Multiple system atrophy—the nature of the beast

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SUMMARY Multiple system atrophy (MSA) is generally considered a rare disease, but may account for up to 10% of patients with Parkinsonism. The profusion of names for this disease, which may present to general physicians, psychiatrists, cardiologists, autonomic specialists, general neurologists and those with a special interest in Parkinsonism (this author's own perspective) or cerebellar disorders, together with ignorance of its protean manifestations, may account for its under-recognition and misdiagnosis. In this article, the history and nosology of the condition are considered, and provisional diagnostic criteria are advanced. The usefulness (or otherwise) of ancillary investigations is addressed, and the shortcomings of current methods of treatment are stressed. As with idiopathic Parkinson's disease, the ultimate goal of eradicating the disease entails better diagnosis in order to establish the cause, and thence to develop a radical treatment capable of preventing or arresting the disease process.

Multiple system atrophy (MSA)¹ is a degenerative disease of the central nervous system. Clinically it may present with any combination of extrapyramidal, pyramidal, cerebellar and autonomic signs and symptoms, and may change its clinical emphasis as it evolves. Pathologically, it is characterised by cell loss and gliosis occurring in a selection of the following "at risk" structures: substantia nigra, caudate, putamen (especially posterior part), globus pallidus (especially pars externa), inferior olives, pontine nuclei, cerebellar Purkinje cells, intermediolateral cell columns of the spinal cord and Onuf's nucleus. Locus coeruleus, dorsal motor nucleus of vagus, vestibular nuclei, pyramidal tracts and anterior horns may also be involved. This pattern of involvement may hold the key to the mechanism of cell loss, explaining why certain cells are susceptible to whatever causes the disease whilst adjacent cells and structures are spared. Together with this distribution of cell loss, the absence of Lewy bodies distinguishes it from idiopathic Parkinson's disease and the lack of neurofibrillary tangles separates it from Steele-Richardson-Olszewski disease and post-encephalitic Parkinsonism.

MSA has always been considered a rare condition, yet it has also attracted a number of different and complex names related to its varied clinical and

pathological features (see fig). This has resulted in considerable confusion among neurologists. The main aim of this review is hopefully to bring together the strands to weave a coherent picture of the condition.

The history of MSA

Once a disease has been delineated, it is always instructive to return to earlier descriptions which, with hindsight, probably dealt with the same condition. Although other French and German workers may have described cases of this condition in the late nineteenth century, Déjerine and Thomas,² in 1900, in

Fig Simple is beautiful.

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describing two sporadic cases, were the first to introduce the term olivopontocerebellar atrophy (OPCA). Their first case was a woman of 52 years, the second a man of 42. Both developed ataxia, dysarthria, akinesia, rigidity and brisk leg reflexes. The woman developed incontinence of urine, and died after 3 years. The man developed tremor, incontinence of urine, and probable symptomatic postural hypotension (“étourdissements”). Pathological examination of the first case revealed atrophy of the olives, pons and cerebellum. The substantia nigra and striatum were not examined, or at least not commented upon.

The next piece of the jigsaw was a paper by Bradbury and Eggleston in the *American Heart Journal* in 1925 entitled “Postural hypotension. A report of three cases”.³ Here they described three male subjects whose symptoms began in middle life (aged 36, 47, 60 years) and who were seen after from 3 to 7 years of illness. Common to all three were symptomatic postural hypotension and anhidrosis. Patient 1 had additional impotence and constipation, cases 2 and 3 had unequal pupils and brisk leg reflexes, and case 3 had bilateral extensor plantar responses. Two patients died suddenly, and two years later⁴ they reported post-mortem findings in one of these cases, but unfortunately the central nervous system was not examined. Over subsequent years, a number of authors began to recognise in some patients a clinical association between orthostatic hypotension and disease of the central nervous system, especially Parkinsonism.^{5,6} The case of Langston⁷ was a man of 56 with a 7 year history of autonomic failure followed by Parkinsonism with antecollis, husky and uncontrollable speech, “peculiar involuntary movements resembling laughter” and emotionalism. Young’s patient,⁶ a man of 43, also had a 5 year history comprising autonomic failure, Parkinsonism, an unsteady, staggering gait and a husky voice. A left vocal cord paresis was noted.

The next developments took place in 1960. It is important to remember that this was before the levodopa era, and to keep in mind that today the degree of clinical response to levodopa is the single most useful diagnostic pointer in the differential diagnosis of Parkinsonism. Shy and Drager in 1960⁷ described “A neurological syndrome associated with orthostatic hypotension”. They had seen four cases, and reported two in detail, with pathology in one. Both were male. Case 1 began at age 39, and was seen at age 46 after 7 years of disease. Case 2 began at age 49, and died at age 55½ after 6½ years of disease. Both had marked autonomic failure, slurred speech, impaired co-ordination and distal muscle wasting. Both had tremor at rest affecting the hands, and case 1 also had tremor on movement. Case 1 had pyramidal signs, case 2 equivocal plantar responses and fasciculations. Both are said to have had external ocular muscle

paresis, but in case 1 this was a slight exophoria and in case 2 “inability to converge and weakness of the medial rectus muscle bilaterally”. Both had reduced facial expression, case 2 noted slowness of movements, and rigidity was present in both.

Post-mortem examination of case 2 showed cell loss and/or gliosis in many areas, but most marked in the caudate, substantia nigra, olives, locus coeruleus, cerebellum and intermediolateral cell columns of the spinal cord; the putamen, globus pallidus and pons were also affected. In the introduction, the authors defined the full syndrome as comprising the following features: orthostatic hypotension, urinary and rectal incontinence, loss of sweating, iris atrophy, external ocular palsies, rigidity, tremor, loss of associated movements, impotence, the findings of an atonic bladder and loss of the rectal sphincter tone, fasciculations*, wasting of distal muscles, evidence of a neuropathic lesion in the electromyogram that suggests involvement of the anterior horn cells*, and the finding of a neuropathic lesion in the muscle biopsy. Items with an asterisk* were found only in case 2. It is of interest to note that neither cerebellar nor pyramidal signs appear in this definition of the full syndrome.

