Multiple system atrophy: an update

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Multiple system atrophy (MSA) is a sporadic and rapidly progressive neurodegenerative disorder that presents with autonomic failure in combination with parkinsonism or cerebellar ataxia. Over the past 5 years, substantial progress has been achieved in understanding the pathogenesis of the disease. Important insights into the epidemiology and genetics of MSA have confirmed the key pathogenic role of α-synuclein. Advances in the early recognition of this disease have resulted in revised diagnostic criteria, including, for the first time, neuroimaging indices. Finally, novel therapeutic options targeting disease modification have been investigated in clinical trials. These include riluzole, recombinant human growth hormone, and minocycline. Although the trials did not find any positive effects on disease progression, they generated important trial expertise in MSA and were only possible because of the establishment of international networks.

Introduction

In 1969 Graham and Oppenheimer introduced the term multiple system atrophy (MSA) to combine the entities of striatoniigral degeneration, olivopontocerebellar ataxia, and Shy-Drager syndrome. MSA is characterised by a variable combination of autonomic dysfunction, parkinsonism that is poorly responsive to levodopa, cerebellar ataxia, and pyramidal symptoms. The pathological features comprise neuronal loss in the basal ganglia, cerebellum, pons, inferior olivary nuclei, and spinal cord accompanied by gliosis. 20 years after the introduction of the term MSA, abundant argyrophilic filametous glial cytoplasmic inclusions (GCIs) were described as the pathological hallmark of the disease. The finding of misfolded, hyperphosphorylated, fibrillar α-synuclein as a main component of GCIs has classified MSA as an α-synucleinopathy, together with Parkinson’s disease and dementia with Lewy bodies, and has substantially determined the direction of research on MSA pathogenesis.

The clinical diagnosis of MSA has been defined by consensus criteria first published in 1998 and its assessment has been supported by the development of the unified MSA rating scale (UMSARS) in 2004. Advances in clinical recognition have led to a revision of the diagnostic criteria in 2008, including, for the first time, neuroimaging features. This Review provides an update on the main achievements in MSA pathogenesis and the novel clinical diagnostic criteria since 2004 and discusses the most recent insights into epidemiology, genetics, and clinical investigations. We also provide an outline of the main outcomes of clinical trials targeting disease modification in MSA.

Epidemiology and prognosis

The estimated annual incidence of MSA is about 0.6 per 100,000 per year, reaching 3 per 100,000 per year in the population older than 50 years. Prevalence ranges from 1-9 to 4.9 per 100,000 inhabitants. In 221 patients with probable MSA in the multicentre registry of the German Competence Network on Parkinson’s disease, mean age at onset of MSA was 60 years (SD=9; range 34–83 years), and both sexes were affected equally. Mean survival ranges between 7 and 9 years after initial clinical presentation, although there can be substantial variation. A prospective study on survival, which included 100 patients with MSA, has confirmed the relatively poor prognosis of the disease as compared with Parkinson’s disease, with an average survival of less than 9 years.

A natural history study undertaken by the European MSA Study Group (EMSA-SG) indicated a predominance of parkinsonian features in 58% of patients (MSA-P subtype) or cerebellar ataxia in 42% of patients (MSA-C subtype) in a cohort of 50 patients at eight sites in Europe. In a group of 67 patients from nine clinical centres, the North American MSA Study Group (NAMSA-SG) determined a similar predominance of the parkinsonian subtype with 60% of MSA-P in comparison to 13% of MSA-C subtype (the remaining 27% of the patients presented with a mixed motor syndrome, a classification not recommended by the second consensus statement on the diagnosis of MSA). By contrast, in the Japanese population, the disease presents differently, with predominance of the cerebellar subtype (83.8%) as compared with only 16.2% of the MSA-P subtype in a cohort of 142 patients from four neurological centres. The apparent ethnic differences might indicate variations in genetic predisposition or environmental exposure, but the exact causes remain poorly understood.

