

6 Multiple System Atrophy

Professor NP Quinn

Emeritus Professor of Clinical Neurology, Institute of Neurology, London, UK

Introduction

Multiple system atrophy (MSA) is a sporadic adult-onset neurodegenerative disease. It is characterised clinically by parkinsonism, cerebellar features and autonomic failure in varying combinations, and pathologically by the presence of neuronal loss, gliosis and α -synuclein positive oligodendroglial cytoplasmic inclusions (GCIs)^{1,2} in a selection of structures. These include supratentorially the striatum (particularly posterior putamen) and substantia nigra, infratentorially the inferior olives, pons and cerebellum, and the intermediolateral cell columns and Onuf's nucleus in the spinal cord. Mean age at onset is 57 years, and population prevalence in the UK is about 4-5/100,000. Recent reviews are recommended for further reading.³⁻⁵

Clinical Features and Diagnosis

Correct diagnosis of multiple system atrophy (MSA) is important for many reasons. Prior to 1989 there were essentially no diagnostic criteria for MSA. In that year GCIs were first described¹ as a pathological hallmark of MSA, regardless of whether patients were predominantly parkinsonian, and labelled as striatonigral degeneration (SND), predominantly cerebellar, and labelled as sporadic olivopontocerebellar atrophy (sOPCA), or were predominantly autonomic, and labelled as the Shy-Drager syndrome (SDS). In the same year Quinn⁶ suggested some preliminary diagnostic criteria, dividing cases of MSA according to their predominant motor disorder into SND-type (the majority), and OPCA-type (the minority). In 1998, broadly similar criteria were operationalised in the Gilman et al consensus criteria which have since been revised in 2008.⁷ In parallel, SND- and OPCA- type MSA are now called MSA-P and MSA-C respectively.

Prior to the 2008 update, none of the previous sets of diagnostic criteria included ancillary investigations, with the exception of the use of imaging to exclude other conditions, rather than to positively diagnose MSA. The diagnosis remains largely clinical. However, in the latest criteria there is more scope for investigations to support a clinical diagnosis.

Differential Diagnosis

The differential diagnosis of MSA covers a number of other conditions. The commonest diagnostic error is for patients with MSA-P to remain misdiagnosed in life as idiopathic Parkinson's disease (IPD). An autonomic presentation of MSA may be confused with pure autonomic failure (PAF), which usually has Lewy body pathology, or with some cases of PD presenting with autonomic failure. Most cases of MSA presenting with autonomic failure develop other neurological features within 5 years, but in rare cases the interval can be longer. Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) also enter into the differential diagnosis of MSA-P, as does (rarely) primary lateral sclerosis (PLS). Cerebrovascular disease may give rise to a mixed picture mimicking MSA. On the cerebellar side, about a third of patients with idiopathic late onset cerebellar ataxia (ILOCA) will ultimately turn out to have MSA.⁸ Sometimes late onset atypical Friedreich's ataxia may be misdiagnosed as MSA-C, as may SCAs 2 and 3,⁹ which may present a combination of cerebellar and parkinsonian features, the latter sometimes levodopa-responsive,^{10,11} but one would expect a positive family history. Later onset cases of a pure cerebellar syndrome due to the SCA 6 mutation may lack an obvious family history.⁹ Occasional patients with primary progressive multiple sclerosis, may also cause confusion, as can subjects with fragile X tremor ataxia syndrome (FXTAS).¹² A large study¹³ found pre-mutations in 4 of 626 cases of clinical MSA. Most of the remaining cases of sporadic adult onset ataxia (SAOA), probably have sporadic cerebellar-olivary atrophy.¹⁴

In the Queen Square Brain Bank from 1989 to 2013, of 169 brains of cases clinically diagnosed as MSA, 126 (75%) were confirmed pathologically as MSA. Conversely, of 165 pathologically confirmed cases of MSA, 128 (78%) had been diagnosed in life as MSA. The commonest cause for

misdiagnosis was PD, followed by PSP (unpublished observations).

