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Recent advances in multiple system atrophy

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ABSTRACT

Multiple system atrophy (MSA) is a fatal orphan neurodegenerative disorder that manifests with autonomic, parkinsonian, cerebellar, and pyramidal features. It is characterized by the accumulation of misfolded α-synuclein (αSyn) in oligodendroglia and neurons, affecting multiple parts of the central, autonomic and perípheral system. Both the etiology and pathogenesis of MSA are unknown, although a genetic component has been proposed. Accumulation of aberrant αSyn in oligodendrocytes, preceded by relocation of p25α protein from myelin into oligodendroglia, results in the formation of insoluble glial cytoplasmic inclusions (GCIs). These changes are associated with proteasomal, mitochondrial and lipid transport dysfunction, oxidative stress, reduced trophic transport, neuroinflammation and other noxious factors. Their interaction induces dysfunction of the oligodendroglial-myelin-axon-neuron complex, resulting in the system-specific pattern of neurodegeneration characterizing MSA as a synucleinopathy with oligodendroglio-neuronopathy. Propagation of modified toxic αSyn species from neurons to oligodendroglia by "prion-like" transfer and its spreading to associate neuronal pathways result in multi-system involvement. No reliable biomarkers are currently available for the clinical diagnosis and prognosis of MSA and neither effective neuroprotective nor disease-modifying therapies of MSA are available, although novel treatment strategies targeting αSyn are under discussion. Multidisciplinary research to elucidate the genetic and molecular background of the deleterious cycle of noxious processes to develop reliable diagnostic biomarkers and to deliver targets for effective treatment of this hitherto incurable disorder is urgently needed.

Introduction

Multiple system atrophy (MSA) is a rare, adult-onset, progressive, fatal neurodegenerative disorder of uncertain etiology that presents clinically with a variable combination of autonomic, parkinsonian, cerebellar and pyramidal features[1]. Together with Parkinson disease (PD) and Lewy body dementia (DLB), MSA belongs to the neurodegenerative group of α-synucleinopathies, which are characterized by accumulation of misfolded α-synuclein (αSyn)[2,3]. MSA is subdivided into (1.) a parkinsonian variant (MSA-P) associated with striatonigral degeneration (SND) (2.) the cerebellar subtype with olivopontocerebellar atrophy (OPCA) if cerebellar features predominate[4] and (3.) a combination of the two, referred to as mixed MSA[5]. The annual incidence in the 50-99 years age group is 3 cases/100,000 persons; the estimated point prevalence is 1.9 to 4.9 cases, increasing to 7.8/100,000 persons per year over age 50 (PD is about 45 times more common). In the Western hemisphere, MSA-P involves about 70%, whereas in Asian populations, the cerebellar subtype (MSA-C) predominates in two-thirds of the patients, with genetic or epigenetic factors possibly exerting an influence[1]. The different symptom assessment scales for MSA have been compared[6]. Motor symptom onset is 56±9 years, however, non-motor features including cardiovascular autonomic failure, respiratory and urogenital disorders may precede the motor symptoms by some years[7,8]. The prevalence of rapid eye movement (REM) sleep disorders in MSA is up to 88%[9]. The mean survival from symptom onset of 6 to 10 (mean 9.5) years[10] is similar for both phenotypes[11], while in Japan, MSA-C had a better prognosis than patients with parkinsonism or autonomic failure at onset [12].

Recent consensus criteria differentiate possible, probable and definite MSA, the latter confirmed by postmortem examination[4,13]. Two or more of six red flags (warning signs) had a specificity of 98.3% and a sensitivity of 84.2%[14]. Several subtypes, e.g., "minimal-change" aggressive and prolonged "benign" forms do not fit into the current classification[10,15-19]. Due to overlapping clinical presentation, the distinction between MSA, early disease PD or atypical parkinsonian disorders (DLB, progressive supranuclear palsy/PSP) may be difficult[20-22]. A recently described atypical MSA (aMSA) was identified as frontotemporal lobar degeneration with αSyn (FTLD-synuclein)[23,24].