In the previous year Van der Eecken, Adams and van Bogaert had made a brief presentation to the American Association of Neuropathologists entitled “Striopallidal-nigral degeneration. An hitherto undescribed lesion in paralysis agitans” which was published in 1960.⁸ They called attention to the finding of pronounced shrinkage and brownish discoloration of parts of the putamen and globus pallidus as well as the usual depigmentation of the substantia nigra. Microscopically, one of the most striking lesions was the virtual disappearance of the small cells of both caudate and putamen.

The same authors (Adams *et al*) in 1961 published a longer paper entitled: “Dégénérescences nigro-striées et cerebello-nigro-striées”.⁹ In it, they gave clinical and pathological details of 3 patients (2 M, 1 F) with sporadic disease. All had an akinetic-rigid syndrome with tremor (slight action, slight rest, and 4–5 Hz respectively). Reflexes were brisk in all three, plantars extensor in case 2, and there was ataxia and intention tremor in case 3. Cases 1 and 3 had severe speech disturbance, case 1 had blackouts and impotence, and case 2 double incontinence. The pathology involved not only striatum and nigra, but also olives and cerebellum in all three cases, with additional pontine lesions in cases 1 and 3. Case 2 also had Lewy bodies in substantia nigra. Neither clinically nor pathologically, therefore, was striatonigral degeneration a pure and restricted entity resulting from pathology of these structures alone.

It seems surprising that accounts of striatal patho-

logy in some cases of Parkinsonism should only have begun to appear in the 1960s. However, some such cases were in fact described earlier, but taken to be part of the spectrum of Parkinson's disease. Thus Messing, in 1930, described the case of a woman aged 62 years¹⁰ who presented "the classical picture of Parkinson's disease". Post-mortem examination of the brain revealed "total atrophy of the ponto-cerebellar system, partial atrophy of the inferior olives and their connections, marked atrophy of the supero-lateral portions of the cerebellum and of the vermis . . . and fibrosis of the globus pallidus . . . together with dysmyelination of the putamen and the anterior portion of the caudate nucleus . . . This was certainly a case of Parkinson's disease, with an unusual additional lesion: atrophy of the cerebellar pathways".

Malamud's 1957 atlas of neuropathology¹¹ devoted one page of text to "Parkinson's disease (paralysis agitans) . . . Besides the postencephalitic and other symptomatic forms of Parkinsonism, there is a primary degeneration form that generally begins in late middle or advanced age . . . The predominant pathology is either in the striopallidum or in the substantia nigra, although some cases show more diffuse cerebral involvement. Case 1: a 73 year old man with a two year history . . . gradually became bedfast . . . He exhibited a pill-rolling tremor . . . , rigidity and weakness . . . , a slurred, unintelligible speech, yet a relatively normal mental status. His course was rapidly downhill. The brain showed symmetrical atrophy of the putamen and globus pallidus, with grayish discoloration of the former". Neither of these accounts document nigral pathology, nor is there any mention of the presence or absence of Lewy bodies. Thus, despite the major discoveries of both Lewy and Tretiakoff in the early 1900s, there was still no neuropathological consensus on the diagnosis of idiopathic Parkinson's disease until almost half a century had elapsed.

Thus far, we have encountered four "conditions" which at first sight appeared separate, but may in fact all include subjects with the same disease: OPCA, idiopathic orthostatic hypotension, the Shy-Drager syndrome and striatonigral degeneration. Graham and Oppenheimer¹ deserve our thanks for writing in 1969: "... unnecessary confusion is caused by inventing new names, of the type "pallido-subthalamo-vestibular atrophy" for unusual syndromes. What we wish to avoid is the 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"".

During the early 1970s it became apparent that patients with neurogenic autonomic failure sometimes had Lewy body pathology rather than the changes of

MSA. A key clinicopathological review by Bannister and Oppenheimer in 1972 entitled: "Degenerative diseases of the nervous system associated with autonomic failure"¹² considered this division. They described 16 pathologically studied cases of autonomic failure: four personal cases (three MSA, one Lewy body) and 12 cases from the literature (eight MSA, four Lewy body). In the five Lewy body cases (4 M, 1 F) mean age of disease onset was 65 years (range 56–73), mean survival 5 years (range 1.5–13) and mean age at death 70 years. In the 11 MSA cases (8 M, 3 F), mean age at onset was 49 years (range 36–58), mean survival 6 years (range 2–11) and mean age at death 55 years. The striking difference in age of disease onset disguises the much worse prognosis of MSA cases. Among the five Lewy body cases, three had pure autonomic failure and two Parkinsonism with autonomic failure; pyramidal and cerebellar signs were absent. Among the 11 MSA patients, all had autonomic failure with pyramidal and/or cerebellar signs, and eight had additional Parkinsonism. Although in this series no MSA patients had isolated Parkinsonism with autonomic failure, this combination can undoubtedly occur. No patients in either group had received levodopa.

Pathologically, all 11 cases of MSA with progressive autonomic failure had involvement of pigmented brainstem nuclei. Intermediolateral cell columns were involved in 10, putamen in 10 and caudate in four whilst the olives were affected in 10, pons in six, cerebellum in 10, pyramidal tracts in five and anterior horns in four.

