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REVIEW ARTICLE

A short clinical history of multiple system atrophy

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Abstract In this article I shall review the history of multiple system atrophy (MSA) divided into three eras—1900 to 1969, 1969 to 1985, and 1985 to the present.

Keywords Multiple system atrophy · Shy Drager syndrome (SDS) · sporadic olivopontocerebellar atrophy (sOPCA)

1900–1969

The history of multiple system atrophy (MSA) starts at the Salpêtrière Hospital in Paris in 1900 with the paper [1] by Dejerine and Thomas entitled "L'atrophie olivo-ponto-cérébelleuse." They described two middle-aged sporadic patients presenting with ataxia and dysarthria who died within three years of follow-up. However, both patients also had akinesia, rigidity, brisk reflexes, and incontinence of urine. Only one had experienced an episode of fainting. One of the patients was shown to have olivo-ponto-cerebellar atrophy (OPCA) on autopsy, but the condition of the nigra and striatum was not reported.

The next landmark development was the publication in 1925 by Bradbury and Eggleston [2] of "Postural hypotension—a report of three cases." These were three males with onset between 36 and 60 years of age and follow-up between three and seven years, all of whom had postural hypotension and anhydrosis. One patient had impotence and the other two had hyperactive or asymmetric reflexes. One patient also had extensor plantar responses, pointing to an association between autonomic failure and neurological dysfunction.

A number of possible early cases of what was later termed MSA were reported over subsequent years prior to the 1960 paper of Shy and Drager [3].

The decade of the sixties was, in my view, the most important "decade of the basal ganglia." In 1961, Adams et al. described striatonigral degeneration [4]. Birkmayer & Hornykiewicz in Europe, and Barbeau in Canada, first described the benefits of low doses of L-dopa in Parkinson's disease. In 1964, Steele, Richardson, & Olszewski described progressive supranuclear palsy (PSP), and in 1967 Hoehn & Yahr, still effectively in the pre-L-dopa era, described the progression of parkinsonism. Also in that same year, Cotzias finally confirmed that large doses of L-dopa were dramatically effective in Parkinson's disease (PD). In 1968, Rebeiz first described a condition that we now call corticobasal degeneration. Finally, 45 years ago in 1969, Graham & Oppenheimer published their classic paper [5] in which they introduced the term "multiple system atrophy."

Shy and Drager's paper [3] was entitled "A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study." Of the two cases they described in detail (one of which came to them via autopsy), both had marked autonomic failure, which was the emphasis of the paper. Both patients had impaired coordination, slurred speech, reduced facial expression, and tremor at rest or with movement; one had pyramidal signs. They concluded their paper by writing that: "*The full syndrome comprises: orthostatic hypotension, impotence, atonic bladder, loss of anal sphincter tone, urinary and rectal incontinence, and loss of sweating. Additionally, rigidity, tremor, and loss of*

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associated movements." They also added a number of clinical features, which have not really borne the test of time: iris atrophy, external ocular palsy, distal muscle wasting, fasciculations, and abnormalities seen on neuropathic electromyography (EMG) and muscle biopsy. [Shy was in fact a neuromuscular specialist]. Autopsy in one of their patients showed cell loss and gliosis in the striatum, nigra, olives, pons, and cerebellum.

The following year Adams et al. [4] published "Dégénérescences nigro-striées et cerebello-nigro-striées" in which they described striatonigral degeneration in three patients with akinesia, rigidity, and tremor. Additionally, one had ataxia and intention tremor; all three had brisk reflexes; one had extensor plantar responses; two had dysarthria; one patient had blackouts and impotence; and another had double incontinence. The pathology involved not only the striatum and nigra, but also the olives, pons, and cerebellum.