In another recent study from the Mayo Clinic Brain Bank,¹⁵ only 62% of 134 clinically diagnosed MSA patients had MSA at autopsy. A second problem is that a diagnosis of MSA is typically made more than half way through the disease course.

Exclusion Criteria

Before considering positive diagnostic pointers, it is worth considering the exclusion criteria that are usually applied. There has never been a pathologically proven case of MSA starting before age 30. The incidence rises thereafter, peaking in the late 50's, and declining thereafter. Cognitive impairment can be seen in (usually late) MSA. It is much commoner in patients with Lewy body disease with cortical involvement (who so often also commonly have postural hypotension), and in patients with PSP. Dementia is therefore still considered an exclusion criterion for making a diagnosis of MSA. The NNIPPS study found that the *profile* of cognitive impairment on the Dementia Rating Scale was similar in fairly advanced MSA and PSP patients, but that impairment was observed at initial assessment in 57% of the PSP group as opposed to 20% of the MSA group. Of note, the MSA group had a 4.5 year duration at study entry, and in impaired MSA cases the diagnosis was confirmed pathologically in 64% as opposed to 95% in the unimpaired cases.¹⁶

Familial MSA is exceptionally rare. Therefore, the presence of atypical parkinsonism in a first degree relative should cast doubt on a diagnosis of MSA. In a large GWAS study (submitted¹⁷) no association of the alpha-synuclein (SNCA) or COQ2 genes with MSA has been identified. However, in rare families with a particular alpha-synuclein mutation (G51D) causing dominantly inherited young-onset PD the pathology revealed both Lewy bodies and GCI-like structures,¹⁸ and similar overlap has been reported in alpha-synuclein gene triplication cases.

Because PSP and corticobasal degeneration (CBD), both poorly levodopa-responsive causes of atypical parkinsonism, enter into the differential diagnosis, and have characteristic **eye movement disorders**, certain oculomotor features should exclude the diagnosis of MSA. Eye movement abnormalities that are acceptable include excessive square wave jerks, mild to moderate hypometria of saccades (but with normal velocity, and latency to onset), spontaneous nystagmus or positioning downbeat nystagmus.¹⁹ Definitely slow saccades would suggest PSP or SCA 2, limitation of downward gaze PSP or, less likely, CBD, and difficulty with initiating saccades, with delayed latency to onset, would suggest CBD.

In most case series, cases of MSA-P outnumber MSA-C by between 2 and 4 to 1. Cerebellar clinics, not surprisingly, have a preponderance of MSA-C cases, which also seem to predominate generally in Japan²⁰ as opposed to other countries.

“Core” Diagnostic Features

The overall theme in terms of major diagnostic criteria is that MSA-P cases present with **parkinsonism** that is usually non- or poorly-levodopa responsive (although up to 30% may have a good response at some stage,²¹ usually waning thereafter), with additional features of cardiovascular autonomic or urogenital dysfunction, with or without cerebellar features or pyramidal signs. Along the **cerebellar** route, the main requirement is to have an ILOCA syndrome with additional cardiovascular autonomic or urogenital disturbance, with or without pyramidal signs or parkinsonism. However, particularly early in the disease, the cardinal core diagnostic criteria may not be fulfilled. In such cases, although current diagnostic criteria do not include them, certain clinical “red flags” may, especially when multiple, point strongly to the diagnosis.

Clinical “Red Flags”

Two thirds of MSA patients have a tremor of the upper extremities. In contrast to IPD, this is only rarely (less than 10% of cases) of a classical pill-rolling nature.²¹ Instead it is usually an irregular jerky postural and action tremor, and close inspection may reveal that the jerkiness is due to myoclonic jerks (polyminimyoclonus), which are sometimes touch- or stretch- sensitive²² and not seen in uncomplicated IPD, or in PSP, but are seen in CBD. A marked tremor, the presence of titubation, or slow progression, should raise the possibility of FXTAS.