Takei and Mirra, in 1973, described seven cases of striatonigral degeneration (with pathology).¹³ Six of the seven had been diagnosed in life as Parkinson's disease, four had pyramidal signs, two ataxia and one orthostatic hypotension. Pathologically, in only one case was involvement limited to the striatum and nigra. They concluded: "Although we treated all our seven cases as examples of SND, which implies a disorder involving two sites, other structures were involved in some cases as well. The term is only justified with the understanding that these two sites are the most dominant of multiple sites of involvement. . . . It would be more meaningful to group these conditions under a simple name, such as multiple system atrophy". Unfortunately, they got carried away with the attractiveness of this notion, proposing that Huntington's disease, Pick's disease and Friedreich's ataxia, among others, be included under this label. Whilst multisystem degeneration might be a useful shorthand term for these different conditions, the term multiple system atrophy refers only to the specific disease (or possibly group of diseases) addressed here.

Returning to the cerebellar presentation of MSA, Miyazaki¹⁴ in 1978 described 45 patients labelled

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clinically as suffering from sporadic adult onset OPCA. Twenty had positive autonomic function tests for subclinical orthostatic hypotension; 17 of these (85%) subsequently developed urinary incontinence, seven (35%) had extrapyramidal symptoms, and eight (40%) had pyramidal signs.

In their review of striatonigral degeneration,¹⁵ Adams and Salam-Adams excellently summarised the clinical heterogeneity of MSA: “SND, OPCA and SDS symptomatically can occur singly or combined in all possible ways. Each of the clinical syndromes may mark the beginning of the disease, but if the patient survives for many years the appearance of the other two syndromes can be predicted”. Unfortunately, the review ends by proposing the term “striatonigral-cerebellar-autonomic degeneration”! An additional problem in clinical assessment of these patients is that it can be well nigh impossible to state whether a patient with severe Parkinsonism incorporating marked dysarthria and postural instability has cerebellar signs, and vice-versa. Moreover, the increase in tendon jerks in a rigid limb and the occasional presence of a “striatal toe” or “dystonic foot response” makes it difficult to recognise pyramidal signs in extrapyramidal disease.

One of the particular features of multiple system atrophy is that it sits astride a number of disciplines and sub-specialities. Part of the difficulty experienced by many physicians in conceptually getting to grips with the condition stems from precisely this characteristic. For me, the analogy of the blindfolded men examining different parts of an elephant and coming away with different impressions of the nature of the beast is an excellent one. Much of what has been written about MSA has been written by doctors with a special interest in the autonomic nervous system, for obvious reasons since the disease offers such an excellent model for its understanding. However, prominent autonomic symptoms may be absent in very many patients early in the disease, and indeed throughout its course in some subjects. My own perspective of MSA, viewing from a Parkinson's disease clinic, is of an irregular lumpy iceberg. Above the surface is one mini-iceberg of pure autonomic failure, and another of OPCA. Beneath the waves lie the bulk of MSA cases, these “striatonigral” variants who, unrecognised, swell the ranks of Parkinson's disease clinics, participating in drug trials and transplantation programmes. The gradual recognition of their existence owes itself to three factors. Firstly, exposure to many Parkinsonian patients makes it easier to recognise what is typical and hence what is atypical. Secondly, the pathological proof in those cases clinically recognised as MSA who have had a post-mortem examination helps to confirm and hence validate clinical diagnostic criteria. And thirdly the

picture emerging from large post-mortem series of Parkinsonian brains is that cases of MSA are more common than previously thought, and also frequently mis-diagnosed in life.

Before examining larger and more recent series, it is salutary to consider a paper from Tygstrup and Nørholm¹⁶ in 1963, prior to the introduction of levodopa. They reported the necropsy results in 12 patients from a larger series who had died from 1 week to 4 years after a stereotactic operation for Parkinsonism. All showed degeneration of substantia nigra. However, only five had Lewy bodies: two of the remaining seven had multiple system atrophy. Takei and Mirra¹³ found MSA in 7.9% of 89 brains of patients with Parkinsonism. This led them to feel “that striatonigral degeneration is not an extremely rare disease, but that this group constitutes a significant proportion of Parkinsonian cases.” Duvoisin, largely on clinical grounds, estimated that in his own consulting practice OPCA accounts for 5 to 6% of all Parkinsonism.¹⁷ In my own experience in the King's College Hospital Parkinson's disease clinic, almost every study on Parkinson's disease has included patients who later turned out to have clinical or pathologically proven MSA. The difficulty in diagnosis is greatest in untreated patients: four of 20 (20%) patients in a neuropsychological study of *de novo* patients with Parkinson's disease¹⁸ turned out to have pathologically proven ($n = 1$) or clinical ($n = 3$) MSA. Jellinger (personal communication) found it in 11% of 110 brains in his 1957–70, 3.6% of 490 brains in his 1971–87, and 5.1% of 600 brains in his total 1957–87 series of brains from patients with Parkinsonism dying in three hospitals in and around Vienna. In the United Kingdom, the Parkinson's Disease Society established a Brain Bank in 1984. Patients volunteer for the register, and are assessed at yearly intervals by a consultant neurologist with a special interest in Parkinson's disease. Disregarding those cases especially sent to the Brain Bank by neurologists because of atypical disease, 11% of the first 83 brains received had MSA, and a further 7% did not have IPD. It is possible that this figure for MSA is an over-estimate of the prevalence of the condition, since clearly in the first years of operation of a brain bank more registered individuals with MSA than with IPD will die because of differing prognosis. It should, however, reflect the incidence of the disease. MSA is therefore not a rare disease. If, say, 10% of the Parkinsonian population of the UK were affected, this would make prevalence 16.4 per 100,000, that is, more than twice that of Huntington's disease.