MSA-P usually progresses substantially faster than Parkinson’s disease, and the UMSARS shows a rapid annual decline. Particularly in the early stages, motor function impairment can be observed, accompanied by increased diffusivity in the putamen on diffusion-weighted MRI. The striatal pathology then spreads across the whole cortex with disease progression. Dysautonomia also deteriorates, although no correlation with global MSA impairment is seen. Nevertheless, early autonomic failure does predict shorter survival time, as does female sex, older age of onset, and shorter interval until clinical milestones are reached (e.g., frequent falling, cognitive disability, unintelligible speech, dysphagia, dependence on wheelchair, and use of urinary catheters). As indicated in a study by O’Sullivan and colleagues, many disability milestones accumulated over a short period of time in MSA define the poor prognosis of the disease (figure 1).
Clinical presentation and diagnosis

Patients with MSA present with a heterogeneous combination of autonomic failure, urogenital dysfunction, cerebellar ataxia, parkinsonian features, and pyramidal signs. A survey of the clinical presentation of MSA in Europe was provided by the EMSA registry, which included 437 patients from 19 centres in ten countries (panel 1). This large clinical study indicated a uniform distribution of the disease throughout Europe with similar presentation of the disease among all the centres involved, with urinary dysfunction (83%) being more common than symptomatic orthostatic dysregulation (75%), and parkinsonism (87%) being more common than cerebellar ataxia (64%).

The second consensus statement on MSA retains the diagnostic categories of MSA-P and MSA-C that are dependent on the predominant motor presentation at evaluation, and also retains the designation of possible, probable, and definite MSA. The definite diagnosis is based on the neuropathological evidence of GCIs in association with striatonigral degeneration or olivopontocerebellar ataxia. The disease onset is defined by the time of initial manifestation of any motor (parkinsonism or cerebellar dysfunction) or autonomic feature (except for erectile dysfunction), although subclinical autonomic neuropathy is likely to start several years before overt disease. Possible MSA is thought to be a sporadic progressive adult-onset (older than 30 years of age) disorder with either parkinsonism or cerebellar dysfunction and a symptom suggestive of autonomic dysregulation. Further support of the clinical diagnosis of possible MSA is provided by several additional features (panel 2). The diagnosis of probable MSA requires the presence of urinary dysfunction or orthostatic hypotension with a decrease in blood pressure of at least 30 mm Hg systolic and 15 mm Hg diastolic within 3 min after standing up, as well as a motor syndrome that includes parkinsonism with a poor response to levodopa or a cerebellar syndrome (panel 2). The diagnosis is further assisted by a list of supporting and non-supporting features (panel 3), as well as further investigations such as autonomic function tests and neuroimaging, which might help the differential diagnosis. Use of bladder function assessment often detects early abnormalities consistent with neurogenic disturbance. Tests include urodynamics that frequently indicate detrusor hyper-reflexia and abnormal urethral sphincter function followed later in disease progression by increased residual urine volume as detected by ultrasound. Cardiovascular autonomic dysfunction in MSA is investigated by either a standing blood pressure test, if the patient is still ambulatory, or by tilt-table testing.

Data from a recent study by Orimo and colleagues indicated different mechanisms underlying the degeneration of cardiac sympathetic nerves in Parkinson’s disease and MSA. Reduced cardiac uptake of ¹²³I-metaiodobenzylguanidine (MIBG) was associated with decreased number of tyrosine hydroxylase-immunoreactive nerve fibres in the epicardial nerve bundle in patients with Parkinson’s disease but not in controls or in patients with MSA. MIBG scintigraphy remains a useful cardioautonomic marker in the differential diagnosis of Parkinson’s disease versus MSA. Possible neuroimaging criteria, including structural and functional imaging, have been introduced to assist the diagnosis of MSA. Routine MRI, diffusion-weighted imaging MRI, voxel-based morphometry, and transcranial sonography have been suggested as options to support differentiation between MSA, Parkinson’s disease, and other atypical parkinsonian disorders. Furthermore, functional presynaptic and postsynaptic dopaminergic imaging by PET and single photon emission computed tomography (SPECT) has been advocated in the early diagnosis of MSA. However, each of the methods listed has only suboptimum accuracy, and most studies have been done in patients with clinically defined disease (ie, when additional investigation might have little purpose in the diagnosis of MSA).