1969–1985

In 1969 Graham and Oppenheimer [5] were the first to coin the term multiple system atrophy in their paper entitled "Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy." In that paper they stated: "*…unnecessary confusion is caused by inventing new names, of the type 'pallido-subthalamo-vestibular atrophy' for unusual syndromes. What we wish to avoid is a multiplication of names for 'disease entities' which, in fact, are merely the expression of neuronal atrophy in a variety of overlapping combinations. We therefore propose to use the term 'multiple system atrophy.*'"

A further key development in 1972 was the publication by Bannister and Oppenheimer [6] of a paper entitled "Degenerative diseases of the nervous system associated with autonomic failure." This included twelve autopsied cases from the literature plus four new cases of their own. Five of these sixteen cases, all with Lewy body pathology, presented with autonomic failure. Two of these went on to develop parkinsonism. The other fourteen cases, with multiple system atrophy, mostly started with autonomic failure and went on to develop other neurological deficits, including parkinsonism. This paper therefore underlined the entities of: 1) pure autonomic failure (with Lewy body pathology and no other neurological deficits); 2) Parkinson's disease with autonomic failure, and 3) multiple system atrophy (MSA). Some terminological confusion reigned for a while as MSA cases were described to have progressive autonomic failure (PAF). Later, PAF was used as the abbreviation for pure autonomic failure, a Lewy body condition with no additional neurological symptoms.

However, the limits and definition of MSA remained unclear. In personal correspondence in 1989 Oppenheimer wrote the following to me: "*I am a bit worried by the use of MSA as the name of a disease, like MS. I originally used the term in the context of autonomic failure, when I became convinced that there were two distinguishable conditions in which AF occurred, one characterised by Lewy bodies and the other by striatonigral degeneration. As the latter condition was so frequently linked with OPCA, I felt that a term was needed to cover both SND and OPCA. I chose multiple system atrophy—probably unwisely, as this term would seem to be applicable to other conditions such as Friedreich's ataxia. What I did not do was to define the limits of applicability of the term MSA. I could not even reach a firm opinion on whether all cases of OPCA—with or without autonomic failure—were suffering from one and the same disease.*" Although the nosology of MSA seems clear-cut in hindsight, it was clearly not so clear even at that time, but started to crystallize twenty-five years ago in 1989 (Fig. 1).

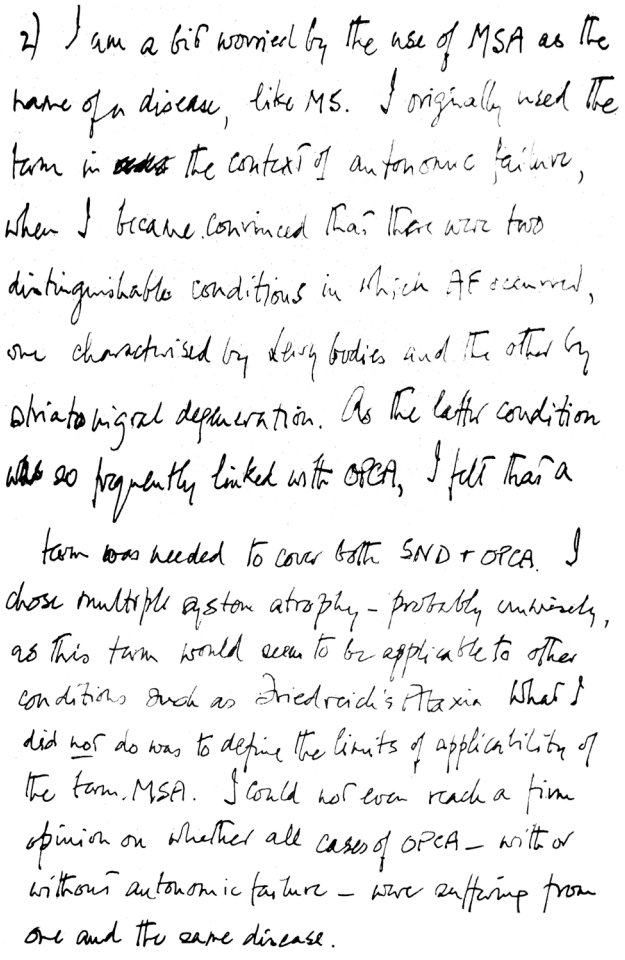
2) I am a bit worried by the use of MSA as the name of a disease, like MS. I originally used the term in the context of autonomic failure, when I became convinced that there were two distinguishable conditions in which AF occurred, one characterised by Lewy bodies and the other by striatonigral degeneration. As the latter condition was so frequently linked with OPCA, I felt that a term was needed to cover both SND + OPCA. I chose multiple system atrophy - probably unwisely, as this term would seem to be applicable to other conditions such as Friedreich's Ataxia. What I did not do was to define the limits of applicability of the term MSA. I could not even reach a firm opinion on whether all cases of OPCA – with or without autonomic failure – were suffering from one and the same disease.

