Multiple-system atrophy (MSA) is a rare (global estimated incidence of 1.8/100,000, and prevalence of 3.5/100,000) progressive, neurodegenerative disease that is characterised by autonomic failure in addition to various features of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. In fact, the term multiple-system atrophy was introduced in 1969 as an efficient way to encompass the disease entities of olivopontocerebellar ataxia, striatonigral degeneration, and the Shy–Drager syndrome. The more recent detection of α-synuclein, aggregates which make glial cytoplasmic inclusions (GCI) in all three of these diseases, lends credence to a unified concept of MSA. The origin of α-synuclein in GCI as well as the pathogenesis of MSA remain uncertain, although there has been some recognition that the misfolding and aggregation of α-synuclein plays an important role in pathogenesis. What is clear is that neuronatomically, MSA is characterised by severe neuron loss supratentorially in the substantia nigra and posterior putamen; infratentorially in the pons, cerebellum and inferior olives; and spinally in the intermediolateral cell columns. Nonetheless, the pathogenic mechanisms underlying MSA remain unknown, making it difficult to develop effective treatment therapies targeted at specific pathophysiological mechanisms, and to date there are no available treatments aimed at slowing or halting disease progression. The purpose of this review is to highlight salient issues related to clinical presentation, diagnosis, biomarkers, and outcome measures in hopes of enhancing future clinical trials in MSA.

Clinical Presentation

Clinically, MSA is typically classified into two subtypes: subtype C (MSA-C) characterised predominantly by cerebellar ataxia, and subtype P (MSA-P) characterised predominantly by parkinsonism. Of note, the MSA-C subtype has been reported to be relatively more prevalent than subtype P in Japanese populations, whereas subtype P has been reported to be more prevalent than subtype C in European and North American populations. MSA-P and MSA-C appear to share a similar natural history, with a median duration from onset to death of almost 10 years. Rapid eye movement (REM) sleep behavioural disorder, although not specific for MSA, is often one of the earliest symptoms of MSA, which is seen in more than 50% of patients. In addition, depressive symptoms often precede the onset of motor symptoms. Autonomic failure, expressed either as urinary incontinence (UI) or orthostatic decrease of blood pressure (ODBP) must be present for a clinical diagnosis in both subtypes of MSA. However, standard measurements of blood pressure over three minutes to detect orthostatic hypotension may prove too short a duration and often miss ODBP in a significant number of MSA patients compared to measurements conducted over 10 minutes. It has been recommended therefore to conduct blood pressure measurements for this period of time.

Regardless of subtype and initial presentation, virtually all patients with MSA will develop parkinsonism during the course of the disease. An akinetic-rigid syndrome typically presents bilaterally but can be asymmetric in severity. The typical parkinsonian type of resting tremor is rare, although two-thirds of patients have irregular, jerky actions or postural tremor. In fact it is this irregular, small-amplitude myoclonic movements (termed polymiminymoclonus) of the hands and/or fingers in an outstretched posture, which is sometimes touch- or stretch-sensitive, that is indicative of MSA. A quivery voice with increased pitch reminiscent of myoclonic speech is also suggestive of MSA, as is significant dysphagia. Also, early falls (i.e. in the first year of disease) are not uncommon.

Cerebellar dysfunction (limb and gait ataxia, dysarthria) are present in more than two-thirds of MSA patients, regardless of initial subtype or origin. The presence of two or more “red flags”, including early instability, rapid progression, abnormal posture, bulbar dysfunction, respiratory dysfunction and emotional incontinence in subjects with parkinsonism is indicative of MSA. Cognitive impairment, exhibited mainly as frontal system or executive dysfunction in MSA patients is considered to be ubiquitous (present in up to 75% of patients) but is not in itself diagnostic. Typical dementia features have been reported in up to 18% of patients. Finally, pain is an under-recognised symptom of MSA and is more severe and common in MSA-P subjects, affecting mainly lower limbs followed by neck and back pain. As in other neurologic disorders, pain intensity has been shown to correlate more with affective function than motor severity.