Insights into the pathogenesis of MSA: novel pathological, genetic, and experimental evidence

A growing body of evidence has been collected in the past 5 years regarding the pathogenesis of MSA. As mentioned earlier, the core feature of MSA pathology is the widespread presence of GCIs, which are the obligatory subcellular feature for a definite diagnosis. The density of GCIs containing α-synuclein correlates significantly with neuronal deterioration and disease duration. A new pathological grading system was proposed in 2005 to quantify GCI density and neuronal loss associated with striatonigral degeneration and olivopontocerebellar ataxia. Although the origin of α-synuclein deposition in GCIs is not yet understood, the crucial role of...
oligodendroglial pathology in MSA pathogenesis has been highlighted by the discovery of early p25α accumulation in oligodendrocytes from patients with MSA.32 p25α, also known as tubulin polymerisation-promoting protein, is an oligodendroglia-specific phosphoprotein functionally associated with myelination. In patients with MSA, p25α is shifted into oligodendroglial cell bodies preceding α-synuclein aggregations.33 Furthermore, p25α stimulates α-synuclein aggregation in vitro,34 and up to 50% of oligodendroglia show abnormal

Panel 1: Overview of the results provided by the European Multiple System Atrophy registry

Characteristics
- 437 patients: 52.8% men, 47.2% women
- Mean age at disease onset: 57.8 years
- Mean disease duration: 5.8 years
- MSA-P: 68.2%
- MSA-C: 31.8%

Dysautonomia (symptomatic dysautonomia present in 99% of patients)
- Urinary symptoms (83%)
  - Urge incontinence (73%)
  - Incomplete bladder emptying (48%)
  - Erectile dysfunctions in males (84%)
- Orthostatic dysregulation (75%)
  - Orthostatic blood pressure drop of at least 20 mm Hg systolic or 10 mm Hg diastolic (59%)
  - Orthostatic blood pressure drop of at least 30 mm Hg systolic or 15 mm Hg diastolic or more (46%)
  - Chronic constipation (33%)

MSA-P
Parkinsonism in 87% of cases (61% in MSA-C) accompanied by:
- Rigidity (93%)
- Postural instability (89%)
- Postural tremor (54%) and resting tremor (33%)
- Freezing of gait (38%)

MSA-C
Cerebellar ataxia in 64% of cases (47% in MSA-P) accompanied by:
- Gait ataxia (86%)
- Limb ataxia (78%)
- Ataxic dysarthria (69%)

Pyramidal signs
- Babinski sign (28%)
- Generalised hyper-reflexia (43%)

Neuropsychiatric features and sleep disturbance
- Depression (41%)
- Hallucinations (5.5%)
- Dementia (4.5%)
- Insomnia (19%)
- Daytime sleepiness (17%)
- Restless legs (10%)

Panel 2: Diagnostic criteria for MSA

Probable MSA
A sporadic, progressive, adult-onset (>30 years) disease characterised by:
- Autonomic failure involving urinary incontinence (with erectile dysfunction in males)
or
- Orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and either
  - Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
  - A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Possible MSA
A sporadic, progressive, adult-onset (>30 years) disease characterised by:
- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
- At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
- At least one of the additional features:
  - Possible MSA-P or MSA-C
    - Babinski sign with hyper-reflexia
    - Stridor
  - Possible MSA-P
    - Rapidly progressive parkinsonism
    - Poor response to levodopa
    - Postural instability within 3 years of motor onset
    - Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
    - Dysphagia within 5 years of motor onset
    - Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
    - Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
  - Possible MSA-C
    - Parkinsonism (bradykinesia and rigidity)
    - Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
    - Hypometabolism on FDG-PET in putamen
    - Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

Reproduced from Gilman and colleagues,8 with permission of Lippincott Williams & Wilkins Publishers. FDG=18F-2-fluoro-deoxy-D-glucose. MSA=multiple system atrophy. SPECT=single photon emission computed tomography.
accumulation of p25α, which is often co-localised with α-synuclein positive GCIs. These findings have strengthened the hypothesis of a primary oligodendrogliopathy that precedes neuronal degeneration in MSA. However, abnormal accumulation of fibrillar α-synuclein has also been reported in neuronal cytoplasm and nuclei (NCIs and NNIs), as well as in neurites in human brains affected by MSA. Although these inclusions have not been accepted as a defining neuropathological criterion of MSA, they are likely relevant for the disease process. Data from recent postmortem studies have suggested that NNIs develop early in the disease process in pontine nuclei and inferior olives of MSA. Furthermore, neuronal p25α aggregation has been reported in MSA, both independently and associated with α-synuclein in some NCIs, similar to that seen in Lewy bodies in Parkinson’s disease and dementia with Lewy bodies. This similarity indicates neuronal dysfunction in α-synucleinopathies through common pathways, which involve cytoskeleton disruption with protein dislocation and aggregation. Based on this evidence, two parallel degenerative processes in MSA have been proposed: GCI-linked oligodendrogliopathy with secondary neuronal degeneration, and neuronal α-synucleinopathy associated with aggregation formation (NNIs, NCIs, and neurites).