Rapid disease progression with early instability and falls are common to MSA, PSP and CBD relative to IPD. However, falls as a presenting feature, or within the first year of the disease, would be more in favour of PSP than MSA. Thus, in the NNIPPS study²³ 50% of PSP and 23% of MSA patients experienced falls and postural instability within the first, and 79% and 45% within the first 3 years of disease. Otherwise unexplained cardiovascular autonomic failure occurs commonly in MSA, invariably in PAF, and in a minority of patients with IPD. However, because of their relative disease frequencies, parkinsonism plus postural hypotension is more commonly due to PD than to MSA, and uncommon in PSP or CBD.

Urinary frequency and urgency are common in IPD and PSP as well as in MSA. However, incontinence not due to severe motor slowing, and incomplete bladder emptying, would not be expected in IPD, but occur in most patients with MSA²⁴ and a substantial minority of those with PSP. Male erectile dysfunction is virtually universal and early in patients with MSA, but is more difficult to interpret in older patients with PSP and IPD.

Many MSA patients also have cold, dusky, violaceous extremities²⁵ which blanch on pressure, with poor circulatory return (the “cold hands sign”). Peripheral oedema not accounted for by drugs is relatively common in MSA, as is Raynaud’s phenomenon.²⁶

Abnormalities of sleep and breathing are common in MSA. At least two thirds of patients have rapid eye movement (REM) sleep behaviour disorder (RBD).²⁷ They may talk or shout in their sleep, strike out at their bed partner, and even fall out of bed. This is commonly a very early, symptom and, curiously, usually improves as the disease progresses. It can be seen in a third or more of patients with IPD, and may be a feature common to alpha synucleinopathies,²⁸ as it appears to be relatively uncommon in PSP. Patients with MSA may also experience nocturnal or diurnal stridor, worsening or new onset of severe snoring, and involuntary inspiratory sighs or gasps during the day, all of which are uncommon in IPD, PSP and CBD.

The speech of patients with MSA can be almost diagnostic. Patients with MSA-P, in addition to the hypophonic monotony of parkinsonian speech, usually have an increase in pitch, and a quivery (possibly myoclonic) croaky strained element to their speech. On the other hand, patients with MSA-C may have a more typical slurring cerebellar dysarthria. In contrast, patients with PSP usually have a lower pitched, growling dysarthria that terminates in groaning noises in the advanced stages. Significant dysphagia is a prominent feature of both MSA and PSP, more in the latter, and an uncommon and late feature in IPD.

The new development of emotional incontinence with weeping or, less commonly, laughing, when moved by e.g. an event, or music, or something on the TV, is very common in PSP but also common in MSA, whereas it is uncommon in IPD.

Over time, most patients with IPD develop typical mobile dystonic or choreo-dystonic movements of the extremities on chronic levodopa treatment. In contrast, patients with MSA frequently have more sustained dystonic dyskinesias, sometimes unilateral, often involving the face and neck,²⁹ sometimes mimicking a ‘risus sardonicus’,³⁰ and patients with PSP may develop levodopa-induced oromandibular dystonia. Dystonia is also common in untreated MSA patients.²⁹ Other postural abnormalities that are more common in MSA relative to other parkinsonian disorders are disproportionate antecollis,³¹ camptocormia, and lateral deviation of the trunk (“Pisa syndrome”).³² Contractures of the extremities are very common in CBD, relatively common in MSA, and uncommon in PSP and IPD.

If there is any suspicion of atypical parkinsonism (and one should always be suspicious of the diagnosis, not only that made by others but also continually reviewing one’s own diagnosis), all of the above should be enquired about. To an astute clinician multiple clinical “red flags” can indicate a diagnosis of MSA with a high probability even if full core criteria are not satisfied⁵. A study³³ comparing “red flags” between IPD and MSA-P cases looked at 6 categories: early instability, rapid progression, abnormal postures, bulbar dysfunction, respiratory dysfunction and emotional incontinence, and found that when 2 or more were positive the specificity for predicting probable MSA was 98% and the sensitivity 84%.

