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REVIEW

Pathology and genetics of multiple system atrophy: an approach to determining genetic susceptibility spectrum

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Abstract Recent advances in the molecular pathology and genetics of multiple system atrophy (MSA) indicate that the disease involves plural pathogenic mechanisms. The determination of the morphological spectrum of MSA using quantitative pathological analysis points to the need for further investigation to determine the population-bound phenotype distribution of MSA. These notions support the hypothesis that a spectrum of genetic susceptibility factors underlies MSA pathogenesis. A possibly effective strategy for determining this genetic susceptibility spectrum is to perform an association study of important genes for neurodegenerative diseases, which are prevalent in a population, using linkage disequilibrium mapping in MSA patients with well-characterized morphological phenotypes.

Introduction

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disease that clinically presents with various combinations of parkinsonism, cerebellar ataxia and autonomic failure [26, 70]. MSA is characterized pathologically by glial (oligodendroglial) cytoplasmic inclusions (GCIs) [52, 65], which are immunopositive for α-synuclein [45, 76, 90] and other minor proteins. Biochemical evidence suggests that oxidative and nitrative alterations of α-synuclein protein [2, 16, 24, 59, 60, 68] contribute to MSA pathogenesis. Epidemiologic evidence suggests that certain environmental toxins are associated with the increased risk of MSA [12, 29, 53, 87, 88]. Genetic background is also an important factor for MSA pathogenesis, because most neurodegenerative diseases have familial forms that have facilitated linkage studies leading to the discovery of pathogenic genes. However, family-based linkage studies of the genes responsible for MSA are impossible because this disease is usually sporadic and there are very few families reported to have MSA [75, 97]. Therefore, progress in the determination of genetic susceptibility factors is more likely to come from association studies of candidate genes in large MSA cohorts. These studies should be conducted taking into account the observation that there is a spectrum of pathological involvement of the striatonigral (SN) and olivopontocerebellar (OPC) regions in MSA [63]. In this review, we discuss recent advances in the molecular pathology and genetics of MSA, and propose a possibly effective strategy for determining the spectrum of genetic susceptibility factors to clarify MSA pathogenesis.

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Molecular pathology of multiple system atrophy

The development of extensive GCIs in the central nervous system is a characteristic pathological feature of MSA (Fig. 1). GCIs contain a filamentous structure that can be recognized by an antibody against α-synuclein [45, 76, 90]. This discovery has lead to biochemical evidence showing that the major component of GCIs is abnormally misfolded, relatively insoluble α-synuclein [10, 46, 85], which is heavily coated with an amorphous material [21]. Oxidative and nitrative alterations play a major role in the modification of α-synuclein [2, 16, 24, 59, 60, 68], and this possibly causes the dysregulation of cellular processes. Moreover, α-synuclein interestingly has a

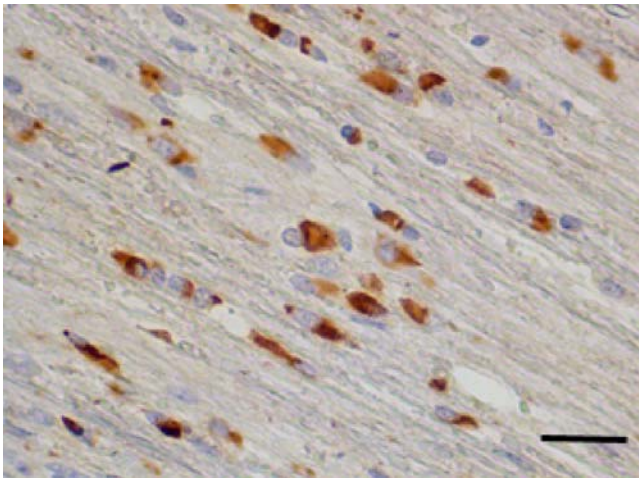

Fig. 1 Examples of GCIs in the cerebellar white matter. GCIs are immunopositive for α-synuclein. *Bar* = 20 μm

synergistic action with τ-protein, which is another important molecule for neurodegerative diseases (reviewed in [22, 93]). However, α-synuclein is a neuronal protein that is transiently expressed only in developing but not mature oligodendrocytes [14, 71]. Moreover, there is no increase in the level of α-synuclein mRNA in MSA brains [62] or GCI-bearing oligodendrocytes [47]. Therefore, the origin of α-synuclein in GCIs and the mechanism by which GCIs are formed remain to be elucidated.