An idea of the age of onset and prognosis can be obtained from tables in the large reviews of pathologically proven MSA of Oppenheimer¹⁹ ($n = 41$, in a chapter on the neuropathology of progressive auto-

nomic failure) and of Gosset *et al*²⁰ ($n = 35$, in an article on SND and OPCA, reproduced in Adams and Salam-Adams' chapter in the Handbook of Clinical Neurology on SND¹⁵). Between them, these tables document 59 different cases of pathologically proven MSA with age of onset in 58 and disease duration in 57. Median age of disease onset was 53 years (range 36 to 74), with 62% starting between 45 and 59 years, and 90% between 40 and 64 years. Older patients with Parkinsonism and autonomic failure are thus more likely to have Lewy body disease. Median disease duration to death was 5 years (range 1 to 11), and 88% were dead within 7 years of disease onset. Some authors have stressed a male preponderance of cases. Thus, in considering 41 cases of "autonomic failure with MSA", Oppenheimer found 26 males and 15 females. However, Gosset *et al*, considering 35 cases of "SND and OPCA" found 14 males, 20 females and one sex unknown. Taken together, these series document MSA in 58 cases of known sex. Males were affected in 31 cases, females in 27. It is possible that because impotence and urinary symptoms tend to be noted more in males than anorgasmia and urinary disturbance in (especially parous) females, an artificially high rate of autonomic disturbance may be recorded among the former. However, MSA seems to affect the sexes equally.

Nosology and diagnostic criteria

It can reasonably be asserted that Shy and Drager were responsible for first placing the combination of autonomic failure, neurological signs and the associated CNS pathology firmly on the neurological map. However, confusion reigns over how the term Shy-Drager syndrome should be used. The two patients they described had clinical features incompatible with idiopathic Parkinson's disease (IPD). The term cannot therefore be used as a form of shorthand to refer simply to Parkinsonism with autonomic failure (which can be due either to Lewy body disease or MSA), though many physicians use it that way. Also, should the autonomic failure always precede the neurological features? This uncertainty is exemplified by Chokroverty,²¹ who wrote: "Although there are occasional reports of patients with Shy-Drager syndrome presenting initially with somatic neurological manifestations before dysautonomic symptoms, it is difficult to decide whether these patients do in fact have the Shy-Drager syndrome". Moreover, one of his previously published cases (case 1 in an article in *Brain*²² entitled "The syndrome of primary orthostatic hypotension") developed somatic neurological features 3½ years after the onset of pure dysautonomia and, at necropsy, had classic pathological findings of "the Shy-Drager syndrome".¹⁹ Does Shy-Drager syndrome refer only to the full clinical syndrome they

described (which I have never seen), or to the pathology which revealed atrophy of multiple systems? My own view is that, whilst acknowledging their major contribution in recognising the somatic neurological features associated with some cases of autonomic failure and in describing the underlying pathology, we should cease to use the term Shy-Drager syndrome since its meaning has become so imprecise. If the term is to be retained at all, then I think it should refer to the clinical picture of Parkinsonism with autonomic failure *plus* features incompatible with IPD, viz lack of response to levodopa, or the presence of pyramidal or cerebellar signs.

Progressive autonomic failure (PAF) is a term that gradually supplanted idiopathic orthostatic hypotension. More recently, terminology has again changed, so that PAF now stands for pure autonomic failure.²³

But how is autonomic failure defined? All physicians recognise "barn-door" autonomic failure when confronted with it, but where does mild autonomic dysfunction (as seen in many patients with Parkinson's disease and also some normal subject) end and autonomic failure begin? The autonomic research community have not yet agreed universal criteria for a diagnosis of autonomic failure.²¹ There are certainly a number of tests of autonomic function which have been validated in control populations, and for which it is possible to state that an individual lies outside the normal range, or one or two standard deviations from the mean. But how many of these single tests need to be how abnormal before autonomic failure is diagnosed, and how can the diagnosis be made in less severe cases without recourse to an autonomic function laboratory? McLeod and Tuck²⁴ require abnormal results in two or more of the following tests: the response of blood pressure to change in posture and isometric contraction, heart rate response to standing, variation in heart rate with respiration, Valsalva ratio, sweat tests and plasma noradrenaline measurements. Moreover, none of the usual tests of autonomic function can distinguish between autonomic failure as part of MSA and as part of Lewy body disease, although dynamic tests of circulating noradrenaline concentrations may help (see below).

Even the definition of orthostatic hypotension varies greatly from one group to another (table 1).²⁵⁻³² Beyond the question of what numerical drop in systolic/diastolic/mean blood pressure on assuming the erect posture is significant, other confounding factors abound. How long should the subject be supine before standing? Should the patient's blood pressure be recorded after active standing (some MSA patients may be unable to do this because of their motor disability) or using a tilt-table (the latter will give a different pulse and blood pressure profile),³³ and for how long? Should Korotkow phase IV or V be used?

Table 1 Some definitions of orthostatic hypotension

Schatz <i>et al</i> , 1963 ²⁵ : The simultaneous occurrence of dizziness and syncope with a decline in standing blood pressure of 30/20 mm Hg.
Thomas & Schirger, 1963 ²⁶ : The simultaneous occurrence of giddiness, syncope or both, in association with a persistent drop of at least 50 mm Hg in systolic and a corresponding drop in diastolic pressure upon standing.
Johnson <i>et al</i> , 1965 ²⁷ : A fall in systolic pressure of more than 20 mm Hg.
Nick <i>et al</i> , 1967 ²⁸ : An orthostatic drop of > 40 mm Hg systolic and > 30 mm Hg diastolic.
Thomas & Schirger, 1970 ²⁹ : A minimal orthostatic drop of 25 mm Hg in diastolic blood pressure from supine to standing position on at least one of many blood pressure readings.
Thomas <i>et al</i> , 1981 ³⁰ : A consistent and persistent fall of 30 mm Hg or more in systolic and 15 mm Hg or more in diastolic pressure, accompanied by clinical symptoms.
Cohen <i>et al</i> , 1987 ³¹ : The presence of orthostatic syncope or presyncope and sphygmomanometric confirmation (orthostatic reduction in systolic BP by > 30 mm Hg, or mean arterial pressure by > 20 mm Hg).
Bannister & Mathias, 1988 ³² : When a fall of more than 20 mm Hg systolic pressure on standing is found in a patient with symptoms, further investigation is justified.

