Multiple System Atrophy - State of the Art

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Abstract

Multiple system atrophy (MSA) is a rare and fatal neurodegenerative disorder that is characterized by a variable combination of parkinsonism, cerebellar impairment, and autonomic dysfunction. Some symptomatic treatments are available while neuroprotection or disease-modification remain unmet treatment needs. The pathologic hallmarks are the accumulation of aggregated alpha-synuclein (α-syn) in oligodendrocytes forming glial cytoplasmic inclusions (GCI), which qualifies MSA as a synucleinopathy together with Parkinson’s disease (PD) and dementia with Lewy bodies (DLB). Despite progress in our understanding of the pathogenesis of MSA, the origin of α-syn aggregates in oligodendrocytes is still a matter of an ongoing debate. We critically review here studies published in the field over the past 5 years dealing with pathogenesis, genetics, clinical signs, biomarker for improving diagnostic accuracy, and treatment development.

Keywords

Atypical parkinsonism · MSA · Alpha-synuclein · Oligodendrocyte

Introduction

Multiple system atrophy (MSA) is a rare and fatal neurodegenerative disorder that is characterized by a variable combination of parkinsonism, cerebellar impairment, and autonomic dysfunction [1]. According to the predominance of parkinsonism or cerebellar impairment, patients are further divided into MSA-P and MSA-C subtypes. Some symptomatic treatments are available while neuroprotection or disease-modification remain unmet treatment needs [2]. The pathologic hallmark is the accumulation of aggregated alpha-synuclein (α-syn) in oligodendrocytes forming glial cytoplasmic inclusions (GCI), which qualifies MSA as a synucleinopathy together with Parkinson’s disease (PD) and dementia with Lewy bodies (DLB) [3–5]. The origin of α-syn in GCI remains under debate and the exact mechanisms underlying the pathogenesis are not well understood. In this review, we focus on studies published in the field over the past five years dealing with pathogenesis, genetics, clinical signs, biomarker for improving diagnostic accuracy and treatment development.

Pathogenesis

MSA is characterized by severe neuron loss in several brain regions, in particular in the putamen, substantia nigra, pons, inferior olive, and cerebellum, while the number of oligodendrocytes (despite myelin loss) seems to be preserved compared with healthy controls [6]. It remains unknown if MSA is a primary oligodendropathy or if GCI formation is secondary to changes in neurons or other cells, while the contribution of neuronal α-syn pathology may be more prominent than initially thought [7].
The Origin of Oligodendroglial α-Syn

A recent study based on single-cell capture and quantitative real time PCR has challenged the former view that oligodendrocytes in MSA patients do not express α-syn [8•]. α-Syn protein expression was further observed in a small fraction of striatal oligodendroglial progenitor cells (OPC) in MSA-P patients [9•]. Moreover, α-syn protein and its transcripts were documented in oligodendrocytes generated from mouse and human embryonic stem cells, in induced pluripotent stem cells derived from fibroblasts of MSA patients, and in oligodendrocytes of adult MSA brains [10•]. The expression of α-syn protein and its transcripts decreased during maturation and was lower in mature oligodendrocytes compared with OPC [10•]. These findings point to the possibility that α-syn aggregates forming GCI in MSA are of oligodendroglial origin. However, a cell-to-cell transfer may also contribute to the pathogenesis of MSA since oligodendrocytes can also take up different exogenous α-syn species in a dynamin-dependent mechanism [11, 12].

