which does not exclude the possibility of its acceleration by accumulation of αSyn in glia as GCIs [9,23]. Further research on the basic pathogenic mechanisms, the interplay of the disease process with various pathobiological and 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 [26].

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