Should symptoms be produced? Does failure to record an abnormal drop on one occasion mean the patient does *not* have orthostatic hypotension? Does a single recording of abnormal postural drop mean the subject *has* orthostatic hypotension? What importance should one attach to post-prandial orthostatic hypotension, or when the patient is being treated with levodopa or a dopamine agonist?

Quite apart from these uncertainties about the diagnosis of autonomic failure, the diagnosis of MSA also rests on shifting sands. The most recent criteria used at the Mayo Clinic³¹ require: "The presence of autonomic failure (see table 1). When striatonigral or olivopontocerebellar involvement was confirmed on neurological examination, the diagnosis of MSA was made". Unless levodopa unresponsiveness is specified these criteria could potentially include as MSA patients with Lewy body Parkinson's disease with autonomic failure!

The term "Parkinson plus syndrome" has recently enjoyed favour among neurologists attempting to separate out cases with atypical Parkinsonism whose features are incompatible with the idiopathic disease. Whilst this expression is useful, particularly in avoiding definitive alternative diagnosis where none can be made with certainty, it neglects the single most suspicious feature, viz the lack of response to levodopa. Perhaps "Parkinson minus syndrome" would be just as clinically useful. Thus, a dramatic clinical motor response to treatment with levodopa at an adequate dose for an adequate period of time is for practical purposes always seen in patients with pathologically proven uncomplicated Lewy body Parkinson's disease.³⁴ A poor or absent response is the rule in MSA patients, although transient significant benefit has occasionally been reported.³⁵ In the absence of clear pyramidal or cerebellar signs, this difference constitutes a major clinical tool for differentiating between IPD and MSA. It therefore seems appropriate that it should be included among diagnostic criteria for MSA with Parkinsonian features. One drawback, however, concerns patients who cannot tolerate an adequate trial of levodopa (with peripheral

decarboxylase inhibitor) because of faintness or sickness. Nevertheless, whilst some such patients seem to have IPD, a higher proportion of pathologically proven MSA subjects have manifested such intolerance to levodopa preparations. Curiously, some of these are able to tolerate bromocriptine (with domperidone), but usually without dramatic resultant clinical benefit.

Although a few patients may display inappropriate laughter or crying, numerous clinical accounts of pathologically confirmed MSA have called attention to the striking preservation of intellect in the face of severe motor disability. Dementia seems therefore not to be an integral feature of MSA. Coincidental Alzheimer's disease can certainly occur in MSA patients,³⁶⁻³⁸ but at a rate no higher than among the general age-matched population. In addition, a number of cases showing Parkinsonism, dementia and autonomic dysfunction, with poor or absent response to levodopa, in life have been shown at post-mortem to be suffering from "cortical" or "diffuse" Lewy body disease.³⁹ For practical purposes, dementia rules out uncomplicated MSA.

Lewy bodies have been found restricted largely to pigmented brainstem nuclei in some patients also showing the striatal pathology of MSA.⁴⁰⁻⁴⁸ We now appreciate that incidental Lewy bodies, with some degree of cell loss, may be seen in the brains of many individuals who did not manifest clinical Parkinsonism during life.⁴⁹ It does not now seem necessary to propose that cases showing MSA and Lewy bodies have a "transitional variant" of the disease,⁴⁸ merely that this is a chance superimposition of a common pathological finding. However, the finding of incidental Lewy bodies does raise the possibility of an erroneous pathological diagnosis of IPD if the striatum is not also examined. IPD must have Lewy bodies in substantia nigra, but the presence of Lewy bodies and cell loss in substantia nigra is not synonymous with clinical IPD, and hence does not exclude MSA.

The question of inheritance of MSA is best approached through those cases presenting with Parkin-

sonism and autonomic failure. There has been only a handful of cases with pathologically proven MSA where one other family member is affected by Parkinsonism.^{12 13 40} a rate corresponding to the chance occurrence of IPD. The family reported by Lewis in 1964³⁰ is always cited as evidence that MSA can be inherited, but there was no pathology and the clinical features were atypical. Thus, the four cases examined had had the disease for 7, 34 and 19 years, and 6 months respectively. The clinical features included orthostatic hypotension, cerebellar, pyramidal and extrapyramidal signs, but there was also amyotrophy, fasciculation, footdrop and pes cavus. Given this unusual clinical picture and given that no pathologically proven cases of truly familial typical MSA have been recorded, it seems likely that this family did not have MSA. Could they perhaps have had the adult-onset familial leukodystrophy with autonomic failure described by Eldridge *et al*?⁵¹ The other celebrated instance of inherited so-called striato-nigral degeneration is the Joseph family.⁵² In this large dominant pedigree, disease onset usually occurs in the twenties or thirties, and the clinical features vary considerably. Spasticity, ophthalmoplegia, peripheral neuropathy and cerebellar signs frequently occur, with only mild extrapyramidal signs and without prominent autonomic failure. The pathology shows invariant symmetrical degeneration of the cerebellum and thoracic cord, variable degeneration of the basis pontis, oculomotor nuclei, peripheral nerves, nigra, striatum, but the inferior olives are always spared. MSA of SND predominance seems therefore to be a sporadic disease.