Fig. 1 Fragment of a letter (1989) from David R. Oppenheimer to Niall Quinn discussing the suitability of the term "multiple system atrophy". The transcription of the letter is in the main text

1989–2014

On the clinical front, during the 1980's I had the privilege of working for a number of years with the late David Marsden at King's College Hospital in London, where he had established a specialist movement disorders clinic. Unlike today's trainees who hop from clinic to clinic every four months, I was able to follow many patients with parkinsonism over my eight years there. In 1980, the clinical and nosological distinctions between PD, MSA, and PSP were unclear both to me and to many others. However, due to this exposure, with pathological follow-up in many cases, the pieces gradually started to fall into place for me, culminating in a paper [7] entitled "Multiple system atrophy—the nature of the beast," which I wrote in sworn secrecy for the special supplement of the Journal of Neurology, Neurosurgery, & Psychiatry to mark the end of Marsden's ten year editorship. In this paper, I proposed the first set of systematic diagnostic criteria for MSA.

In reviewing the literature it was clear to me that hereditary OPCA comprised a multitude of conditions (most of which are now defined as spinocerebellar ataxias) that were not MSA, and that MSA was essentially a sporadic disease. A vertical supranuclear gaze palsy was clearly critical in distinguishing between PSP and MSA. Parkinson's disease with autonomic failure was much more common than MSA, because Parkinson's was more prevalent. However, the proportion of MSA cases with autonomic failure was greater than the proportion of Parkinson's disease cases, and they usually presented earlier and with more severe symptoms. Most MSA cases did not clinically display an overt dementia, whereas Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) were common, and both were frequently associated with autonomic failure. Although we now know that cortical atrophy and dementia may be seen in advanced cases of MSA, from a clinical diagnostic point of view, having DSM-IV dementia as an exclusion criterion for MSA made sense, as it kept out many subjects with PDD or DLB (who presented with both parkinsonism and autonomic failure, plus dementia). Finally, a review of the literature found no pathologically proven cases of MSA with onset before 30 years of age. Therefore, onset earlier than age 30 became another exclusion criterion.

In the same year, Papp, Kahn, and Lantos [8] published their key neuropathological paper describing for the first time oligodendroglial cytoplasmic inclusions (GCIs), which they found to be present in all cases of sporadic MSA, regardless of whether they were clinically diagnosed as having Shy Drager syndrome (SDS), striatonigral degeneration (SND), or sporadic olivopontocerebellar atrophy (sOPCA). This gave pathological underpinning to the clinical notion of SDS, SND, and sOPCA as one disease, separate from the hereditary adult-onset ataxias.

In 1998 it was discovered that Lewy bodies and Lewy neurites in Parkinson's disease stained positive with antibodies to alpha synuclein. Later that same year, GCIs did so also [9], introducing the umbrella term "alpha-synucleinopathy."

