

Diagnosis and Treatment of Multiple System Atrophy: an Update

Abstract

This review provides an update on the diagnosis and therapy of multiple system atrophy (MSA), a sporadic neurodegenerative disorder characterised clinically by any combination of parkinsonian, autonomic, cerebellar or pyramidal symptoms and signs and pathologically by cell loss, gliosis and glial cytoplasmic inclusions in several brain and spinal cord structures. The term MSA was introduced in 1969 although prior to this cases of MSA were reported under the rubrics of striatonigral degeneration, olivopontocerebellar atrophy, Shy-Drager syndrome and idiopathic orthostatic hypotension. In the late nineties, α -synuclein immunostaining was recognised as the most sensitive marker of inclusion pathology in MSA: due to these advances in molecular pathogenesis, MSA has been firmly established as an α -synucleinopathy along with Parkinson's disease (PD) and dementia with Lewy bodies. Recent epidemiological surveys have shown that MSA is not a rare disorder (~5 cases per 100,000 population), and that misdiagnosis, especially with PD, is still common due to its variable clinical presentation. The diagnosis of MSA is largely based on clinical expertise, and this is well illustrated by the consensus diagnostic criteria which comprise clinical features only (divided into four domains including autonomic dysfunction, parkinsonism, cerebellar dysfunction and corticospinal tract dysfunction). Nevertheless, several autonomic function, imaging, neurophysiological and biochemical studies have been proposed in the last decade to help in the differential diagnosis of MSA. No drug treatment consistently benefits patients with this disease. Indeed, parkinsonism often shows a poor or unsustained response to chronic levodopa therapy although one third of the patients may show an initial moderate-to-good dopaminergic response. There is no effective drug treatment for the cerebellar ataxia. On the other hand, features of autonomic failure such as orthostatic hypotension, urinary retention or incontinence, constipation and impotence, may often be relieved if recognised by the treating physician. Novel symptomatic and neuroprotective therapies are urgently required.

Introduction

The clinical picture of multiple system atrophy (MSA) in its full blown form is distinctive (Fig. 1). The patient is hypomimic with orofacial and anterior neck dystonia resulting in a grinning smile akin to 'risus sardonius' and sometimes disproportionate antecollis. The voice is often markedly impaired with a characteristic quivering high-pitched dysarthria. The motor disorder of MSA is often mixed with parkinsonism, cerebellar ataxia, limb dystonia, myoclonus and pyramidal features occurring at the same time. However, akinesia and rigidity are the predominant features in 80% of patients, and cerebellar ataxia within the remaining 20% and according to the predominant motor presentation MSA patients may be labelled as either parkinsonian or cerebellar variant of MSA (MSA-P, MSA-C). Dysautonomia is characteristic of both MSA subtypes, primarily comprising urogenital and orthostatic dysfunction.

Clinical diagnosis and clinical diagnostic criteria

The clinical diagnosis of MSA is fraught with difficulty and there are no pathognomonic features to discriminate

the common parkinsonian variant (MSA-P) from PD. In a clinicopathologic study¹, primary neurologists (who followed up the patients clinically) identified only 25% of MSA patients at the first visit (42 months after disease onset) and even at their last neurological follow-up (74 months after disease onset), half of the patients were still misdiagnosed with the correct diagnosis in the other half being established on average 4 years after disease onset. Mean rater sensitivity for movement disorder specialists was higher but still suboptimal at the first (56%) and last (69%) visit. In 1998 an International Consensus Conference promoted by the American Academy of Neurology was convened to develop new and optimised criteria for a clinical diagnosis of MSA², which are now widely used by neurologists. These criteria specify three diagnostic categories of increasing certainty: possible, probable and definite (Table 1). The diagnosis of possible and probable MSA are based on the presence of clinical features listed in Table 1, with clear exclusion criteria. A definite diagnosis requires a typical neuropathological lesion pattern as well as deposition of α -synuclein-positive glial cytoplasmic inclusions³ (Fig. 2). However, whether the Consensus criteria will improve recognition of MSA patients especially in early disease stages needs to be investigated by prospective surveys with neuropathological confirmation in as many cases as possible.