When one turns to OPCA, the genetic picture is more complex. Among adult-onset cases of OPCA, rather less than half seem to be inherited, as a dominant trait; the remainder have apparently arisen sporadically. Neither clinical features alone nor pathology may suffice to differentiate between the inherited and the sporadic form in an individual case, although group differences exist. Thus, in Berciano's 1982 review⁵³ of 117 cases of pathologically confirmed OPCA, 39% of 54 familial cases showed Parkinsonism (55% of 63 sporadic cases), 50% pyramidal signs (46%), 96% cerebellar signs (87%) and 39% sphincter disturbance (48%). Pathologically, in addition to involvement of olives, pons and cerebellum, striatum was affected in 22% of familial cases (38% of sporadic) and substantia nigra in 46% (48%). Thus, neither Parkinsonian features nor sphincter disturbance, and neither striatal nor nigral pathology, clearly differentiates between familial and sporadic cases of OPCA. However, mean age of onset in hereditary cases is earlier than in sporadic cases (28 years versus 49 years in the clinicopathological study of Berciano⁵³; 39 years versus 49 years in the clinical

study of Harding⁵⁴). Moreover, mean disease duration to death in familial cases was 14.9 years, and in sporadic cases was 6.3 years.⁵³ In the clinical study of Harding⁵⁴ on 36 living sporadic cases of late onset cerebellar ataxia, mean duration of symptoms was 12.5 years. Only three (8%) patients had impassive facies, but no other extrapyramidal features. Nine patients (25%) had urinary symptoms. This series clearly differs from what we recognise as MSA, partly because only cerebellar ataxia was needed for inclusion, and perhaps partly because, in an effort to exclude cases with paraneoplastic cerebellar degeneration, patients with a subacute course or a disease duration of less than two years were excluded. Ophthalmoplegia was more frequent, and pigmentary retinal degeneration and optic atrophy only found, in familial cases.⁵⁴ Since the predominantly striatonigral variant of MSA is sporadic, it seems appropriate to include in the rubric of MSA only sporadic cases of OPCA (although this restriction would be at variance with the wider usage of the term by Oppenheimer himself to include familial OPCA). Moreover, to be considered as clinically probable cases of MSA, they should also display either Parkinsonian features or autonomic failure, or both.

Neuropathological examination of the brain and spinal cord cannot at present distinguish between many cases of familial OPCA and sporadic cases of MSA, although the value of intermediolateral column cell counts in this respect has not been fully assessed. Should this deter one from separating such cases? I think not. A myocardial infarct due to coronary atherosclerosis may look the same in someone with familial hypercholesterolaemia as in a heavy eater and smoker, yet the ultimate cause is different: on the one hand genetic, on the other acquired. It should not surprise us that a similar or even an identical pathological picture should develop via a common mechanism triggered by different root causes, one genetic and one perhaps acquired.

A number of MSA subjects may display abnormal eye movements. Most commonly, this consists of impaired or absent convergence, hypometric voluntary saccades and/or saccadic pursuit, and sometimes a supranuclear gaze palsy for up (and rarely down) gaze.⁵⁵ Indeed, MSA is one of a number of causes of the clinical picture of progressive supranuclear palsy, which is often erroneously taken to be synonymous with Steele-Richardson-Olszewski disease. Thus, a number of cases of MSA would fulfil the clinical diagnostic criteria for Steele-Richardson disease proposed by both Golbe *et al*⁵⁶ and Lees.⁵⁷ Because of the potential for confusion between the two diseases, I would propose that a predominant downgaze paresis should constitute an exclusion criterion for the clinical diagnosis of MSA.

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Table 2 Multiple system atrophy: proposed diagnostic criteria

SND type (predominant parkinsonism)		OPCA type (predominantly cerebellar)
Sporadic adult-onset non/poorly levodopa responsive parkinsonism*	Possible	—
Above, plus severe symptomatic autonomic failure† + /or cerebellar signs + /or pyramidal signs	Probable	Sporadic adult-onset cerebellar ± pyramidal syndrome* with severe symptomatic autonomic failure† + /or parkinsonism
p/m confirmed	Definite	p/m confirmed

*Without DSM III dementia, predominant downgaze PSNP or other identifiable cause.

†Postural syncope or presyncope and/or marked urinary incontinence or retention not due to other causes.

Sporadic: one other case of typical clinical IPD among 1st or 2nd degree relatives allowable.

Adult onset: onset age 30 years or above.

On the basis of the above considerations, and following the proposals of groups formulating diagnostic criteria for multiple sclerosis⁵⁶ and for Alzheimer's disease,⁵⁷ I propose the diagnostic classification set out in table 2. Undoubtedly this will need further modification in the future, particularly in regard to the definition of autonomic failure, and also in the light of pathological verification of cases fulfilling these diagnostic criteria. Moreover, this clinical diagnostic schema mirrors the drawbacks considered above, in that it fails to exclude cases of Steele-Richardson disease not yet displaying a predominant downgaze paresis.

"Red flags" (table 3)

Besides the poor response to levodopa, and the additional presence of pyramidal or cerebellar signs or autonomic failure as major diagnostic criteria, certain other clinical features may either raise a suspicion of MSA, or at least suggest that one might not be dealing with IPD.

Symmetrical onset and absence of a classical resting tremor have often been proposed as features distinguishing MSA from IPD. However, marked and persistent asymmetry and the presence of a classical resting tremor may both be seen in cases of pathologically proven MSA. Early instability and falls suggest a cause other than IPD. A consequence of this is that among patients whose Parkinsonism is revealed by, and persists after, treatment with neuroleptic agents (eg prochlorperazine) given to combat vague feelings of unsteadiness, those with alternative causes

Table 3 "Red flags": clinical features raising doubts about a diagnosis of ideopathic Parkinson's disease

Early instability and falls	?Absent/atypical levodopa AIMs
Rapid progression	?Disproportionate antecollis
Irregular jerky tremor	?PH of hypertension
Myoclonus	?Contractures
Poor or absent response to an adequate trial of levodopa	?Raynaud's or ergotism
Autonomic failure	
Abnormal eye movements beyond IPD range	
Severe dysarthria/dysphonia	*Peripheral neuropathy
Pain unrelieved by levodopa	*Pyramidal signs
Severe levodopa intolerance	*Cerebellar signs
	†DSM III dementia

*Never part of IPD.