Etiology

The causes of MSA are unknown. Epidemiological studies are limited by low case numbers and diagnostic difficulties[25,26]. MSA is generally a sporadic disorder, but there are familial cases, and in some pedigrees, the disease has been transmitted in an autosomal dominant or recessive inheritance pattern[27,28]. A recent genome-wide estimate suggested MSA heritability due to common risk variants at 2.9 to 6.65%[29]. No definite risk factors have been identified, although mutations of the COQ2

gene have been linked to MSA in Japanese families[30-32], and SNCA (encoding αSyn and other loci) have been associated with increased risk for MSA[33,34]. However, these findings were not replicated by others[29,35,36]. The presence of GCI-like oligodendroglial inclusions in familial PD due to SNCA mutations also suggests that PD and MSA form a continuum of αSyn pathology[37]. Gaucher disease causing glucocerebrosidase gene (GBA) variants [38] but neither association with GBA mutations[39] nor with C9orf72 hexanucleotide repeat expansions have been found[40], whereas contribution of LRRK2 exonic variants to susceptibility of MSA are under discussion[41,42]. RNA sequencing analyses of MSA brain have revealed alterations in a number of genes including α and β hemoglobin[43] and uncovered disruption of line RNAs along with protein coding genes related to iron metabolism and immunological response regulation, indicating complexity in transcriptional pathology of MSA[44]. RNA analysis of MSA brain uncovered a wide dysregulation of microRNAs (mRNA) resulting in downregulation of the carrier protein family SLC1A1 and SLC6A6[45]. The role of mRNA in the pathogenesis of neurodegenerative disorders has been summarized recently[46]. Genome-wide changes of αSyn mRNA expression may be important for the increased deposition of αSyn in MSA brain[30,47], but the lack of causative mutations makes generating valid models of MSA difficult[48]. G51D SNCA and A53E single point mutations, as well as SNCA triplications, give rise to a histopathological phenotype with inclusions in both neuronal and oligodendroglial cells comparable to both PD and MSA[49-51]. Sparse evidence supports the notion that epigenetic factors or environmental toxins may play a role in MSA development[26,52], which was not confirmed in a tg MSA mouse model[53].

Neuropathology

The histological core features of MSA are (1) four types of cellular αSyn immunoreactive inclusions, i.e. GCI within oligodendrocytes (the presence of which is required for the postmorten diagnosis of definite MSA[13], less frequent glial nuclear (GNI), neuronal cytoplasmic (NCI), and neuronal nuclear inclusions (NNI), (2) astroglial cytoplasmic inclusions and neuronal threads, also composed of αSyn[54], (3) selective neuronal loss and axonal degeneration involving multiple regions of the nervous sytem[2,55], and (4) myelin degeneration with reduction of myelin basic protein (MBP), both with accompanying astrogliosis[2]. GCIs and the resulting neurodegeneration occur in typical multisystemic distribution encompassing the striatonigral and OPC systems, autonomic nuclei of the brainstem (locus ceruleus, nucleus raphe, dorsal vagal nuclei, etc.), spinal cord and sacral visceral sensory pathways[56-59].

The biochemical composition and distribution of GCIs and other inclusions have been summarized recently[2,60-62]. Based on semiquantitative assessment of GCIs and neuronal loss, the striatonigral and OPC lesions were assessed into four degrees of severity[63], but there is an overlap between the degeneration

of both systems[64]. The number of GCIs increases with disease duration, and there is a positive correlation between their density and the degree of neurodegeneration[60,65]. Region-specific astrogliosis is positively correlated with αSyn pathology in MSA in contrast to PD[66]. Glial and neuronal inclusions also involve many other parts of the central and peripheral nervous system underpinning the multisystem character of MSA[2,36,67]. The thickness of the retinal fiber and macular ganglion cell complex is reduced[68]. Accumulation of phosphorylated αSyn also occurs in subpial and periventricular astrocytes after long disease duration[69,70]. Cortical and subcortical gray matter atrophy in MSA-P and neocortical neuronal loss may underly cognitive impairment in MSA[71-75], which may also be associated with the presence of Lewy-body like inclusions in neocortex[67], while others found no pathological changes related to cognitive impairment in MSA[76].