Several studies have reported propagation of synucleinopathy and dopamine cell loss following inoculation with preformed α-syn fibrils of PD patient-derived α-syn in wild-type rodents and non-human primates [13]. It has also been shown that inoculation with brain homogenates of MSA patients in transgenic M83+/− mice induces motor impairment and widespread deposits of phosphorylated α-syn [14]. These mice are hemizygous for the A53T α-syn mutation causing familial autosomal-dominant PD. Noteworthy, inoculation with brain homogenates of MSA patients in wild-type mice did not cause any dysfunction [15]. This suggests fundamental differences between α-syn species in PD and MSA patients. Similar to the prion field, some authors have hypothesized that different strains may explain why α-syn mainly accumulates in neurons in PD and in oligodendrocytes in MSA. In this regard, inoculation with α-syn ribbons and fibrils in the substantia nigra of naïve rats induced distinct patterns of synucleinopathy with more abundant inclusions for ribbons. Ribbons also induced some inclusions in oligodendrocytes, but this was only occasionally observed after additional associated adenovirus mediated overexpression of A53T mutated α-syn in neurons of the substantia nigra [16].

Oligodendroglial Pathology

An increased number of OPC was observed in post-mortem brain tissue of MSA patients [9•, 17]. One of these studies further reported α-syn accumulation in striatal OPC in MSA patients, whereas the second did not observe such aggregates. The number of OPC was also increased in one of the transgenic MSA mouse models, whereas the number of mature oligodendrocytes was similar between transgenic and wild-type mice. Additional in-vitro findings in an oligodendroglial cell line suggest that α-syn aggregates may impair OPC maturation and oligodendrogenesis, and may explain the findings in the transgenic mouse model of MSA [9•].

Some evidence suggests that the oligodendroglial protein p25α (also called tubulin polymerization promoting protein, TPPP), which plays a critical role in myelin maturation, relocates early from the myelin sheath to the cytoplasm in MSA [18]. This relocation is supposed to impair myelin synthesis and seed α-syn aggregation in oligodendrocytes. A recent study has expanded these findings by showing that p25α not only relocates from peripheral processes but also from the nucleus to the perinuclear cytoplasm in MSA patients [19].

Other Mechanisms

Neuroinflammation as illustrated by a high amount of activated astrocytes and microglia is believed to contribute to the pathogenesis of MSA [20]. However, possible interactions between neuroinflammation and α-syn aggregation are not well understood. In this regard, higher astrocyte activation has been reported in the vicinity of GCI-bearing oligodendrocytes in frontal and visual cortices in MSA patients [21]. Based on additional in-vitro data and increased astrocyte activation after intracerebral injection of MSA-patient derived α-syn, the authors concluded that GCI formation and astrocyte activation may be induced by extracellular α-syn secreted by neurons [21]. In light of the ongoing debate about the origin of oligodendroglial α-syn (see above), astrocyte activation following aggregation of oligodendroglial α-syn or primary activation of astrocytes inducing GCI formation are alternative explanations.

Mitochondrial dysfunction, oxidative stress, and impaired autophagy have also been connected to the neurodegenerative process in MSA [2, 22]. The results of a recent study further suggest that mitochondrial dysfunction and oxidative stress might contribute to GCI formation by impacting autophagy, the latter being more relevant than the proteosome for the degradation of α-syn in oligodendrocytes [23]. Interestingly, exogenous application and endogenous overexpression of α-syn alone did not alter the autophagic flux in this study.

Similar to Alzheimer’s disease, insulin resistance (i.e., decreased insulin/insulin like growth factor-1 signaling) was observed in post-mortem brain tissue of MSA patients and brains of transgenic MSA mice [24]. More specifically, expression of insulin receptor substrate-1 phosphorylated at serine residue 312 (IRS-1pS312), a marker of insulin resistance, was increased in neurons and oligodendrocytes in the putamen of MSA patients, but not in the temporal cortex, a less vulnerable structure. The expression of IRS-1pS312 was more prominent in oligodendrocytes with α-syn aggregates. These findings suggest that insulin resistance occurs in MSA in regions where the neurodegenerative process is most severe and point to a possible relation between GCI and insulin resistance.
Genetics

Despite recent progress, the genetics of MSA remains a hard nut to crack. A homozygous mutation and compound heterozygous mutations in the COQ2 gene were described in two multiplex families in 2013 [25•]. COQ2 is essential for the synthesis of coenzyme Q10. This study additionally described several rare variants that were associated with sporadic MSA. However, the significance of these observations remains unclear, since several studies have not confirmed or only partly replicated these findings [26–32]. Nevertheless, post-mortem studies have shown a small but significant decrease in coenzyme Q10 levels in the cerebellum of MSA patients, pointing to a possible role of this enzyme in the pathogenesis of MSA [33, 34].