†Uncommon in both IPD and MSA.

of Parkinsonism may be over-represented.

Rapid clinical deterioration despite dopaminergic treatment is also highly suspicious. Indeed, many physicians recognise this, and only consider MSA in Parkinsonian patients with cerebellar features or pyramidal signs together with profound autonomic failure who deteriorate towards death within 5 or 6 years. Yet a number of cases of MSA survive 10 years or longer after the onset of clinical symptoms or signs, and may never develop cerebellar or pyramidal signs. Failure to recognise this leads to a self-fulfilling prophecy whereby MSA cases with longer disease progression are not diagnosed as such in life. Similarly, failure to recognise the unusual nature of the case makes a post-mortem examination less likely to be sought.

Dating the onset of the disease is also problematical. Should one take the first sign of relatively non-specific impotence or sphincter disturbance, or date disease onset only from the onset of symptomatic postural hypotension or of the first motor symptoms and signs? Indeed, do any of these features in fact correspond to the actual onset of the disease process? There is now evidence to suggest that the onset of IPD may considerably antedate the first clinical signs, perhaps by 20 years or even more. Given the redundancy margin of central neuronal populations, it seems probable that in MSA, too, disease onset may long antedate clinical features. In this respect, it is of interest to examine the past history and previous records of cases of clinical MSA. A number have had arterial hypertension diagnosed, and sometimes treated, several years before the first symptoms, only to later become normo- or hypotensive. Could this relate to early denervation hypersensitivity causing supine hypertension? It is tempting also to speculate on the significance of Raynaud's phenomenon occurring before, or during, treatment with dopaminergic

drugs. I vividly recall a patient with apparent untreated IPD who, on pergolide monotherapy, developed severe vasospasm of all fingers of both hands. His Parkinsonism did not improve and he went on to die of pathologically proven MSA. Was the Raynaud's a manifestation of an ergot drug acting on an already abnormal autonomic nervous system? Another man had attended 27 years earlier with a complaint of dizziness of unknown cause, which subsequently settled. Could this have been, in retrospect, the first sign of his illness?

Myoclonic jerks, usually affecting the fingers, of small amplitude, and often stretch-sensitive, occur in a number of patients with MSA, but are otherwise rare in non-demented Parkinsonians. An irregular, jerky tremor of the hands is also a feature more commonly seen in MSA than IPD.

Bizarre contractures of the hands may be more common in non-idiopathic Parkinsonism. Well recognised in post-encephalitic cases, and in Parkinsonism-dementia, they can also occur in MSA.^{36 38 38} A more frequent and characteristic feature suggesting MSA is the development of a relatively fixed, disproportionate antecollis^{38 39} hampering feeding, communication and vision.

Speech is almost always more severely affected in MSA than in IPD. As well as the low volume monotony of Parkinsonism, a quivering, irregular, severely hypophonic or slurring dysarthria is "often so characteristic that the diagnosis can be suggested by listening to the patient on the telephone".⁵⁹ Respiratory stridor, especially at night, is also a helpful diagnostic pointer, since vocal cord paralysis commonly occurs.⁶⁰

Marked focal muscular atrophy and fasciculations, whilst reported in some cases with MSA,⁷ are in my experience most unusual.

Pain, characteristically in, or maximal in, the most severely affected limbs, is not uncommon in IPD. In such cases, it is usually dramatically improved or abolished when levodopa turns the patient "on".⁶¹ Some cases of MSA may experience similar deep aching limb pains⁵⁹ which, in contrast, persist throughout the day and are not relieved by levodopa.

In a patient with Parkinsonism, the significance of the presence and degree of autonomic symptomatology may be very difficult to assess. I recently asked 34 patients (23 male, 11 female, mean age 49.6, SD 8.9 years, mean disease duration 11, SD 4.9 years) to complete an autonomic questionnaire. All had been diagnosed as suffering from Parkinson's disease, and were attending a weekend meeting for younger sufferers organised by the Parkinson's Disease Society. The group could certainly have included one or more cases of MSA, but overall I had no reason to doubt the diagnosis of IPD. Nocturia at least once

nightly was experienced by 85%, daytime frequency of six times or more by 74%, and 71% had been "caught short" with a dribble at least occasionally. Twenty five per cent said their hands and feet were bone dry in hot or humid conditions, 15% experienced increasing faintness between the onset of Parkinson's disease and dopaminergic treatment, and 37.5% subsequent to treatment (corresponding figures for postural black-outs were 6% and 9% respectively). Normal erections were achieved only occasionally or never by 23% of males, with occasional erectile problems in as many as 73%. Our judgement of the diagnostic significance of autonomic symptoms in Parkinsonism as a pointer to autonomic failure must be weighed against these rates, and also those for an age-matched control population (work in progress).

Investigations

Autonomic function tests can demonstrate various aspects of autonomic failure, but not its cause. However, resting supine plasma noradrenaline (NA) levels, and their response to standing, may help to differentiate between groups of subjects with MSA and those with pure autonomic failure (which most commonly shows Lewy body pathology¹⁰). Thus, MSA patients usually have normal or slightly elevated plasma NA levels, whereas those with PAF usually have low plasma NA levels.⁶² In contrast to normal subjects, neither group increases the plasma NA level on standing.⁶² However, the clinical usefulness of plasma NA levels as a diagnostic tool in individual cases has not been demonstrated.⁶²

Computed tomographic (CT) scanning appears to be of only limited usefulness in the diagnosis of MSA. In subjects with a predominantly cerebellar presentation, cerebellar and/or brainstem atrophy may be seen, but since this is also seen in many familial cases of adult onset cerebellar atrophy this finding may not help in differential diagnosis. Among cases presenting a predominantly, or a pure, Parkinsonian syndrome the CT scan is usually normal. In only a minority of cases will the scan demonstrate clear atrophy of posterior fossa structures. Striatal CT images are normal in all forms of MSA.