The brain specific protein tubulin polymerization promoting protein (TPPP/p25) is a strong marker of GCIs [41, 43]. The aggregation of α-synuclein is also associated with rab3, which is a member of the Ras super family of small GTP-binding proteins [15]. The protein 14-3-3 also accumulates in GCIs [25, 38, 40]. 14-3-3 is a chaperon protein that regulates various types of signal transduction pathway through a phosphorylation-dependent protein–protein interaction [18]. Interestingly, 14-3-3 and α-synuclein are also involved in the development of cytoplasmic inclusions, which are generated by the overexpression of trinucleotide CAG repeat stretches of the huntingtin gene [89]. Heat shock protein 90 has been reported to play a major role in the formation of α-synuclein aggregates in GCIs [86]. Of note, the Parkinson's disease (PD)-associated protein DJ-1 is also involved in the formation of GCIs [54]. Finally, a variety of other molecules that abundantly exist in the central nervous system are involved in the formation of GCIs (reviewed in [94]).

MSA also induces the formation of inclusion bodies in the neurons of the inferior olivary nucleus, pontine nucleus, putamen and occasionally in the cerebral cortex [3, 5, 56, 63, 66, 100]; however, the role of these inclusion bodies in the induction of neuronal degeneration is not yet fully understood. Neuronal cytoplasmic inclusions (NCIs) in the pontine nucleus and putamen appear as round or ovoid homogenous or skeinlike structures, occupying a large area of the neuronal cytoplasm, whereas those in the inferior olivary nucleus are irregular in shape [4, 56, 72]. The major component of NCIs is also modified α-synuclein [55]; however, some NCIs are reported to have immunoreactivity for p25α, but none for α-synuclein [6]. Neuronal intranuclear inclusions (NNIs) are composed of densely packed, granulofilamentous structures [56]. The presence of both NCIs and NNIs in some neurons has occasionally been observed. A quantitative investigation of NCIs and NNIs in 14 MSA cases showed that NCI formation is accelerated by the progression of the disease process, and that NNI formation occurs earlier than NCI formation [56]. Further investigation is needed to elucidate whether NCI and NNI formations are the primary events that govern MSA pathogenesis.

Accumulating genetic evidence of multiple system atrophy

From the molecular pathology of GCI formation, the α-synuclein gene has become the most probable gene responsible for MSA pathogenesis. However, a genetic analysis of pathologically confirmed MSA cases failed to find any pathogenic mutations in the α-synuclein gene [50, 64]. Moreover, a case-control association study using a haplotype tagging approach showed that multiple regions in the α-synuclein gene are not associated with MSA pathogenesis [61], whereas they are associated with a sporadic cause of PD [51]. Likewise, other genes such as those of apolipoprotein E [9, 49, 50], τ [49, 50], dopamine β-hydroxylase [11, 31], ubiquitin C-terminal hydrolase-1 [32], fragile × mental retardation 1 [8, 23, 37, 98], and leucine-rich kinase 2 [33] showed no association with MSA pathogenesis. Several genes associated with the inflammatory process were studied with regard to MSA pathogenesis. Several studies indicate that polymorphisms of interleukin-1A [13], interleukin-1B [57], interleukin-8 [34], and intercellular adhesion molecule-1 genes [34] are associated with an increased risk of MSA. Another study demonstrated the association between a polymorphism of the α-1-antichymotrypsin gene and the risk of MSA [19]. Moreover, the promoter region polymorphism in the tumor necrosis factor gene has also been reported to be associated with the risk of MSA [58]. Further studies with much larger cohorts are needed to confirm these findings.