CSF and Imaging Biomarkers

A number of studies have recently sought to promote candidate biomarkers to aid in MSA diagnosis utilising blood and cerebrospinal fluid (CSF), but no reliable biomarkers have been validated in terms of diagnostic specificity. In addition to the prominent role of α-synuclein, the most promising biomarkers thus far include plasma norepinephrine levels, plasma catecholaminergic vesicular storage levels and plasma and CSF neurofilament light chain protein. In addition, the utility of such biomarkers as outcome measures in clinical trials is based upon the assumption that these biomarkers are valid proxies for the pathophysiologic changes associated with MSA and/or can serve as reliable surrogates that are reasonably likely to predict clinical benefit. Although structural brain magnetic resonance imaging (MRI) may be unremarkable in the early stage of disease, two MRI abnormalities are common as the disease progresses. The first of these has been described as the “hot-cross bun” sign seen on T2 or FLAIR MRI reflecting selective loss of myelinated transverse pontocerebellar fibres in the pontine raphe with preservation of the corticospinal tract and tegmentum. Although highly suggestive for MSA, this sign has also been described in other disorders such as spinocerebellar ataxias, leptomeningeal carcinomatosis, and vasculitis. The second neuroimaging abnormality described as a “putaminal slit” caused by a hyperintense signal in the dorsolateral margin of the putamen also has high positive predictive value for the diagnosis of MSA. Similar to the higher sensitivity of T2*-weighted echo gradient MRI to reveal putaminal abnormalities, these imaging techniques seem to be more sensitive for the detection of the hot-cross bun sign than classical T2-weighted MRI. Therefore, imaging protocols in MSA studies
should include $T_2^*$-weighted echo gradient imaging or equivalent sequences.3

In regards to molecular neuroimaging, a reduction in $^{18}FDG$-PET uptake in both the putamenal nuclei with a rostral-caudal gradient is the most prominent finding in MSA-P, although decreased $^{18}FDG$-PET uptake can also be detected in the thalamus, brainstem, and cortical areas. The current consensus diagnostic criteria4 for MSA established hypometabolism in the putamen nucleus, mesencephalic region and cerebellum as being supportive for MSA-P. Additionally, the development of PET radiotracers that can image aggregated α-synuclein has been a development priority for a number of companies seeking not only to define disease state but promote a biomarker that can track disease progression and treatment effects of MSA therapies. Despite the fact that several chemical entities have moderate affinity for α-synuclein, their binding affinities and selectivity versus tau and beta amyloid have made them less than ideal as candidate PET radiotracers. However, AC Immune in partnership with Biogen, have developed two compounds that show affinity for α-synuclein with good target engagement for various synucleinopathies and selectivity; one of which (Cpd-H) has a pharmacokinetic profile that should permit its use as a possible PET tracer that could potentially be used in future MSA clinical trials.

Diagnostic Difficulties
The heterogeneity of clinical phenotype noted above and lack of diagnostic biomarkers renders the diagnosis of MSA in clinical trial settings quite challenging, particularly in patients at the early stages of the disease where a disease-modifying drug may be most likely to show benefit. Not surprisingly, the most common misdiagnosis for patients with MSA-P is 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 Parkinson’s disease presenting with autonomic failure. Most patients of MSA presenting with autonomic failure develop other neurological features within five years, but in rare cases this interval can be longer. When considering cerebellar signs and symptoms, approximately 25% of patients with idiopathic late onset cerebellar ataxia (ILOCA) will ultimately turn out to have a diagnosis of MSA.

The introduction of consensus diagnostic criteria5 in 2008 was intended to improve diagnostic accuracy and aid clinical trial conduct. These criteria recognize definite, probable, and possible MSA. Definite MSA requires neuropathologic demonstration of GCIs with neurodegenerative changes in striatonigral or olivopontocerebellar structures. Probable MSA requires a sporadic, progressive adult-onset disorder including rigorously defined autonomic failure and poorly levodopa responsive parkinsonism or cerebellar ataxia. Unfortunately, lack of response to L-dopa is present in less than 50% of patients and although this response to L-dopa might be suboptimal, when present it is surprisingly sustained with a mean duration of 3 to 3.5 years, suggesting that levodopa responsiveness should be critically reconsidered as a requirement for the diagnosis of probable MSA-P. Possible MSA requires a sporadic, progressive adult onset disease including parkinsonism or cerebellar ataxia and at least one feature suggesting autonomic dysfunction, plus one other feature that may be a clinical or a neuroimaging abnormality. Despite the acceptance of the consensus criteria over the past ten years, clinical trials have not meaningfully benefited in terms of homogeneity of patient populations or signal detection. Of note, a large series of MSA patients from the Mayo Clinic Brain Bank exhibited an unexpectedly low diagnostic accuracy, suggesting further refinement of these consensus criteria may be needed. Of 134 patients with clinically diagnosed MSA, only 83 (62%) had definite MSA confirmed at autopsy6.