MSA usually manifests in middle age (the median age of onset is 53), affects both sexes equally, and progresses relentlessly with a mean survival of 6-9 years. MSA patients may present with akinetic-rigid parkinsonism that usually responds poorly to levodopa, and whilst this has been identified as the most important early clinical discriminator of MSA and PD, a subgroup of MSA patients may show a good or, rarely, excellent, but usually short-lived, response to levodopa. In patients presenting initially with pure isolated parkinsonism, the presence of atypical features that are usually absent in PD (so-called red flags) may alert the clinician towards MSA (Table 2). Progressive ataxia, mainly involving gait, may also be the presenting feature of MSA^{4,5}, and appears to be more common than the parkinsonian variant in Japan compared to Western countries⁶. Autonomic failure with



Gregor Wenning obtained an MD at the University of Münster (Germany) in 1991 and a PhD at the University of London in 1996. He received his neurology training at Münster, Tübingen, London and Innsbruck. Presently he holds a professorship at the Department of Neurology, University Hospital, Innsbruck. He is affiliated to the movement disorders unit and in charge of the neurodegeneration research laboratory.



Felix Geser received his training in medicine and theology at the University of Innsbruck (Austria) and Freiburg (Germany). Presently he is a PhD student at the Department of Neurology, University of Innsbruck, investigating the natural history of MSA within the framework of the European MSA Study Group.



Figure 1: A patient with MSA with hypomimia, asymmetric orofacial dystonia more marked on the left and cervical dystonia affecting the platysma. The patient had a very distinctive quivering, strangled high-pitched dysarthria as is seen in 80% of MSA patients.

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symptomatic orthostatic hypotension and/or urogenital and gastrointestinal disturbances may accompany the motor disorder in up to 50% of patients at disease onset.

MSA is a progressive disease characterised by the gradual accumulation of disability reflecting involvement of the systems initially unaffected. So for example, patients who present initially with extrapyramidal features commonly progress to develop autonomic disturbances, cerebellar disorders, or both. In a recent large study on 230 cases carried out in Japan, MSA-P patients had more rapid functional deterioration than MSA-C patients, but showed similar survival⁶.

Investigations

The diagnosis of MSA still rests on the clinical history and neurological examination. Attempts have been made, however, to improve diagnostic accuracy through analysis of CSF and serum biomarkers, autonomic function tests, structural and functional neuroimaging and neurophysiological techniques⁷. Typical results that may be obtained using these various investigational tools are summarised in table 3.

Treatment

Autonomic failure

Unfortunately there is currently no curative therapy for autonomic dysfunction and so the therapeutic strategy is symptomatic and determined by the extent of impairment of the quality of life in these patients. In all cases it is important to remember that the progressive course of MSA means that a regular review of the treatment is mandatory to adjust measures according to clinical needs.

The rationale in treating the symptoms of orthostatic hypotension is based on increasing the intravascular volume with a reduction of volume shift to lower body parts when changing to an upright position. The selection and combination of therapies depends on the severity of symptoms in the individual patient, rather than the extent of blood pressure drop during a tilt test.

The simplest non-pharmacological options include sufficient fluid intake, high salt diet, more frequent along with smaller meals per day to reduce postprandial hypotension (by spreading the total carbohydrate intake) and custom made elastic body garments. During the night, head-up tilt increases the intravascular volume by up to 1L within a week, which is particularly helpful in

improving early morning hypotension. This approach is especially successful in combination with fludrocortisone, which further supports sodium retention.

The next group of drugs to consider are the sympathomimetics. These include ephedrine (with both direct and indirect effects), although at higher doses side effects develop including tremulousness, loss of appetite, and urinary retention in men.

Among the large number of vasoactive agents that have been evaluated in MSA only one, the directly acting / -adrenergic agonist midodrine, meets the criteria of evidence based medicine^{8,9}. Side effects are usually mild and only rarely lead to discontinuation of treatment because of urinary retention or pruritus, predominantly on the scalp.

Another promising drug appears to be the norepinephrine precursor L-threo-dihydroxyphenylserine (L-threo-DOPS), which has been used for this indication in Japan for years and the efficacy of which has now been shown by a recent open, dose finding trial¹⁰.

If the above mentioned drugs do not produce the desired effects, selective targeting is needed. The somatostatin analogue octreotide is often beneficial in postprandial hypotension, presumably because it inhibits release of vasodilatory gastrointestinal peptides and importantly it does not enhance nocturnal hypertension¹¹.

The vasopressin analogue, desmopressin, which acts on renal tubular vasopressin-2 receptors, reduces nocturnal polyuria and improves morning postural hypotension.

The peptide erythropoietin may be beneficial in some patients by raising red cell mass, secondarily improving cerebral oxygenation.

A broad range of drugs (Table 4) have been tried in the treatment of postural hypotension, but the value and side effects of many of these have not been adequately determined in MSA patients using appropriate endpoints.