Demyelination in MSA mainly involves the striatonigral and OPC regions and is associated with reduction of myelin proteins[77], but no portion of the nervous system appears to be spared. Whether myelin loss is secondary to neuronal or axonal loss or whether it is a primary lesion, which in turn leads to neuronal and axonal loss, is unknown. White matter degeneration causes a destruction of neuronal loops, resulting in dysfunction of the whole-brain network[78], and may be related to disorders of cerebral autoregulation[79]. Differences in expression of a disease-related metabolic pattern correlate with disease severity in MSA[80].

αSyn pathology has also been detected in Schwann cells of cranial, spinal and autonomic nerves[70,81], inducing postganglionic sudomotor denervation[82], and in neuronal cytoplasm and processes of sympathetic ganglia (in 42.3% of MSA cases[83]), causing multidimensional autonomic failure [84]. In the peripheral nervous system, αSyn aggregates have been observed in sympathetic ganglia, skin nerve fibers[85,86] and Schwann cells[70], which have also been described in MSA models[53], whereas other studies showed absence of phosphorylated αSyn immunoreactivity in dermal nerve fibers in contrast to PD[85,87].

α-Synuclein in MSA

αSyn, a heat stable cytosolic protein, primarily located in presynaptic nerve terminals, when present in oligodendrocytes in MSA and tg models, has undergone post-translational modifications (oxidation, nitration, phosphorylation, etc.) enhanced by oxidative stress (OS)[88-90]. αSyn in GCIs of MSA is phosphorylated at residue Ser-129 and ubiquinated as is the case in Lewy bodies (LBs)[91,92].

Elevated levels of membrane-associated detergent-soluble αSyn were seen in disease-affected regions of MSA brains containing both neuronal and glial inclusions 5- to 10-fold higher than in patients with PD[93]. However, most of the soluble αSyn was also present in areas with few GCIs, suggesting that altered solubility precedes the formation of GCIs and that

increased soluble monomeric αSyn may result in a conversion into insoluble, filamentous αSyn aggregation, which could result in neurodegeneration [94]. MSA brain contains various levels of αSyn isoforms, 140 and 112 isoforms being significantly increased, whereas αSyn 126 isoform was decreased[95,96]. This corresponds to the regional pathology, including GCI distribution, although accumulation of monomeric αSyn may not be merely caused by the formation of GCIs. MSA brain also contains increased levels of parkin isoforms and an aggregation-prone synphilin-1A isoform. This suggests alterations in protein-protein interactions that may be important in aggregation processes and may result in neurotoxicity and/or neuroinflammation[95]. Autophagy is involved in the protein aggregate formation in MSA oligodendroglia[97]. There is widespread mRNA dysregulation in MSA patients, which is recapitulated in murine models[45], and circulating mRNAs discriminate MSA from PD [98]. Inhibition of UCH-L1 in oligodendrocytes resulting in microtubule stabilization may prevent αSyn aggregate formation by activating the autophagic pathway[99].

Accumulation of αSyn in oligodendrocytes may induce their dysfunction resulting in reduced trophic support and demyelination, as suggested by the MBP-hαSyn tg mouse model[100,101]. Most affected regions are basal ganglia and cerebellum, with loss of myelin staining, astrogliosis, and axonal alterations, correlating with the severity of both the GCI pathology and the level of αSyn expression. The leading role of GCI pathology is supported by the "minimal change" (MC-MSA) forms, where severe GCI burden is associated with less severe neuronal loss but shorter disease duration[18].

Changes in MBP levels in MSA brains suggest myelin lipid dysfunction and instability[77,101,102], which, together with an aberration in protein distribution may lead to myelin dysfunction in MSA[103]. Region-specific increased matrix metalloproteinase activity may contribute to the disease progress by promoting blood-brain barrier dysfunction and myelin degradation[104].