Similar to PD, variants of the GBA gene encoding glucocerebrosidase and that is mutated in Gaucher disease seem also to be associated with MSA [35]. Additional genetic studies searching for mutations of the prion and C9Orf72 genes in MSA patients were negative [36–39]. Finally, genome-wide association studies (GWAS) have suggested some associations between genetic polymorphisms and MSA. However, the largest GWAS based on the comparison between 918 MSA patients and 3864 controls did not find any genetic association, including the SNCA gene encoding α-syn and COQ2 [40•]. Expanding this study by adding more samples may allow that some potentially relevant associations may reach significance in the future.

Clinical Signs

Among symptoms of cardiovascular autonomic failure, orthostatic hypotension (OH) is the most frequent clinical feature. OH is defined as a drop in systolic (≥20 mm Hg) and/or diastolic (≥10 mm Hg) pressure within 3 minutes in upright position. A large study in 349 MSA patients has shown that measuring blood pressure over 3 minutes may be too short since it misses OH in a significant number of patients compared with measurements conducted over 10 minutes [41]. Our recommendation would therefore be to conduct blood pressure measurements for at least 10 minutes.

Sleep breathing disorders and sudden death during sleep are frequent in MSA. A large retrospective study in 136 MSA patients reported an association between stridor onset within the first 3 years of disease and shorter survival, whereas the overall survival between patients with and without stridor was not different [42•]. In addition, we have explored a potential association between sleep apnea, which is present in up to 69% of MSA patients, and mortality. Although sleep apnea was associated with mortality in a univariate analysis, this association was no longer significant when adjusting for disease duration and other factors of disease severity [43].
related quality of life. Furthermore, the neuropathologic processes underlying cognitive impairment in MSA are not well understood. One study did not report differences in the amount of cell loss, α-syn burden, Alzheimer-related Aβ pathology, and neurofibrillary tangles when comparing several brain regions in cognitively impaired and unimpaired MSA patients, whereas cognitive impairment was significantly associated with the presence of Lewy body-like neuronal inclusions in the neocortex in another study [7, 51].

Attempts to Improve Diagnostic Accuracy

Current diagnosis criteria of “possible” and “probable” MSA primarily rely on clinical symptoms, whereas “definite” MSA requires post-mortem confirmation [1]. During the last revision of these criteria, additional features were added for the diagnosis of “possible” MSA. These include abnormalities on brain imaging and have allowed increasing the sensitivity in early disease stages, which remains nevertheless only moderate. Currently, no validated biomarker exists for the diagnosis and prognosis of MSA. This chapter will focus on recent attempts to improve diagnostic accuracy. Hopefully, validated biomarkers may help in the future to improve diagnostic accuracy and also prognostic guidance.

Imaging

Several abnormalities have been described on brain magnetic resonance imaging (MRI), keeping in mind that MRI can also be normal in MSA, especially in early disease stages. Although not pathognomonic, the “hot-cross bun” sign on MRI is highly suggestive for MSA [52]. Similar to the higher sensitivity of T2*-weighted echo gradient MRI to disclose putaminal abnormalities, this technique seems also to be more sensitive for the detection of the hot-cross bun sign than classical T2-weighted MRI [53, 54]. Therefore, when suspecting a diagnosis of MSA, MRI should include T2*-weighted echo gradient imaging or equivalent sequences.