In the management of neurogenic bladder (including measurements of residual urine volumes) clean intermittent catheterisation 3 to 4 times per day is a widely accepted approach to prevent the secondary consequences of poor micturition. It may be necessary, in some cases, to provide the patient with a permanent transcutaneous suprapubic catheter if mechanical obstruction in the urethra or motor symptoms of MSA prevent uncomplicated catheterisation.

Pharmacological options with cholinergic agonists or antagonists or / -adrenergic substances are usually not successful in reducing postvoid residual volume in MSA, but anticholinergic agents like oxybutynin can improve symptoms of detrusor hyperreflexia or sphincter-detrusor dysynergy in the early course of the disease. Recently, / -adrenergic receptor antagonists (prazosin and moxislyte) have been shown to improve voiding with reduction of residual volumes in MSA patients¹². Urological surgery must be avoided in these patients because post-operative worsening of bladder control is common.

The necessity of a specific treatment for sexual dysfunction needs to be evaluated individually in each MSA patient. Male impotence can be partially circumvented by the use of intracavernosal papaverine, prostaglandin E1 or penile implants. Preliminary evidence in PD patients¹³ suggests that sildenafil may also be successful in treating erectile failure in MSA: a recent trial confirmed the efficacy of this compound in MSA, but also suggested caution because of the frequent cardiovascular side-effects¹⁴. Erectile failure in MSA may also be improved by oral yohimbine.

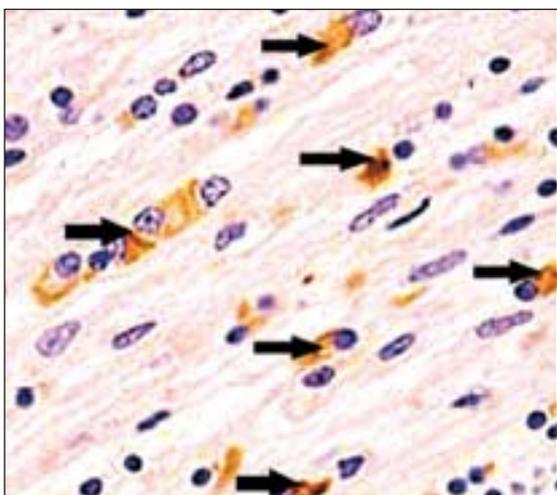


Figure 2: / -synuclein immunostaining reveals GCIs in subcortical white matter. Courtesy of Prof. K. Jellinger.

Constipation can be relieved by increasing the intraluminal volume which may be achieved by using a macrogol-water-solution.

Inspiratory stridor develops in about 30% of patients. Continuous positive airway pressure (CPAP) may be helpful in some of these patients. In only about 4% of cases is a tracheostomy needed.

Motor disorder

General approach

Because the results of drug treatment for the motor disorder of MSA are generally poor, other therapies are all the more important. Physiotherapy helps maintain mobility and prevents contractures, and speech therapy can improve speech and swallowing and provide communication aids. Dysphagia may require feeding via a nasogastric tube or even percutaneous endoscopic gastrostomy

(PEG). Occupational therapy helps to limit the handicap resulting from the patient's disabilities and should include a home visit. Provision of a wheelchair is usually dictated by the liability to falls because of postural instability and gait ataxia but not by akinesia and rigidity per se. Psychological support for patients and partners needs to be stressed.

Parkinsonism

Parkinsonism is the predominant motor disorder in MSA and therefore represents a major target for therapeutic intervention. Although less effective than in PD and despite the lack of randomised controlled trials, levodopa replacement represents the mainstay of antiparkinsonian therapy in MSA. Open label studies suggest that up to 30-40% of MSA patients may derive benefit from levodopa at least transiently^{15,16}. Occasionally, a beneficial effect is evi-

Table 1: Guidelines established by the American Autonomic Society and the American Academy of Neurology for the clinical diagnosis of MSA. Modified from Gilman *et al.*²

A. Nomenclature of clinical domains, features (disease characteristics) and criteria (defining features or composite of features) used in the diagnosis of MSA

Domain	Criterion	Feature
Autonomic and urinary dysfunction	Orthostatic fall in blood pressure by 30 mmHg systolic or 15 mmHg diastolic <i>or</i> Persistent urinary incontinence with erectile dysfunction in men <i>or both</i>	Orthostatic hypotension (by 20 mmHg systolic or 10 mmHg diastolic) Urinary incontinence or incomplete bladder emptying
Parkinsonism	Bradykinesia <i>plus</i> rigidity <i>or</i> postural instability <i>or</i> tremor	Bradykinesia (progressive reduction in speed and amplitude of voluntary movements during repetitive actions) Rigidity Postural instability (loss of primary postural reflexes) Tremor (postural, resting or both)
Cerebellar dysfunction	Gait ataxia <i>plus</i> ataxic dysarthria <i>or</i> limb ataxia <i>or</i> sustained gaze-evoked nystagmus	Gait ataxia (wide based stance with irregular steps) Ataxic dysarthria Limb ataxia Sustained gaze-evoked nystagmus
Corticospinal tract dysfunction	No defining features	Extensor plantar responses with hyperreflexia