Oligodendrocytes differentiated from MSA-derived stem cells have been suggested to express αSyn in contrast to those derived from healthy controls or PD patients, but suppress its expression during maturation[105,106], indicating the possibility that an endogenous intra-oligodendroglial αSyn source may contribute to the GCI formation and thus they may play a primary role in triggering neurodegeneration. Oligodendroglial precursor cells (OPCs) show increased density in MSA white matter affected by GCI pathology and myelin degeneration suggesting repair (remyelination) efforts[107]. While αSyn has been shown to impair oligodendrocyte progenitor maturation in MSA preventing the formation of mature oligodendroglial cells[108,109], others have shown a link between the intracellular level of human αSyn and the maturation of primary OPCs[108]. The data on oligodendroglial dysfunction in MSA support the notion that neurodegeneration may occur secondary to

demyelination and lack of trophic support by GCI-bearing oligodendroglia.

Transgenic animal models of MSA

The causative role of GCI-like pathology for the induction of neurodegeneration in MSA was confirmed experimentally in tg mice expressing human αSyn in oligodendrocytes under various oligodendroglia-promotors[90,100,110,111]. The selectivity of glial and neuronal degeneration in human MSA and in these models is still unresolved, since there are regional disparities between mouse lines. While one model demonstrated most severe pathology in the spinal cord, PLP-αSyn tg mice[90] showed the classical distribution with basal ganglia, cerebellum and autonomic centers severely affected[110-113]. The regional disparities between mouse lines sharing the same basic defect could result from different efficiencies of the promoter expressing αSyn or because the various promoters target different subtypes of oligodendrocytes. Since none of the available tg mouse lines reproduced the specific predominace of SND or OPCA in human disease[62], a more accurate characterization of the mouse models of MSA is required.

Prion-like transmission of αSyn

The source of αSyn in GCIs in oligodendrocytes and the role of many of their polypeptides and protein components is enigmatic, although these have been shown to express αSyn mRNA[105]. αSyn, previously suggested to be an exclusively neuronal protein, can be transferred to grafted oligodendrocytes from host rat brain neurons overexpressing αSyn, supporting a neuron-to-oligodendrocyte transfer[114]. Three possible causes were discussed – redistribution of αSyn from neurons to oligodendrocytes, suppression of neuronal expression from oligodendrocytes, and neuronal clearance of αSyn. αSyn released from degenerating neurons both mediates formation of abnormal inclusion bodies and induces neuroinflammation, which might also favor the formation of intracellular αSyn aggregates as a consequence of cytokin release and the shift to a pro-inflammatory environment[115]. Pathogenic mechanisms leading to elevated αSyn in neurons underlie neuronal secretion and subsequent uptake of αSyn by oligodendroglia in MSA [116].

Recent evidence suggests that – similar to preclinical models of PD – αSyn spreads through the brain in a "prion-like" manner in MSA to other functionally connected neuronal networks[117], resulting in a system-like pattern of neurodegeneration that is typical of MSA[118]. "Prion-like" seeding, introduction of toxic environment, and intrinsic disruption of proteostasis may synergetically contribute to the induction and spread of αSyn inclusions[119]. MSA may be caused by a unique strain of αSyn proteins, which is different from the putative prions causing PD and from those causing spontaneous neurodegeneration in TgM83(+/+) mice[120]. However, the same studies failed in wildtype/healthy mouse brain and no oligodendroglial αSyn aggreation was seen, therefore the core pathology of MSA could not be reproduced. Experimental studies showed that

oligodendrocytes may take up αSyn from the extracellular space[114], but no typical GCI-like aggregations were observed. Primary oligodendroglial dysfunction may therefore result in ectopic accumulation of αSyn in these cells[60]. Alternatively, specific αSyn conformational strains were proposed to be responsible for the degeneration of MSA-like αSyn seeding[121]. However, this needs further verification, as inoculation of MSA-derived αSyn into brains of healthy, non-tg mice did not induce GCI-like pathology[120], and none of the available models has so far achieved the phenotypic resemblance to true MSA[122]. Hence, aside from α-SYN strains that can expose distinct interaction surfaces and spread between cells, additional factors are required in order to drive a complete MSA phenotype. These processes are likely multifactorial and potentially driven by the presence of αSyn strains on a background that promotes but also sustains the formation of GCIs[123].