Beyond the description of single abnormalities, several strategies have explored the diagnostic potential of MRI when combining either the simultaneous assessment of several brain regions or the use of different MRI sequences. The first approach is exemplified by a study performing automated volume measures of 22 subcortical regions [55•]. The volume of the midbrain, putamen, and cerebellar grey matter were the most discriminative between parkinsonian disorders and yielded a diagnostic accuracy of 100% for the distinction between MSA and PD. The second approach is illustrated by multimodal imaging where a combination of T2* relaxation rates and mean diffusivity in the putamen, two measurements of microstructural damage, allowed a distinction between MSA-P and PD with an accuracy of 96% [56]. We expect that future progress with MRI will provide additional assistance to the clinician for the differential diagnosis between parkinsonian disorders. However, challenges remain with patients showing no significant imaging abnormalities in early disease stages and the necessity to confirm findings of imaging studies in patients with a post-mortem diagnosis of MSA.

Autonomic dysfunction is believed to be the result of preganglionic dysfunction in MSA. Recent evidence has challenged this view since cardiac [123I]-metaiodobenzylguanidine (MIBG) uptake, a measure of post-ganglionic cardiac norepinephrine uptake, is decreased in up to one-third of MSA patients, independent of disease duration and severity [57]. These findings suggest that autonomic failure in MSA is not limited to preganglionic dysfunction and challenges the usefulness of MIBG single photon-emission computed tomography for the differential diagnosis between MSA and PD.

Fluid Biomarkers

The diagnostic value of several candidate blood and cerebrospinal fluid biomarkers for MSA has been assessed in recent years. Most studies have focused on total α-syn, markers of axonal degeneration (e.g., neurofilament and tau), or catecholamines. Although significant differences between MSA, PD, and other parkinsonian disorders were found for some markers, none provided sufficient sensitivity and specificity for a differential diagnosis [58]. In light of these limitations and similar to current clinical practice for the diagnosis of Alzheimer’s disease, several biomarker panels have been proposed, including neurofilament, catecholamine metabolites, and proteins such as α-syn, DJ-1, and tau [58]. These combinations provide sensitivity and specificity >80% for the differential diagnosis between MSA and PD. These encouraging findings now need replication and validation in larger and independent biomarker cohorts.

Peripheral Tissue Biomarker

Deposits of phosphorylated α-syn and small fiber neuropathy have been consistently described in skin biopsies of PD patients [59, 60]. In contrast to PD, phosphorylated α-syn does not or only exceptionally accumulate in dermal autonomic fibers in MSA patients, whereas α-syn deposits are found in somatosensory fibers of the subepidermal plexus and dermal nerve fiber bundles [61•, 62•]. Several studies have suggested that nerve fiber density in the skin is higher in MSA patients compared with PD, but some loss of sudomotor gland innervation suggesting post-ganglionic impairment has also been reported [61•, 63, 64]. Further studies are necessary to confirm the distinct patterns of phosphorylated α-syn and fiber density in MSA and PD.
Several studies have described α-syn deposits in the enteric nervous system in PD patients suggesting that colonic biopsies may be a window to access the neurodegenerative process for the diagnosis of PD. However, some control subjects also show these deposits, and the sensitivity and specificity of current techniques is suboptimal for the diagnosis of PD [65]. Two studies have assessed colonic and gastroduodenal biopsies in patients with MSA and PD. Both found α-syn immunoreactivity in the enteric nervous system in MSA and PD patients, pointing to a limited interest of this approach for the differential diagnosis between MSA and PD [66, 67].

Treatment

Treatments are available for some symptoms, mainly for autonomic dysfunction, while disease-modification or neuroprotection remain unmet treatment needs. Several compounds have been tested in preclinical models and clinical trials in recent years. The results of these efforts are summarized below.