B. Diagnostic categories of MSA

Possible MSA-P	Criterion for parkinsonism plus two features from separate other domains. A poor levodopa response qualifies already as one feature, hence only one additional feature is required.
Possible MSA-C	Criterion for cerebellar dysfunction plus two features from separate other domains.
Probable MSA-P	Criterion for autonomic failure/urinary dysfunction plus poorly levodopa responsive parkinsonism.
Probable MSA-C	Criterion for autonomic failure/urinary dysfunction plus cerebellar dysfunction.
Definite MSA	Pathological confirmation: high density of α -synuclein-positive GCIs associated with degenerative changes in the nigrostriatal (SND) and olivopontocerebellar pathways (OPCA).

dent only when seemingly unresponsive patients deteriorate after levodopa withdrawal. Pre-existing orthostatic hypotension is often unmasked or exacerbated in levodopa treated MSA patients associated with autonomic failure, whilst in contrast, psychiatric or toxic confusional states appear to be less common than in PD. Results with dopamine agonists have been even more disappointing. Wenning *et al.*¹⁶ reported a response to oral dopamine agonists only in 4 of 41 patients, and none of 30 patients receiving bromocriptine improved, but 3 of 10 who received pergolide had some benefit. Twenty two percent of the levodopa responders had a good or excellent response to at least one additional orally active dopamine agonist. Anti parkinsonian effects were noted in 4 of 26 MSA patients treated with amantadine¹⁶, but there was no significant improvement in an open study of 9 patients with atypical parkinsonism, including 5 subjects with MSA¹⁷.

Blepharospasm as well as limb dystonia, but not antecollis, may respond well to local injections of botulinum toxin A.

Ablative neurosurgical procedures such as medial pallidotomy fail to improve parkinsonian motor disturbance in MSA. Although recently there was a beneficial effect of bilateral high frequency subthalamic stimulation in four patients with MSA-P both in the short-term and long-term¹⁸.

Cerebellar ataxia

There is no effective therapy for the progressive ataxia of MSA-C.

Occasional successes have been reported with cholinergic drugs, amantadine, 5-hydroxytryptophan, isoniazid, baclofen and propranolol, but for the large majority of patients these drugs prove to be ineffective.

One intriguing observation is the apparent temporary exacerbation of ataxia by cigarette smoking. Nicotine is known to increase the release of acetylcholine in many areas of the brain and probably also releases noradrenaline, dopamine, 5-hydroxytryptophan and other neurotransmitters. Nicotinic systems may therefore play a role in cerebellar function and trials of nicotinic antagonists such as dihydro-beta-erythroidine might be worthwhile in MSA-C.

Practical therapy

Because of the small number of randomised controlled trials, the practical management of MSA is largely based on empirical evidence (↔) or single randomised studies (∅), except for a few randomised controlled studies of midodrine (∅∅). The present recommendations are summarised in the table 4.

Future therapeutic approaches

Two European research initiatives European MSA-Study Group (EMSA-SG) and Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) are presently conducting multicentre intervention trials in MSA aimed at halting or attenuating disease progression. Even if primary outcomes are negative these trials will generate important insights into the natural history and etiopathogenesis of MSA, thus identifying future targets for therapeutic intervention.