Pathogenic mechanisms of MSA

Evidence from animal models and human postmortem studies suggest that the accumulation of misfolded αSyn plays a central role in the disease process[58,62], which can be considered a synucleinopathy with specific glioneuronal degeneration, associated with early myelin dysfunction and neuronal degeneration related to retrograde axonal disease[55,124]. Although one may speculate that primary neuronal pathology leads to secondary oligodendroglia degeneration as suggested by the finding that NCIs exist in areas lacking GCIs[67], the fact that distribution and severity of neurodegeneration reflect subregional GCI densities supports the hypothesis of a primary oligodendrogliopathy[60,62]. In early stages of the disease, in addition to GCIs, diffuse homogenous αSyn staining in neuronal nuclei and cytoplasm was observed in many parts of the central nervous system. The density of the GCIs is unrelated to that of NNIs[125]. The number of NNIs was much larger than the NCI count in the pontine nuclei in some MSA cases, suggesting that NCI formation is accelerated by the progression of the disease process and that NNI formation may be an earlier phenomenon than NCI formation[15].

The earliest stages of MSA pathogenesis are likely to involve a relocation of p25α (TPPP - tubulin polymerization-promoting protein), an oligodendroglia-specific phosphoprotein and stabilizer of microtubules and myelin integrity[126], from the myelin sheaths to the oligodendroglial soma. This is associated with myelin dysfunction, reduction of full-length MBP, demyelination of small-caliber axons and an increase in oligodendroglial soma size, preceding αSyn aggregation[127]. The interaction between p25α and αSyn promotes phosphorylation and aggregation into insoluble oligomers and GCIs implies that mitochondrial dysfunction can lead to secondary p25α relocation, probably linked to dysregulation of lipid metabolism and dysfunctional myelination, probably a fundamental event in MSA pathogenesis[128].

The aggregation of αSyn is suggested to interferes with the

process of oligodendrogenesis, preventing the formation of mature oligodendroglia cells[108,109]. Transgenic oligodendroglial expression of human αSyn causing a phenotype that resembles human MSA demonstrated that accumulation of αSyn in oligodendroglia induces subsequent degeneration of both oligodendroglia and neurons[100,129]. Enhanced FAS (Fas cell surface death receptor) gene expression is an early hallmark of oligodendroglial pathology in MSA that may be related to αSyn-dependent degeneration[130,131]. Predegenerative expression of the transcription factor IκBα as an early event in the course of MSA may cause destructive neuroinflammation tissue responses, and thus contribute to cellular demise[130]. Recently, differential involvement of the cysteine protease inhibitor cystatin C, associated with increased risk for neurodegeneration, has been observed in MSA phenotypes, suggesting its role in the pathogenesis of this disorder[132].

Formation of GCIs interferes with oligodendroglial and neuronal trophic support leading to death of these cells and to initiation of neuroinflammation by activation of quiescent microglia[133], suggesting that pathological αSyn triggers neuroinflammatory responses in the MSA brain[60,134]. Microglial activation may contribute to the progression of the neurodegenerative process in MSA via increased levels of reactive oxygen species in degenerating areas[135]. Currently available data support the hypothesis that misfolded αSyn contributes to OS through a pathway that induces microglia activation as well as antioxidant responses and requires an additional protein structure[136], but OS appears unlikely to be the sole mechanism for αSyn aggregation.

The cell death mechanisms in MSA are poorly understood. Increased iron levels in degenerating brain areas suggest that OS may play a significant role in the selected neuronal loss in MSA, and microglial activation may contribute to the increased levels of reactive oxygen species in the degenerating areas[135]. Loss of phosphoprotein DARPP-32 and calbindin-D 28k in areas of less prominent / absent neuronal loss indicates calcium toxicity and disturbance of the phosphorylated state of proteins as relatively early events[137]. While experimental studies support the dysfunction of the proteasome and autophagosome systems in oligodendroglial α-synucleinopathy[97,138], excitotoxic cell death was not aggravated by GCI pathology[53].

Various mechanisms possibly related to cell death include X-linked inhibitor of apoptosis protein (XIAP) that is upregulated in GCI- and NCI-bearing oligodendrocytes and neurons[139], proteasomal[140] or autophagosomal dysfunction[141], supported by experimental studies[97,101,135]. Neuronal death may also be related to an altered communication between neurons and oligodendrocytes due to perturbation of their neurotrophic transport[142].