Although the molecular mechanisms of misfolding, aggregation, and fibrillation of α-synuclein might partly overlap among the α-synucleinopathies, disease-specific cascades that are determined by genetic and environmental factors are likely to discriminate these disorders. By contrast with Parkinson’s disease, few families have been reported with a family history of MSA. Importantly, a genome-wide screening in MSA for candidate single nucleotide polymorphism associations has reported a significant association between these polymorphisms (rs11931074, rs3857059, and rs3822086) at the SNCA locus and the risk for developing MSA. This genetic breakthrough points to a primary role of α-synuclein processing in the pathogenesis of MSA. The role of environmental factors is still elusive. Results from several controlled studies have shown increased risk of MSA with occupational and daily habits, including exposure to solvents, plastic monomers, additives, metals and various other toxins, and history of farming. However, another recent study did not confirm these initial findings.

The role of oligodendroglial α-synucleinopathy as a trigger of MSA-like neurodegeneration has been investigated in transgenic mice with targeted over-expression of human α-synuclein under the control of specific oligodendroglial promoters. Insolubility and hyperphosphorylation of α-synuclein reproduced the main features of human GCI pathology in transgenic mice and further induced neuronal cell death involving: i) axonal α-synuclein aggregation and axonal degeneration; ii) mitochondrial dysfunction;

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Panel 3: Supporting and non-supporting features for the diagnosis of multiple system atrophy

**Supporting features**
- Orofacial dystonia
- Disproportionate antecollis
- Camptocormia (severe anterior flexion of the spine) with or without Pisa syndrome (severe lateral flexion of the spine)
- Contractures of hands or feet
- Inspiratory sighs
- Severe dysphonia
- Severe dysthria
- New or increased snoring
- Cold hands and feet
- Pathological laughter or crying
- Jerky, myoclonic postural or action tremor

**Non-supporting features**
- Classic pill-rolling rest tremor
- Clinically significant neuropathy
- Onset after age 75 years
- Family history of ataxia or parkinsonism
- Dementia (on DSM-IV)
- White matter lesions that suggest multiple sclerosis
- Hallucinations not induced by drugs

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Figure 2: Possible pathogenic pathways in MSA as seen in transgenic mouse models

Findings from transgenic mouse models with oligodendroglial α-synucleinopathy indicate three possible pathogenic pathways in MSA. GCI pathology could trigger microglial activation, which causes chronic oxidative stress and ultimately leads to neuronal cell death (1). Alternatively, GCI pathology could exacerbate susceptibility to exogenous oxidative stress and lead to neuronal cell death in striatonigral and olivopontocerebellar systems (2). GCI pathology could lead to secondary axonal α-synuclein aggregation or oligodendroglial mitochondrial dysfunction, which eventually lead to neuronal cell death (3). Oligodendroglial α-synucleinopathy is shown with a sickle-shaped cytoplasmic inclusion composed of misfolded α-synuclein. In the dying neuron, condensed chromatin, disruption of the nuclear membrane, and cell shrinkage is seen.

3NP=3-nitropropionic acid. GCI=glial cytoplasmic inclusion. MSA=multiple system atrophy.
Panel 4: Milestones of MSA research in the period 2004–09

- SNCA variants increase the risk for MSA
- Recognition of MSA as a primary oligodendrogliopathy
- Availability of transgenic MSA mouse models
- Revision of Gilman criteria

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Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms “multiple system atrophy”, “striatonigral degeneration”, “oliveopontocerebellar atrophy”, “Shy-Drager syndrome”, “autonomic failure”, “imaging”, “alpha-synuclein”, and “therapy” from 2004 to September, 2009. Articles were also identified through searches of the authors’ own files. Only papers in English were reviewed.