Prognosis

Sadly, the prognosis for most patients with MSA is grave. Several series have found mean survival from first symptom to be 7-9 years, broadly similar to the prognosis in PSP or CBD. Moreover, the course of these three diseases is unremittingly downhill. There are, however, a few very rare cases with late autonomic failure have survived for 15-19 years.³⁴

Investigations

Many different investigations have been explored in MSA, but they are only beginning to feature in accepted diagnostic criteria. The utility of the various investigations depends on the question that is being asked. In patients with predominant parkinsonism, the most common diagnostic question that investigations are called upon to resolve are:

- Does the patient have IPD or not?
- If it is clear that the patient does not have IPD, do they have PSP or do they have MSA?

Some investigations can help answer Question 1 but not 2, and others vice versa. In the examples given below, a notation such as IPD versus MSA signifies that the technique has some ability to discriminate between IPD and MSA. IPD versus MSA/PSP indicates that the technique can help differentiate between IPD and [MSA/PSP], but not necessarily between MSA and PSP.

For patients with a cerebellar presentation, the main question, after excluding known genetic causes, or secondary causes of a sporadic presentation, is whether the patient's ILOCA will turn out to be MSA-C, or not (thus SAOA).

Brain Imaging

The most useful investigation in routine clinical practice is probably standard MRI. In selected centres, cardiac MIBG SPECT scanning and sphincter EMG can also be helpful

Structural imaging (MRI)

Routine 1.5 Tesla MRI may demonstrate a linear hyperintense rim at the lateral border of the putamen, putaminal atrophy or, on T₂-weighted images, posterior putaminal hypointensity relative to globus pallidus.^{35,36} Specificity is good, relative to IPD and to PSP, but sensitivity is low. Infratentorially one may see cerebellar atrophy, atrophy and a "hot cross bun" appearance in the pons (not specific to MSA), and hyperintensity of the middle cerebellar peduncles (also seen in many cases of FXTAS). The midbrain to pons ratio³⁵ can help distinguish between PSP and MSA.

A number of MR methods have been applied, mainly in research settings. These include diffusion weighted imaging (DWI—MSA versus IPD,³⁷ but not MSA versus PSP),³⁸ T₂* weighted MRI³⁹ (MSA versus IPD). Voxel-based morphometry can detect cortical and basal ganglia (versus IPD)⁴⁰ atrophy in MSA-P and infratentorial abnormalities in MSA-C (versus controls).⁴¹ Two excellent papers^{42,43} have reviewed neuroimaging in the diagnosis of MSA, and in the differential diagnosis of parkinsonism.

Functional Brain Imaging (PET/SPECT)

SPECT is more accessible than PET. ¹⁸F-dopa PET scans cannot reliably differentiate between IPD and PSP/MSA,⁴⁴ nor, unsurprisingly, can dopamine transporter SPECT scans.⁴⁵

Brain ¹⁸F-deoxyglucose (FDG) PET scans are emerging as a useful tool for differentiating between IPD, MSA and PSP.⁴⁶

"Autonomic" Investigations

The principal "autonomic" symptoms in MSA are cardiovascular and urogenital.

Cardiovascular

The single most important cardiovascular symptom/sign in MSA is postural faintness/orthostatic hypotension (OH), an otherwise unexplained drop in systolic blood pressure by ≥ 20 or 30 mmHg,

depending on criteria used, in systolic BP 3 minutes after assuming the erect position.⁷ Unfortunately, dopaminergic drugs can cause OH, so it is important to test for orthostatic hypotension early in the disease before these drugs are taken. OH is a feature of both IPD and MSA, although in PD it usually appears later, and affects a lower proportion of patients, than in MSA. The presence of OH or the demonstration of more widespread abnormalities on a battery of cardiovascular autonomic function tests can tell whether a patient has autonomic failure, but in most studies⁴⁷ *not* whether this is due to IPD or MSA-P, although a recent Italian study using discriminant analysis of test results suggests that this can be achieved in their laboratory.⁴⁸ Cardiovascular AFTs may help to distinguish between MSA-P and PSP. They may be more useful in differentiating between MSA-C versus SAOA and SCAs.