Several MSA patients have relatives with PD [95]. MSA and PD have similarities at the molecular level, i.e., the accumulation of α-synuclein protein aggregates, namely, GCIs in MSA [90] and Lewy bodies in PD [77], indicates that similar pathogenic mechanisms are involved

in these two disorders. However, a case control study demonstrated that a family history of PD is not a risk factor for MSA [88]. Therefore, the association between MSA pathogenesis and the genetic susceptibility factors of PD remains to be elucidated. Interestingly, patients with sporadic PD are associated with certain haplotypes or genotypes of the τ gene [17, 30, 44, 67], which plays a crucial role in the pathogenesis of other neurodegenerative parkinsonian syndromes, such as progressive supranuclear palsy and corticobasal degeneration. Endeavors to find MSA patients who have relatives with PD or other neurodegenerative parkinsonian syndromes are needed to clarify the genetic background of MSA.

Plural pathogenic mechanisms of multiple system atrophy

Growing evidence suggests that oligodendrocytic synucleinopathy underlies MSA pathogenesis. Morphological analyses of pathologically confirmed MSA cases showed significant correlations between the frequency of GCIs and the severity of neuronal degeneration [35, 63]. An apoptotic cell death mechanism exists in oligodendrocytes but not in the neurons of MSA patients [69]. The mouse model of MSA showed that the overexpression of α-synuclein in oligodendrocytes results in neuronal degeneration in the central nervous system [73, 78, 99]. These findings indicate that the GCI formation contributes markedly to neuronal degeneration, and plays a central role in MSA pathogenesis. However, the question is whether GCIs always induce neuronal degeneration in every vulnerable region in patients with MSA. A recent neuropathological study using a novel pathological index called the 'neuronal cell loss predominance score' demonstrated that neuronal degeneration is always severe, whereas the appearance of GCIs is mild in the substantia nigra [63]. These findings indicate that neurodegeneration in the substantia nigra is not simply influenced by the accumulation of oligodendroglial α-synuclein aggregates. Furthermore, the study also demonstrated that the density of GCIs in the SN region is significantly lower than that in the OPC region [63]. From these observations, it is tempting to hypothesize that GCI formation is the cause of primary lesions in the OPC region, but not in the SN region, and also that factors other than GCIs contribute to the neurodegenerative process in the SN region.

The formation of NCIs is another cytopathological feature of MSA in which filamentous α-synuclein aggregates; however, the frequency of NCIs is not associated with a particular MSA morphological phenotype [63], and whether NCI formation primarily causes neuronal degeneration remains to be clarified. Moreover, the Purkinje cell layer in the cerebellum, which is severely affected in MSA, has no NCIs in its remaining Purkinje cells [48, 63]. The absence of NCIs suggests that the Purkinje cells are not involved in the pathogenic mechanism associated with α-synuclein aggregation, but they are highly vulnerable to oligodendroglial dysfunction owing to GCI formation. Neurons in the substantia nigra have incidental Lewy bodies [84], which appear in only 10% of MSA cases [63]; however, there are no MSA-specific NCIs in the remaining neurons in the substantia nigra. The absence of NCIs in the substantia nigra is presumably associated with rapid neuronal degeneration in this area [63]. This notion points to the need for further investigation to elucidate whether the neurons in the substantia nigra of MSA patients have an innate cell death mechanism.

Possibility of population-bound phenotype distribution

In a series of 100 MSA cases, 34% were striatonigral degeneration (SND)-predominant, 17% were olivopontocerebellar atrophy (OPCA)-predominant, and 49% had equivalent SND and OPCA pathologies [63]. This study also indicates that MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) are clinical and pathological phenotypes that may represent different ends of a spectrum. Because selection bias is a crucial factor when the percentages of MSA-P and MSA-C cases are compared between populations, a future comparative morphological study using a similar approach for determining the percentages of MSA-P and MSA-C cases is needed. However, clinical evidence from retrospective case note reviews raises the possibility that MSA-P is relatively more frequent than MSA-C among Caucasians [92]. On the other hand, MSA-C may exist more frequently in the Japanese population [79, 91]. Likewise, it is suggested that in the Chinese population, MSA-C is relatively more frequent than MSA-P [36]. These findings support the hypothesis that there is a population-bound phenotype distribution of MSA (Fig. 2). It is reasonable