The rich clinical symptomatology and semiology of MSA

Alongside the key clinical features of parkinsonism (usually poorly levodopa-responsive), cerebellar symptoms and signs, autonomic failure and often pyramidal signs, a host of other features dubbed "red flags" can assist in the clinical diagnosis of MSA [7, 10]. These include: deformities such as disproportionate antecollis, Pisa syndrome, camptocormia, or contractures; sleep and breathing disturbances such as sleep apnea, new or increased snoring, or stridor; REM sleep behavior disorder (RBD—also common, but less so, in PD); inspiratory sighs; speech disturbances (often hypophonic, high-pitched, strained, croaky and quivery, with slurring—sometimes enabling diagnosis over the phone); early dysphagia; polyminimyoclonus of the fingers mimicking a jerky tremor; atypical levodopa-induced dyskinesias (predominantly dystonic and involving the neck and face—including risus sardonicus); emotional incontinence; peripheral circulatory features such as Raynaud's phenomenon, or cold dusky violaceous extremities with poor circulatory return after blanching on pressure; excess sweating (common also in PD); anhydrosis or heat intolerance; rapid disease progression; and early postural instability or falls. Most, but not all of these features can help to distinguish MSA from PD, and from other cerebellar disorders. However, some of the features differentiating MSA from PD, such as early postural instability and falls, and rapid progression, do not help to distinguish MSA from PSP. Indeed, context determines their relative usefulness in diagnosis.

On the other hand, there are also clinical features that point away from MSA, such as: classical pill-rolling tremor (present in <10%) or jaw tremor (even less common in MSA); disease onset after age 75; hallucinations not caused by drugs; significant dementia in the earlier stages; and a positive family history of atypical parkinsonism or cerebellar syndrome.

The autonomic history should include the number of times urine is passed at night and during the day (e.g. N/D 2–4/5–8), urgency, and incontinence (whether it is mainly due to motor slowing and impaired dexterity, or due primarily to bladder difficulties, including whether and how often incontinence results in just a dribble or whole bladder

emptying). Clinicians should also assess whether there is double micturition—with the patient thinking they have emptied their bladder, but finding that they pass significant amounts only a short time after, which may suggest incomplete bladder emptying. A bowel history is not often useful in diagnosis. In females, an obstetric and gynecological history should be taken with reference to traumatic childbirth, hysterectomy, or other significant problems. In males, prostatic history should be elicited. Clinicians should also ask about erections (e.g. when were your erections last "normal"?; are they completely absent?; or are they present but reduced in frequency, strength, or duration?).

Postural hypotensive symptoms should also be discussed. When the patient admits "dizziness" it is important to distinguish between cerebellar/vestibular causes and orthostatic hypotension (OH). One should ask specifically about vertigo, and distinguish it from other symptoms that may be experienced with OH. It is also useful to ask whether the patient feels his/her unsteadiness to be in the head (OH/vertigo) or in their legs (cerebellar). Other questions should address: episodes of presyncope and/or syncope; visual fading, white-outs, or blackouts; symptoms of postural hypotension such as "coat hanger" pain; and precipitating and relieving factors. As a part of the clinical examination, blood pressure should be measured supine and after 3 minutes standing. Unfortunately, many patients are already on hypotensive medications, such as L-dopa, so that without stopping the medication it is not possible to know whether a significant orthostatic drop is pharmacologically induced, caused by their disease, or due to both. Moreover, it remains difficult to distinguish between OH due to MSA and the more prevalent OH due to PD. One should therefore seize the "golden moment" when one first sees a patient with parkinsonian or cerebellar signs to measure postural blood pressure drop before the situation is confounded by drug therapy.

Note that I have not mentioned any ancillary investigations—in most cases, MSA can be diagnosed clinically by a skilled clinician who asks all the right questions.

Further clinical developments

Once the clinical and pathological definition of MSA was secure, the basis was established for subsequent studies. How common is MSA? What are its clinic-pathological correlations? What is its natural history? How can we measure disease progression? All of these are necessary prerequisites for designing and conducting clinical trials. How can we understand the pathogenesis of MSA and how can we intervene to prevent, halt, or retard its progression?