The burden of neuronal pathology appears to increase multifocally as an effect of disease duration associated with increasing overall αSyn burden. A correlation between 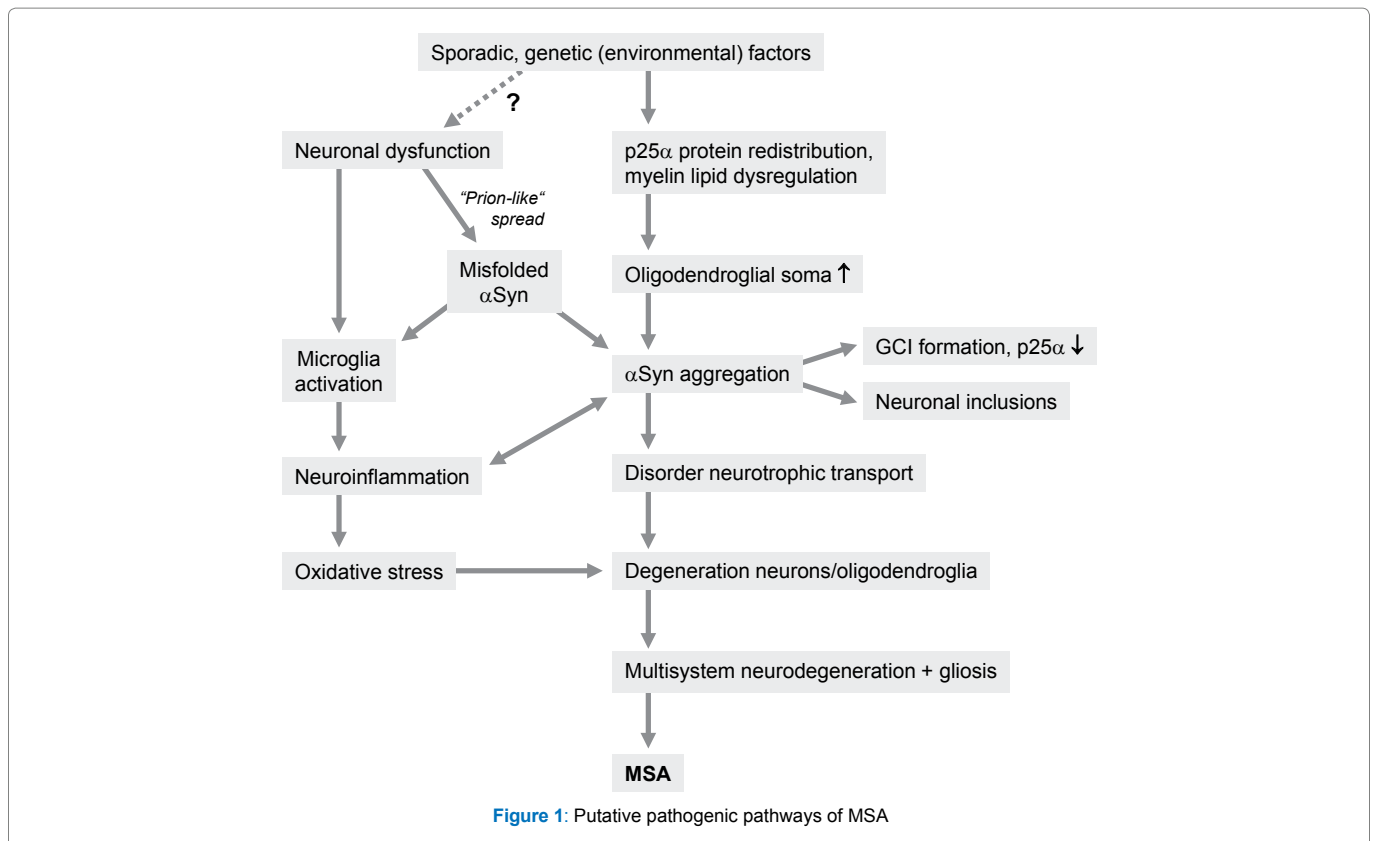neuronal pathology and GCIs and NIs in the severely affected brain regions suggests a link between these phenomena[5], although the underlying mechanisms remain to be elucidated.