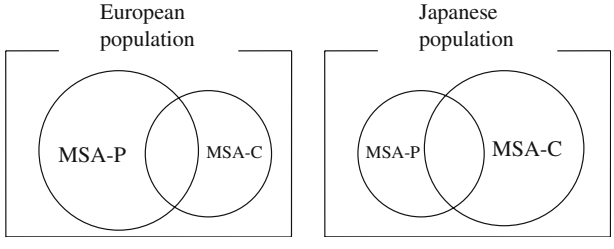

Fig. 2 Schematic description of population-bound phenotype distribution of MSA. Clinical evidence from retrospective case note reviews suggests that MSA-P is relatively more frequent than MSA-C among Caucasians. On the other hand, MSA-C may develop more frequently among Japanese population

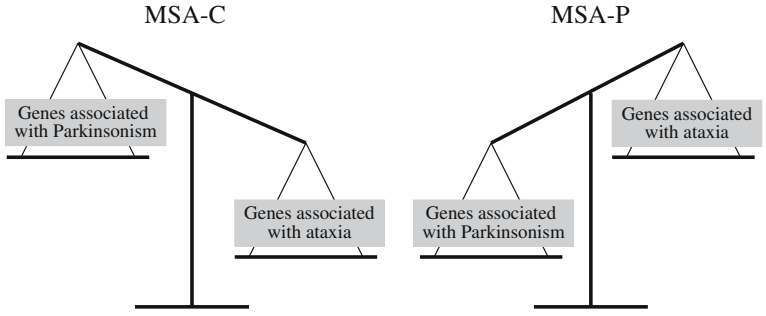

Fig. 3 Hypothesis on spectrum of genetic susceptibility factors in MSA. It is hypothized that there are different subsets of genetic susceptibility factors that are responsible for different ends of a spectrum such as MSA-P and MSA-C

to speculate that the subsets of biological factors, which are responsible for the vulnerability of neurons in the SN or OPC region, determine this difference in the emphasis of pathological phenotypes between populations. A combination of genetic factors is likely to underlie such vulnerability of neurons that differs between the SN and OPC regions in MSA.

Hypothesis on spectrum of genetic susceptibility factors in multiple system atrophy

A genetic approach should be carried out taking into account the notion that there is a spectrum of pathological involvement of the SN and OPC regions, and a possible population-bound phenotype distribution of MSA. Moderate genetic effects caused by a subset of certain genotypes, which are prevalent in a population, may influence the population-bound phenotype distribution of MSA. MSA is genetically distinct from inherited causes of spinocerebellar degeneration [7]. However, some cases of dominantly inherited spinocerebellar ataxia (SCA) have been reported to exhibit parkinsonism [20, 28, 74, 96], autonomic failure [81], and phenocopies of MSA [27, 39, 42]. For SCA cases, the relative prevalence of genotypes differs between Caucasians and Japanese; SCA1 and SCA2 are prevalent in Caucasians, whereas SCA3, SCA6, and dentatorubural pallidoluysian atrophy are prevalent in Japanese [80]. Interestingly, the frequency of normal alleles with a relatively large number of CAG repeats is also associated with the prevalence of these SCA genotypes [80]. For inherited causes of PD, genetic studies of different ethnicities show that mutations of the leucine-rich kinase 2 and DJ-1 are rare in the Asian population [82, 83]. These endeavors to determine the relative prevalence of genotypes that differs between populations may help elucidate the genetic susceptibility factors in MSA pathogenesis. Unlike effective strategies using Mendelian genetics, those for detecting moderate genetic effects in populations have been problematic, and a combination of techniques is recommended [1]. For MSA, it is likely that the linkage disequilibrium mapping of some important genes for neurodegenerative diseases, which are prevalent in a population, can be used for large MSA cohorts in which the morphological spectrum is well characterized [61]. This strategy is formulated on the basis of the hypothesis that there are different subsets of genetic susceptibility factors that are responsible for different ends of a spectrum such as MSA-P and MSA-C (Fig. 3). Hence, genetics based on pathology could be an effective approach to determining the spectrum of genetic susceptibility factors in MSA pathogenesis.

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