A handful of studies have examined the prevalence or incidence of MSA [11]. Studies of its natural history [12–16] have confirmed its unrelenting progression, with a mean survival of seven to nine years from first symptom, although there are cases with faster, and some with considerably slower, progression. The term Shy-Drager syndrome has largely fallen out of use, mainly because of its previous misuse by being applied to all cases of parkinsonism with autonomic failure, most of whom had Parkinson's disease. The two entry routes to clinical diagnosis, formerly labeled SND-type (parkinsonism predominant) and OPCA-type (cerebellar predominant) have been replaced by MSA-P and MSA-C respectively, although the SND/OPCA terminology has been retained for the pathological underpinning of the disease. In Western countries MSA-P seems to outnumber MSA-C by 2–4:1, whereas in Japan [14] and South Korea, and also in Latin America, the opposite seems to be the case. Two excellent recent papers [17, 18] have set MSA-C within the context of idiopathic or sporadic late onset ataxias.

The largest single-centre study of clinico-pathological correlation [19], published in 2004, examined one hundred MSA cases in the Queen Square Brain Bank. Their mean age at onset was 57.5 (34–83) years and mean survival was 7 (2–16) years. Pathologically, one-third were SND-predominant, one-half were mixed, and 17% were OPCA-predominant, with no 100% pure SND or OPCA cases. Among the SND-predominant pathology cases, 35% died with a diagnosis of MSA, and 50% died with an incorrect diagnosis of Parkinson's disease. Among those with OPCA-predominant pathology, 73% died with a diagnosis of MSA and only 16% died with a diagnosis of Parkinson's disease.

In 1999, my original diagnostic criteria [7] were revised in a consensus statement [20], and, in 2008, a second revised set of consensus criteria was published [21], for the first time, including some imaging items. Since 1989 the criteria for *probable* MSA have essentially remained the same—i.e. autonomic failure plus poorly L-dopa-responsive parkinsonism or a cerebellar syndrome. On the other hand, the criteria for *possible* MSA remain complex. If we are to develop disease-modifying therapy for this rapidly progressive and fatal disease, it will be crucial to be able to diagnose it as early as possible. Since imaging changes are non-specific and usually late, we will need to increasingly rely on other biomarkers and place more emphasis on the numerous clinical "red flags" that are present, as long as the examiner asks the right questions and looks for the relevant signs.

The last fifteen years have seen the development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS) [22], a quality of life scale (the MSA-QoL) [23], and the establishment of European, Japanese, and North American MSA study groups, now collaborating in the International Parkinson and Movement Disorder

Society MSA Study Group (MODIMSA). A French national center for MSA has been established between Bordeaux and Toulouse, as well as an MSA research network in the UK. In parallel, a number of MSA support groups have also been established, such as, the MSA Trust in the UK and the MSA coalition (which incorporates the Shy Drager Association) in the United States. There have also been five International Meetings on MSA: in London (1997), Rome (2004), Innsbruck (2007), Naples (2009), and Toulouse (2012).

The last ten years have seen the first MSA-specific clinical trials of potentially disease-modifying treatments. There have been trials of riluzole, recombinant human growth hormone, lithium, minocycline, rifampicin, and rasagaline; unfortunately, with negative outcomes. There have also been clinical trials of intravenous and intra-arterial mesenchymal stem cells with reported benefits, although the rationale and mechanism of these are uncertain. However, these studies have provided valuable information about the disease itself in terms of natural history, diagnosis, imaging, neuropsychology, and clinicopathological correlation, and about the challenges of clinical trial design for MSA.

There have also been important advances in symptomatic treatment, genetic studies, and the development of animal models (both lesional and transgenic), which can also be used to better understand the pathogenesis of the disease and help identify potential treatments.

The field of MSA has developed tremendously in the 45 years since Graham and Oppenheimer's seminal paper, and we are poised to make real progress in slowing, halting, and, best of all, preventing, this terrible disease.

Conflict of interest The author declares he has no conflict of interest.

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