Table 2: “Red flags”: Warning features of MSA*

<i>Motor Red Flags</i>	<i>Definition</i>
Orofacial dystonia	Atypical spontaneous or L-DOPA induced dystonia predominantly affecting orofacial muscles, occasionally resembling risus sardonicus of cephalic tetanus.
Pisa syndrome	Subacute axial dystonia with a severe tonic lateral flexion of the trunk, head, and neck (contracted and hypertrophic paravertebral muscles may be present).
Disproportionate antecollis	Chin-on-chest, neck can only with difficulty be passively and forcibly extended to its normal position. Despite severe chronic neck flexion, flexion elsewhere is minor.
Jerky tremor	Irregular (jerky) postural or action tremor of the hands and/or fingers.
Dysarthria	Atypical quivering, irregular, severely hypophonic or slurring high-pitched dysarthria, which tends to develop earlier, be more severe and be associated with more marked dysphagia compared to PD.
<i>Non-motor Red Flags</i>	
Abnormal respiration	Nocturnal (harsh or strained, high pitched inspiratory sounds) or diurnal inspiratory stridor, involuntary deep inspiratory sighs/gasps, sleep apnoea (arrest of breathing for ≥ 10 secs), and excessive snoring (increase from premonitory level, or newly arising).
REM sleep behaviour disorder	Intermittent loss of muscle atonia and appearance of elaborate motor activity (striking out with arms in sleep often with talking/shouting) associated with dream mentation.
Cold hands/feet	Coldness and colour change (purple/blue) of extremities not due to drugs with blanching on pressure and poor circulatory return.
Raynaud’s phenomenon	Painful “white finger”, which may be provoked by ergot drugs.
Emotional incontinence	Crying inappropriately without sadness or laughing inappropriately without mirth.

*Excluding cardinal diagnostic features of MSA such as orthostatic hypotension, urinary incontinence/retention, levodopa unresponsive parkinsonism, cerebellar (ataxia) and pyramidal signs. Also excluding non-specific features suggesting atypical parkinsonism such as rapid progression or early instability and falls.

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Table 3. Additional investigations in MSA

Investigation	Typical results
<i>Cardiovascular autonomic function tests</i>	Orthostatic hypotension (B 20/10 mmHg systolic/diastolic blood pressure drop) Impaired reflex tachycardia Impaired heart rate variability Impaired Valsalva manoeuvre Impaired rise of plasma noradrenaline upon standing
<i>Clonidine challenge test</i>	Impaired release of growth hormone (controversial)
<i>Thermoregulatory sweat test (TST), quantitative sudomotor axon reflex test (QSART)</i>	Sudomotor dysfunction (an/hypohidrosis) due to pre and postganglionic sympathetic failure
<i>Sympathetic skin response</i>	Abnormal or absent
CSF	Increased neurofilament protein level
<i>External anal sphincter EMG</i>	Denervation (non-specific)
CCT	Unhelpful
<i>MRI (1.5 Tesla)</i>	Basal ganglia abnormalities (putaminal atrophy/hyperintense putaminal rim/putaminal hypointensity, infratentorial signal change – hot cross bun sign), cerebellar and/or brain stem atrophy
<i>IBZM SPECT</i>	Reduced striatal dopamine D2 receptor binding
<i>FDG-PET</i>	Reduced striatal, frontal, and infratentorial metabolism

Table 4. Practical Management of MSA

<p>A. Pharmacotherapy</p> <p>I. For akinesia-rigidity</p> <ul style="list-style-type: none"> Levodopa up to 800-1000 mg/day, if tolerated (↔) Dopamine agonists as second line antiparkinsonian drugs (dosing as for PD patients) (↔) Amantadine as third line drug, 100 mg up to three times daily (↔) <p>II. For focal dystonia</p> <ul style="list-style-type: none"> Botulinum toxin A (↔) <p>III. For orthostatic hypotension</p> <ul style="list-style-type: none"> Head-up tilt of bed at night (↔) Elastic stockings or tights (↔) Increased salt intake (↔) Fludrocortisone 0,1-0,3 mg/day (↔) Ephedrine 15-45 mg t.i.d (↔) L-threo-DOPS (300 mg b.i.d.) (↔) Midodrine 2,5 – 10 mg t.i.d. (∅) <p>IV. For postprandial hypotension</p> <ul style="list-style-type: none"> Octreotide 25-50 mg s.c. 30 min before a meal (↔) <p>V. For nocturnal polyuria</p> <ul style="list-style-type: none"> Desmopressin (spray: 10-40mcg/night or tablet: 100-400mcg/night) (↔) <p>VI. For bladder symptoms</p> <ul style="list-style-type: none"> Oxybutynin for detrusor hyperreflexia (2.5-5 mg b.i.d.t.i.d.) (↔) Intermittent self-catheterisation for retention or residual volume >100 ml (↔) <p>B. Other therapies</p> <ul style="list-style-type: none"> Physiotherapy (↔) Speech therapy (↔) Occupational therapy (↔) PEG (rarely needed in late stage) (↔) Provision of wheelchair (↔) CPAP (∅) (rarely tracheostomy [↔]) for inspiratory stridor 	
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Correspondence address:
Professor Gregor K. Wenning
Department of Neurology
University Hospital
Anichstrasse 35
A-6020 Innsbruck
AUSTRIA
Tel.: 0043 512 504 3920
Fax: 0043 512 504 3852
E-Mail: gregor.wenning@uibk.ac.at

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