Preclinical Development

Because of the accumulation of aggregated α-syn in GCI and the central role α-syn seems to play in the pathogenesis of MSA, many studies have focused on various strategies to inhibit α-syn aggregation and accumulation [68, 69]. In this regard, inhibiting histone acetyltransferases and histone deacetylases with sodium phenylbutyrate, overexpressing the serine protease neurosin that cleaves α-syn, active and passive immunization, as well as reducing the amount of truncated α-syn with the caspase-1 inhibitor VX-765, have proven to be efficacious in transgenic mouse models of MSA [70, 71*, 72, 73]. The antibiotic rifampicin, the monoamine oxidase inhibitor rasagiline, and the antidepressant fluoxetine also demonstrated efficacy and have motivated conducting clinical trials with these compounds in MSA patients (see below, clinical trials section) [74–76]. Based on positive preclinical results, active immunization is also tested in an ongoing phase 1 study in MSA patients (see below, clinical trials section). In addition, the European ARTEMIS consortium is currently testing, individually and in combination, the efficacy of four complementary strategies targeting α-syn (including VX-765 and immunization with Affitope) in vitro and in transgenic MSA mice (http://www.erare.eu/financed-projects/artemis).

Additional preclinical studies have focused on strategies targeting neuroinflammation and insulin resistance. In this regard, inhibition of myeloperoxidase has been tested in a MSA mouse model combing transgenic overexpression of human α-syn in oligodendrocytes and injection of the neurotoxin 3-nitropropionic acid (3-NP). Inhibition of myeloperoxidase had positive effects on motor behavior and cell survival when treatment was started before the injections of 3-NP, but not when using a delayed-start design where 3-NP injections preceded treatment initiation with the myeloperoxidase inhibitor [77, 78]. Together with the observation of insulin resistance in the brains of MSA patients and transgenic MSA mice, we have recently shown that the glucagon-like peptide-1 analogue exendin-4, a well-tolerated and FDA-approved antidiabetic drug, has positive effects on insulin resistance and monomeric α-syn load in the striatum, as well as survival of nigral dopamine neurons in transgenic MSA mice [24].

Clinical Trials

Two studies have assessed the efficacy of the norepinephrine precursor droxidopa on symptomatic neurogenic orthostatic hypotension (Table 1). These trials were not specifically designed to test the compound in MSA but included a relevant number of MSA patients [79, 80]. The first study assessed the efficacy of droxidopa versus placebo after an open-label dose optimization period followed by a 7-day washout and a 7-day treatment period. The primary efficacy endpoint was the change in the composite score of the Orthostatic Hypotension Questionnaire from randomization to the end of the study. At the end of the treatment period, patients receiving droxidopa had significantly lower composite scores compared with placebo. The second trial used a withdrawal design (i.e., after dose optimization and open-label treatment periods, patients were randomized to droxidopa or placebo and followed these treatments for 2 weeks). Although some benefit was observed for secondary outcomes, this trial failed its primary efficacy endpoint since Orthostatic Hypotension Symptom Assessment item 1 scores (dizziness/lightheadedness) from randomization to the end of the treatment period were not different between groups [79]. Orthostatic symptoms and standing blood pressure can have significant fluctuations within the same subject, illustrating the challenges to design trials for treating orthostatic hypotension. Droxidopa has obtained FDA approval in 2015. A trial specifically assessing the efficacy of droxidopa on orthostatic hypotension and other non-motor symptoms in MSA patients is currently being conducted by the French MSA network (NCT02071459).

The results of several trials assessing potential neuroprotective effects were published during the last 5 years. Based on positive findings in preclinical disease models (see above preclinical development), rifampicin and rasagiline were tested in large randomized, double-blind, placebo-controlled studies. Both trials failed to reach their primary efficacy endpoint based on changes in Unified MSA Rating Scale (UMSARS) scores [81, 82]. Another large randomized, double-blind, placebo-controlled trial conducted by the French MSA network and assessing the efficacy of fluoxetine on the...
progression of UMSARS scores was also negative, although results are not yet fully published [83]. Since the loss of brainstem serotonin neurons seems to contribute to respiratory disorders in MSA patients, including sudden nocturnal death [84], designing a trial with fluoxetine to assess its efficacy on these respiratory disorders may be a successful strategy.