Outcome Measures
In addition to the diagnostic difficulties with initial misclassification, the selection of experienced investigators in MSA trials is paramount toward the successful conduct of a controlled clinical trial. This is important not only for diagnostic purposes but to ensure reliable and consistent outcome measures. Due to the disease rarity, complex disease neurobiology and clinical heterogeneity, there are only a handful of clinical research sites of excellence present across a small number of countries. In fact, one of the largest countries (the United States) is the only country close to approaching double-digit numbers of sites of excellence in MSA research. Even in such experienced sites, monitoring of strict adherence to diagnostic criteria is mandatory and we have found it useful to have an independent expert’s supervision of diagnostic procedures to ensure appropriate patient selection. Additionally, our experience across multiple orphan and ultra-orphan neurological indications support Singer et al’s reliance on an oligocentre model that selects the smallest number of very experienced and high-performing sites to ensure proper patient identification and to reduce outcome variability7.

Additionally, a standardised rater training programme covering both diagnostics and assessments for site raters and clinical research monitors has been shown to reduce variability and improve signal detection via a multi-pronged training approach: assessment through audio or video recordings which must achieve at least 85-90% concordance with the score of an expert consensus panel as well as the group consensus score, applied skills assessment training through a live interview with an actor trained to portray a subject with MSA; and ongoing in-study monitoring of assessment data to ensure rater consistency utilising electronic data capture “flags” to identify scoring trends, inconsistencies, and changes in scoring that may infer rater bias or drift.

The most common efficacy outcome measure in MSA trial is the Unified Multiple System Atrophy Rating Scale (UMSARS) which allows scores ranging from 0 to 104, with higher scores indicating greater impairment. This instrument consists of four parts. The first part is the UMSARS activities of daily living subscale (range 0-48), and the second is the motor examination subscale (range 0-56). The third part is measurement of autonomic function, and the fourth is a five-grade overall clinical status, similar to Hoehn and Yahr in Parkinson’s disease. UMSARS has proven to be a reliable,
and valid scale for semi-quantitative assessments of MSA patients with known rates of change associated with natural history. These rates can be used to power models of disease progression with the caveat that changes in slope vary with length of disease with steeper declines seen earlier in the illness (thus requiring fewer patients) while plateauing later in the illness. Unlike Alzheimer’s disease, where the steepest part of the clinical decline is seen in the more moderate patients, MSA patients with the steepest declines are still in a phase of illness that is early enough to have a significant impact on disease progression.

Additionally, accelerated UMSARS progression was predicted not only by shorter symptom duration at baseline, but also by an absent levodopa response. It appears that UMSARS-related disease progression slows down as early as the second year of follow-up, which is important to consider when embarking on therapeutic trials of long duration. Of note, a minimal clinically important change using the UMSARS has not yet been established for MSA patients making it difficult to appreciate the relationship between statistical significance and clinical importance. As the scale was initially validated in Europeans, its validity and applicability across various populations requires further examination. In particular, some items regarding cutting food, handling utensils, and dressing may not apply to some rural and geographically isolated cultures. Furthermore, due to the need to design a scale that was reasonably simple, short, and user-friendly, some prominent features of MSA are not fully covered by the UMSARS and other validated scales may need to be supplemented to evaluate items not covered by the UMSARS that may have an impact on the overall function of MSA subjects, such as bradyphrenia, anhedonia, depression, sleep disorders, fatigue, and overall quality of life.

Finally, the long-term follow-up of MSA patients is restricted by the rapid neurodegenerative process resulting in reduced life expectancy. This may help explain the high rate of attrition and serious adverse events often seen in MSA trials. Given the rapid disease progression, survival rates might be considered as an outcome measure particularly when inclusion criteria are not restricted to early stages of the disease. In contrast, choosing patients earlier in the disease course should help improve attrition. Utilising the correct analysis that takes into account attrition patterns coupled with limitations to those experienced investigators and demanding rigorous training on diagnostic and outcome measures which minimise error variance will help to ensure the chosen sample sizes will be able to detect treatment effects should they exist.

REFERENCES


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