Functional cardiac imaging Sympathetic autonomic deficits in IPD (or other Lewy body diseases) are principally post-synaptic, due to pathology in the sympathetic autonomic ganglia, whereas in MSA it is pre-synaptic. Cardiac ¹³¹I-MIBG SPECT scans can differentiate between pre- and post-synaptic sympathetic denervation.⁴⁹⁻⁵¹ In MSA (and PSP) the post-synaptic element is usually (but not always, especially in advanced cases) intact, giving normal results. In PAF, and in IPD with AF, typically there is impaired uptake of tracer over the heart. Some IPD patients without AF have normal, but most have abnormal, scans.

Urogenital

Onuf's nucleus in the sacral spinal cord is a specialised group of anterior horn cells supplying the nerves to the striated external anal and urethral sphincters. It is involved pathologically in both MSA and PSP, and sometimes in PD. As with somatic anterior horn cell dropout elsewhere, for example in ALS, sprouting occurs to re-innervate denervated muscle fibres, resulting in combinations of increased voltage, increased duration and polyphasia of motor unit potentials. **Sphincter EMG** must be undertaken by an expert, since there are many pitfalls. Technically, automated EMG machines may miss delayed "satellite" potentials. The interpretation of the result is also crucial.^{52,53} Multiple or traumatic childbirth, lower abdominal surgery, including retropubic (but not trans-urethral) prostatectomy, haemorrhoidectomy, and chronic constipation⁵⁴ may all produce an abnormal urethral or anal sphincter result. A retrospective study in pathologically proven cases⁵⁵ indicates that abnormal results are not diagnostically useful, since they can be seen in many cases of PD as well as in almost all cases of MSA. However, a normal result would make MSA very unlikely. The test cannot distinguish between MSA-P and PSP.⁵⁶ It might help differentiate between ILOCA and MSA-C, but this has not yet been established.

Other Investigations

Polysomnography

REM sleep behaviour disorder (RBD) appears to be a "marker" for α -synucleinopathies (IPD, DLB, MSA), in contrast to tauopathies (PSP, CBD) and amyloidopathies (AD). A good clinical history is suggestive, but definite confirmation can be given by polysomnography (PSG) which, in selected cases, may be helpful.²⁸

Sleep apnoea is common in MSA, less so in IPD and PSP. Documentation of sleep apnoea may therefore be helpful in the differential diagnosis (and management) of MSA patients.

Sweating

Hyper- and hypo-hydrosis can occur in both IPD and MSA. Quantitative sudomotor tests may show group differences between IPD and MSA patients, but may not be significantly robust to prove whether a given abnormality in an individual subject is due to IPD or MSA.

Conclusions on Investigations

No single investigation is diagnostic. Combinations of investigations may be more helpful than the results of a single "test". Moreover, some of these investigations are only available in specialised centres, and for many of them their ability to differentiate between MSA and, particularly, PSP and IPD, has only been studied in relatively advanced cases with clinically established diagnoses, and

their predictive value early in the disease is uncertain . They must be used intelligently, according to what question the clinician is trying to answer. Moreover, they are often expensive – the (relatively cheap) skills of an informed clinician are still much more important than expensive tests, for example, a DaT SPECT scan, that will not answer the question being asked.

Treatment

Currently, not only is there no treatment known to influence the underlying disease course, but also the efficacy of symptomatic treatments of MSA is limited. Nevertheless, there are many other ways in which patients can be helped, usually on a symptom-by-symptom basis.