Following positive results in transgenic MSA mice [71•], the SYMPATH consortium (http://sympath-project.eu) is currently testing the safety and tolerability of two vaccines (AFFITOPE PD01A and PD03A) in a phase I trial in 30 MSA patients (NCT02270489). The last patient visit is scheduled for April 2017 and the results are expected for the end of 2017.

The myeloperoxidase inhibitor AZD3241 is currently being tested in a randomized, double-blind, placebo-controlled study in patients with MSA (NCT02388295). Patients are followed for 12 weeks, and the primary objectives are to assess tolerability and to determine the effect of AZD3241 on microglial activation, as measured by 11C-PBR28 binding with positron emission tomography. All patients have now completed the trial and the results should be available soon.

A small randomized, double-blind, placebo-controlled trial has assessed the efficacy of autologous mesenchymal stem cells (MSC) in MSA patients. Patients receiving repeated MSC application into the carotid artery showed a slower progression of UMSARS scores than placebo [85]. Major limitations of this study were the single-center design with the inclusion of only a small number of patients with MSA-C and the presence of hyperintense lesions on diffusion-weighted brain MRI in a significant number of patients, indicative of subclinical stroke. Although encouraging, current evidence is therefore too limited to recommend MSC for the treatment of MSA. A phase 1 study is ongoing at the Mayo Clinic in Rochester to assess safety of CSF delivery of MSC in MSA patients (NCT02315027).

Finally, a small trial assessing the tolerability and safety of lithium versus placebo in 10 MSA patients was stopped prematurely because of significant adverse events [86].

**Conclusions**

Despite progress in our understanding of the pathogenesis of MSA, the origin of α-syn aggregates in oligodendrocytes is still a matter of an ongoing debate. It remains also not well understood if α-syn aggregation is the initial event or occurs secondary to the seeding of other proteins such as p25α. In contrast to PD, there is currently no compelling evidence for prion- or non-prion-like protein spreading in MSA. The discovery of a homozygous mutation and compound heterozygous mutations in the COQ2 gene in two multiplex families was initially considered as a major breakthrough. However,
the significance of these findings is uncertain since additional studies did not or only partially replicated these results. In terms of clinical signs, measuring blood pressure in upright position over 10 minutes increases the sensitivity of detecting OH in MSA patients, early stridor is associated with shorter survival, and cognitive impairment is increasingly recognized as a frequent symptom. There has been progress in imaging, peripheral fluid and tissue biomarker development, albeit without impact on diagnostic accuracy and prognostic guidance. All large clinical trials testing possible neuroprotective effects failed. Hopefully, the translation of the positive results of several preclinical studies to the clinical will be more successful.

Acknowledgements This work was partly funded by grants to W.G.M. (ANR-14-RARE-0001-01 under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases, and FP7/2007-2013 under grant agreement 602999 from the European Union Seventh Framework Program).

Compliance with Ethical Standards

Conflict of Interest Brice Laurens, Sylvain Vergnet, Miguel Cuina Lopez, Alexandra Foubert-Samier, and Pierre-Olivier Fernagut declare that they have no conflict of interest.

François Tison reports a grant from French Gov (PHRC) and travel grants from Novartis France and ORKYN. Wassili奥斯 Gei Meissner reports research grants from University Hospital Bordeaux, PSP France, France Parkinson, MSA Coalition, MJFF, the French Ministry of Health, the French National Research Agency (ANR) and the European Community, payment for lectures from UCB, Novartis, TEVA/Lundbeck, Aguetant, Orkyn and MDS, travel grants from Novartis, TEVA/Lundbeck, and Abbvie, fees for editorial activities from Springer, and consultancy fees from Zambon France and Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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