In conclusion, although the pathogenesis of MSA is currently poorly understood, evidence from animal models and human postmortem studies suggest that the accumulation of misfolded αSyn plays a central role in the disease process[58,62], which can be considered a synucleinopathy with specific glioneuronal degeneration, associated with early myelin dysfunction and neuronal degeneration related to retrograde axonal disease[55,124] (Figure 1). Although one may speculate that primary neuronal pathology leads to secondary oligodendroglia degeneration as suggested by the finding that NCIs exist in areas lacking GCIs[67], the fact that distribution and severity of neurodegeneration reflect subregional GCI densities supports the hypothesis of a primary oligodendrogliopathy[60,62].

MSA has also been suggested to be a primary neuronal disease, the formation of GCIs probably resulting from secondary accumulation of pathological αSyn that may be neuronal in origin[142]. However, strong evidence against a primary neuronal pathology is the fact that GCIs are the hallmark of MSA and not in PD, a disease with similar lesion pattern of αSyn immunoreactive neuronal inclusions in many overlapping circuits but few GCIs, which differentiates these two disorders[133]. Although the source of αSyn is under discussion, "prion-like" spreading of this protein, OS, proteasomal and mitochondrial dysfunction[45] and proteolytic dysbalance, dysregulation of myelin lipids, demyelination, neuroinflammation and energy failure and genetic polymorphism[47] are suggested to contribute to the pathogenesis of systemic neurodegeneration in this unique proteinopathy[143,144].

Potential biomarkers of MSA

Recent international consensus criteria allow the diagnosis of MSA with three levels of certainty: a diagnosis of possible and probable MSA is based on the presence of clinical core features, while that of definite MSA requires postmortem confirmation[4]. In a series of neurodegenerative diseases, the presence of neuroimaging and/or fluid (serum, cerebrospinal fluid/CSF) biomarkers has improved the diagnostic accuracy, prognostic guidance and may serve as efficacy measures or surrogates of target engagement for clinical trials (e.g.[145-152]. Biomarkers include those based on neuroimaging, in particular multimodal magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), MR spectroscopy, and positron emission tomography (PET), peripheral biomarkers (skin, peripheral nerve and other biopsies) and fluid biomarkers from serum, plasma and CSF. In general, there is no single biomarker that will satisfy all requirements, whereas combinations are likely to be of great value in improving the diagnostic accuracy and prognostic guidance[146]. Unfortunately, despite growing research efforts, no biomarker currently exists for the diagnosis and prognosis of MSA.

Figure 1: Putative pathogenic pathways of MSA

Modern neuroimaging techniques have improved clinical accuracy in differentiating MSA and PD. MRI abnormalities in PD are subtle, whereas MSA shows more obvious imaging abnormalities such as the "hot cross bun" (HBC) sign (selective loss of myelinated transverse pontocerebellar fibers in the pontine raphe with selective preservation of the corticospinal tracts), atrophy of the pons, cerebellum, and globus pallidus[153,154], although no single feature is completely sensitive and specific. The same holds for MR spectroscopy and PET[155]. Multimodal MRI reveals different patterns of nigro-striatal involvement between PD and MSA[156], while others found significant differences of FA/RD values in bilateral corticospinal tract (CST) and left anterior thalamic radiation (ATR) in MSA-P versus PD and controls[157,158]. Hypointensity of the dorsolateral putamen in T2-weighted MRI due to iron deposition and more severe white matter abnormalities differentiate MSA-P from MSA-C[75], while dopamine transporter single-photon emission computerized tomography (DAT-SPECT) cannot differentiate MSA from PD [159]. Automated subcortical volume measurement can be used for differentiating MSA from PD and PSP with high accuracy[160]. Since sympathetic denervation in PD involves postganglionic neurons, while in MSA affects preganglionic neurons, cardiac [123I]metaiodobenzylguanidine (MIBG) scintigraphy may also be useful for the differential diagnosis of these disorders[161], but this test has suboptimal diagnostic accuracy[1].