Although the **parkinsonism** of MSA is typically non- or poorly-levodopa responsive, even a poor response is better than none. Moreover, a significant minority (up to 30%) show at some stage a good, and a few an excellent, motor response to L-dopa, but this usually wanes as the disease progresses. Dosage may be limited by unmasking or worsening of OH, or alternatively by unpleasant dystonic spasms of the face or neck. Some of these patients may better tolerate a dopamine agonist. A minority, perhaps 1 in 5, will also derive some benefit from amantadine.

The few patients treated with pallidotomy have not shown significant benefit. STN DBS will not improve on the patient's best L-dopa response. Benefit has been reported after injection of autologous mesenchymal stem cells (MSCs) into carotid and vertebral arteries followed by further repeated intravenous infusions,⁵⁷ but whether or how this resulted from the injected cells is unexplained.⁵⁸ A subsequent randomised trial of intravascular MSC infusions by the same group in MSA-C patients found a significantly smaller increase in total UMSARS scores after 360 days in the real MSC group.⁵⁹

No drugs help the **cerebellar syndrome**.

Urinary urgency and nocturia can be helped by peripherally acting anticholinergics such as oxybutynin or trospium, but these can precipitate retention of urine, especially in patients with incomplete bladder emptying. Desmopressin at bedtime can reduce nocturia, but is not recommended in elderly patients. A post-micturition residual volume of ≥ 100 ml is usually an indication for intermittent self- or carer-catheterisation, but some patients may require pads, a convener, or indwelling urethral or retropubic catheterisation. Male erectile dysfunction responds to sildenafil in both IPD and (less effectively) MSA, but in the latter the risk of symptomatic OH is greater.⁶⁰ Intracavernosal alprostadil (prostaglandin E1) injections are an alternative.

Orthostatic hypotension only needs treatment if it is symptomatic. Simple measures should be used first – high-salt diet, elastic support stockings, head-up tilt of the bed at night, and simple advice about standing up gradually, ingesting 500mls water 15 minutes before orthostatism⁶¹ and getting the head down level with the heart if the patient feels faint, will suffice in many patients. A minority may need the addition of fludrocortisone, midodrine⁶² or L-threo-DOPS.⁶³

Depression or emotional incontinence can often be helped by either a tricyclic or a selective serotonin reuptake inhibitor (SSRI).

RBD may respond to a small dose of clonazepam or melatonin. Significant **sleep apnoea** and **inspiratory stridor** should be managed in the first instance with continuous positive airway pressure (CPAP),⁶⁴ reserving cord lateralisation or tracheostomy for patients who do not respond.

Disease-related **dystonia** or contractures may be helped, or prevented from worsening, by local injections of botulinum toxin. Unfortunately, this usually does not help disproportionate antecollis, in which it may also worsen already impaired speech and swallowing function.

Spasticity rarely needs treatment in its own right, but if marked it is sometimes helped by baclofen. Similarly, **myoclonus** is seldom severe enough to merit treatment, but is sometimes helped by clonazepam or valproate.

Experimental controlled trials of riluzole, synthetic human growth hormone, minocycline, rasagiline, lithium, and rifampicin have not shown significant benefits.

Allied health professionals have a critical role in relieving symptoms and improving patient quality of life in MSA. Physiotherapists aid mobility and can educate the patient in safe turning and transfers, reducing the risk of falls. Occupational therapists can modify the home environment, and an expert wheelchair assessment and provision of a suitable model should be considered before there is significant danger of falling and fracturing long bones. Speech and swallowing therapists can give

advice on speech, swallowing and diet, and breathing. A video fluoroscopic swallow may reveal silent aspiration. Communication aids or a gastrostomy may be required. Finally, the palliative care movement has now extended its remit beyond cancer and ALS to patients with other progressive neurological disorders, and can offer valuable domiciliary, respite and terminal care for patients with MSA.

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