Magnetic resonance imaging, however, may well prove useful in demonstrating striatal pathology in MSA, and its absence in IPD. Early studies using 1.5 tesla T₂ weighted images suggested that cases of "Parkinson's disease" with rapid progression and poor response to treatment showed altered signal particularly in putamen, and it was proposed this might be due to abnormal deposition of iron in this structure. The debate over iron content of the putamenal pigments⁶³ and its relationship to the MRI images continues unresolved at present. However, whatever the ultimate cause of the altered signal, it is

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beginning to look as if MRI scanning can detect the putaminal pathology so characteristic of striatonigral cases of MSA, thus differentiating them from IPD.⁶⁴⁻⁶⁶

Positron emission tomography (PET) scans of MSA patients have so far been few in number. It comes as no surprise that ¹⁸F-fluorodopa scans show low concentration of activity in striatum, as in IPD.⁶⁷ The most modern scanners with sufficient resolution also demonstrate a lower caudate uptake in MSA subjects in contrast to relatively preserved caudate uptake in IPD.⁶⁶ However, it is likely that measures of post-synaptic function will prove more useful in differentiating between MSA and IPD, so that the results of ¹¹C-raclopride studies are awaited with interest. If these scans can demonstrate clear and unequivocal differences, and if a dopamine receptor ligand can be developed for SPET studies, then SPET scanning may emerge as a useful diagnostic tool.

Electrophysiological investigations have been applied to a number of patients with clinical MSA. Nerve conduction studies may sometimes reveal a subclinical polyneuropathy,³¹ and EMG studies may suggest neurogenic atrophy in some individuals.⁷ Thermal threshold, visual and somatosensory evoked responses, and electrical and magnetic central motor conduction times have not yet been adequately explored. The EEG is not useful. One group has demonstrated an abnormal latency and an abnormality of the amplitude ratio of waves V/I of the brainstem auditory evoked responses (BSAEPs) in 11 and 13 patients out of 14 respectively with a clinical diagnosis of MSA.⁶⁸ However, our own unpublished investigations showing normal BSAEPs in a number of, mostly less severely affected, subjects (including one with pathologically proven MSA) lead us to doubt the specificity of this abnormality in patients earlier in the course of the disease.

One particular electrophysiological investigation appears to be extremely useful in supporting a clinical diagnosis of MSA. In an initial study in 14 patients with clinical MSA (Parkinsonism, autonomic failure and pyramidal signs in all 14, additional cerebellar signs in two), individual motor units recorded from the striated component of the urethral sphincter were consistently abnormal, showing polyphasia and long duration.⁶⁹ Subsequent studies in a further 26 subjects with probable, 15 with possible MSA, and 13 with probable IPD, have shown that this investigation has high specificity (0.92) but less sensitivity (0.62) in differentiating between probable MSA and probable IPD.⁷⁰ Moreover, one probable MSA subject with abnormal results has since died, with pathological confirmation of the diagnosis.

It is therefore apparent that no single clinical feature or investigational abnormality is diagnostic of MSA. Rather, the complete clinical picture together with the

results of a number of investigations must be taken into account in making the diagnosis. For the time being, only clinical criteria have been advanced in table 2. However, when more clinicopathological correlation has permitted validation of diagnostic tests, used singly or, more likely, in concert, we may arrive at a schema similar to that for multiple sclerosis, where categories of laboratory supported diagnosis⁵⁶ have appeared.

Treatment

Sadly, the treatment of MSA is most disappointing. Levodopa preparations may transiently give useful improvement, but often either cause no improvement, or give rise to intolerable nausea and vomiting and/or symptomatic postural hypotension.³⁵ However, it should be realised that some patients who seem not to be responding to levodopa can still deteriorate significantly when the drug is withdrawn. Head-up tilt of the bed at night, elastic support stockings, fluorocortisone and/or indomethacin, caffeine, DDAVP or atrial pacing may help cardiovascular problems.^{24,71} Anticholinergics can reduce urinary frequency (but may precipitate retention). Retention with overflow, or incomplete bladder emptying with infections, can be managed with intermittent self-catheterisation (if hand mobility permits) or indwelling suprapubic or urethral catheterisation. High fibre diet, bulk laxatives, suppositories or enemas may be needed for constipation. Tracheostomy for intermittent respiratory stridor (especially at night) must be considered with the utmost care. It may only cruelly prolong a precarious existence before inevitable death. Similarly, cricopharyngeal myotomy or gastrostomy in patients with severe dysphagia is seldom, if ever, indicated. The paramedical specialities of physiotherapy, occupational therapy, speech therapy (often directed at swallowing problems and communication aids rather than improving speech per se) and social work often are of much more practical use than anything the physician can offer. With their grave prognosis and their lack of response to levodopa, these patients are, to my mind, more in need of a breakthrough in neuronal implant treatment than those with idiopathic Parkinson's disease. If embryonic nigral implants can be shown to work in IPD, then logically the next patient groups to be offered (this time striatal) implant treatment should be those with MSA.

We desperately need better diagnosis of MSA if we are to seek the cause, and hence a preventive or retardant treatment, for this terrible affliction. In the meantime, we need to draw on all our skills and compassion to help and comfort those who are struck by this disease.

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