The diagnostic validity of skin punch biopsies for the demonstration of αSyn deposits in Schwann or other cells in peripheral nerves in MSA patients is under discussion and needs further evaluation in pathologically confirmed cases[69,85,86].

The MSA Biomarker Initiative has recently published a critical review of fluid markers based on the evaluation of 60 studies[162], suggesting that combining several CSF fluid biomarkers may be more successful than using single markers. Currently, clinically most useful is a combination of the light chain of neurofilaments, which is consistently elevated in MSA compared to controls and PD[163], metabolites of the catecholamine pathway (dopamine and norepinephrine) and proteins such as αSyn, DJ-1, and total-tau (t-tau). A panel associating DJ-1 + t-tau + phosphorylated tau (p-tau) yielded high sensitivity (82%) and specificity (91%) for the distinction between MSA and PD or controls[164,165]. The best performance was achieved by combining NFL and FLT3 ligand[163], while the combination of DJ-1 + t-tau + p-tau protein in CSF improved the discrimination between MSA from PD and controls[164,166]. The results of proteomics for biomarker discovery and of miRNA expression need validation using independent technologies[162].

Only a few studies revealed a relation between fluid biomarker levels and clinical features, while most did not collect detailed clinical data to allow such and almost no studies had postmortem confirmation. Further research to elucidate the molecular background of the development and progression of the disease process of MSA are urgently needed in order to unmask the interplay of the various pathobiological changes as a basis for the development of reliable biomarkers and as an

emerging template for the development of disease-modifying treatment options of this hitherto incurable disorder.

Modern treatment strategies 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, rasagiline, minocycline, rifampicin, stem cells, etc., treatments that can halt or reverse the disease progression in humans have not yet been identified[167-170]. Symptomatic approaches include dopaminergic and anticholinergic agents, amentadine, paroxetine, non-pharmacological treatment, treatment of orthostatic hypotension, urinary and erectile dysfunction as well as palliative care[171,172]. Active immunization against αSyn has been shown to ameliorate the degenerative pathology and to prevent demyelination in a mouse model of MSA[173], 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[174], postmortem assessment of the short- and long-term effects of gene delivery of the trophic factor neurturin in patients with α-synucleinopathies (including one MSA-P case) showed its mild but persistent expression over 4 years[175]. Prominent targets for disease therapy include (1) pathological αSyn accumulation, (2) microglia activation and neuroinflammation, (3) oligodendroglial dysfunction, and (4) cell death[58]. Combination therapies, eg, immunotherapy against αSyn + antiinflammatory agents or multi-target drugs may be the next step for the treatment of synucleinopathies [176]. A new European project (SYMPATH) is currently assessing a vaccine targeting αSyn (AFFITOPE) in PD and MSA in humans[168].

Deep brain stimulation could not be recommended for MSA patients[177]. Emerging targets for interventional therapies of MSA were summarized recently[58], and therapeutic strategies targeting αSyn *in vivo* and *in vitro* models of MSA (αSyn expression, aggregation, degradation and clearance as well as cell-to-cell propagation) as possible basis for effective disease-modifying alternatives were critically reviewed[168,178].

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.

Acknowledgements

Abbreviations

αSyn	α-synuclein
CSF	cerebrospinal fluid
DLB	Lewy body dementia
GBA	glucocerebrosidase gene
GCI	glial cytoplasmic inclusion
GCIs	glial cytoplasmic inclusions
LB	Lewy body
MBP	myelin basic protein
MRI	magnetic resonance imaging
MSA	multiple system atrophy
MSA-C	cerebellar variant
MSA-P	parkinsonian variant
NCI	neuronal cytoplasmic inclusion
NNI	neuronal nuclear inclusion
OPCA	olivopontocerebellar atrophy
OPC	oligodendroglial precursor cell
OS	oxidative stress
PD	Parkinson disease
PET	positron emission tomography
PSP	progressive supranuclear palsy
SND	striatonigral degeneration
tg	transgene
TPPP	tubulin polymerization promoting protein

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