Towards brain repair in MSA

Neurotransplantation has been discussed as an alternative therapeutic approach in MSA. Striatal grafting has been proposed to “turn MSA into Parkinson’s disease” by recovering dopaminergic response in experimental double lesion models of MSA. However, recent experiments in the transgenic MSA mouse model suggest possible host-to-graft migration of α-synuclein pathology, which might have long-term effects on the functional activity of the grafts, creating the need for further preclinical research on this matter. Furthermore, the search of optimum cell sources for neurotransplantation has identified autologous mesenchymal stem cells as a possible candidate for brain repair in MSA. A report by Lee and colleagues suggested slowed progression in patients with MSA-C who had mesenchymal stem cell grafts, although further preclinical work is necessary to define the mechanisms underlying this effect.

Conclusions

In the past 5 years, substantial progress has been made towards better understanding the pathogenesis of MSA and to improve the diagnosis of this disease (panel 4). Extensive preclinical work has expanded the possibilities to use experimental MSA models to analyse disease-specific mechanisms and to approach candidate therapeutic strategies to create a rationale for clinical trials that might finally lead to successful treatment. The recent progress on the understanding of MSA has only been possible through the combined efforts of international academic networks in Europe (EMSA-SG), North America (NAMSA-SG), and Japan, which provide the necessary infrastructure to study this rare and rapidly progressive disease. Future experimental and clinical research will be needed to further understand the pathogenesis of MSA, validate and define the role of the new clinical diagnostic criteria, and to enhance the

Therapeutic approaches

At present, the therapy of MSA is only symptomatic and mainly targets parkinsonism and autonomic failure. So far, no effective neuroprotective therapy is available. Results from a placebo-controlled double-blind pilot trial with growth hormone therapy indicated a non-significant trend to slower motor progression with treatment. The recently reported results from the Neuroprotection and Natural History In Parkinson Plus Syndromes (NNIPPS) trial did not show any beneficial effects of riluzole treatment for survival or rate of progression in MSA. Minocycline, a tetracycline with neuroprotective efficacy in transgenic MSA mice when given early, did not modify disease progression in MSA after 24 and 48 weeks of double-blind randomised treatment (Minocycline in European MSA [MEMSA] trial, the EMSA-SG, and the German Parkinson Network [Wenning GK, unpublished data]). However, in this trial, minocycline induced suppression of microgliosis as shown by ¹¹C-PK11195 PET imaging, suggesting that the negative outcome might, at least partly, be due to the late start of the minocycline therapy and might suggest that disease-modifying therapies should be initiated early.

Rasagiline, a selective irreversible monoamine oxidase B inhibitor, is a new therapeutic candidate for MSA that is expected to enter a phase 3 trial shortly. Rasagiline induces disease-modifying effects beyond symptomatic efficacy in patients with Parkinson’s disease (ADAGIO [Attenuation of Disease Progression with Azilect Given Once-daily] trial). Furthermore, data from a preclinical study on rasagiline treatment in a transgenic MSA mouse model has shown neuroprotective effects, providing an experimental rationale for rasagiline as a disease-modifying candidate for MSA.

Anti-α-synuclein aggregation strategies are an alternative candidate therapeutic approach for MSA and other α-synucleinopathies currently under intense investigation. Rifampicin is a common antibiotic for the treatment of tuberculosis and leprosy, which has been shown to inhibit aggregation of α-synuclein. There was a reduction in monomeric, oligomeric, and phosphorylated α-synuclein seen in vivo in a transgenic mouse model of MSA after rifampicin treatment, as measured by western blot analysis, which was accompanied by decreased α-synuclein aggregation and associated with reduced neurodegeneration.

Milestones of MSA research in the period 2004–09

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assessment of the disease. This research will also help to
develop novel supportive neuroimaging methods and
other clinical investigations that might improve the
diagnostic precision and facilitate early diagnosis and
treatment. Importantly, more effort will be necessary to
define disease-modifying therapeutic strategies, which
will ultimately lead to better quality of life and increased
survival of patients with MSA.

Contributors
NS defined the search criteria, undertook the literature search, and the
analysis and screening of papers, and wrote the paper, and prepared
panel 4 and figure 2. PB helped with the literature search and primary
systematisation, contributed to the epidemiology and prognosis, and
prepared panel 1. SD helped define the search criteria and undertook
the literature search and primary systematisation. GKW defined the
search criteria, undertook the literature analysis and screening, and
made the final revisions. All authors have seen and approved the final
version.

Conflicts of interests
We have no conflicts of interests.

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