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Multiple system atrophy presenting as parkinsonism: clinical features and diagnostic criteria

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Abstract

To evaluate the possibility that parkinsonian signs may be the only presenting feature of multiple system atrophy (MSA), parkinsonian patients were studied who had no atypical clinical signs and had no symptoms of autonomic dysfunction, but who reported that they had not experienced the anticipated good response to dopaminergic treatment. These stringent criteria identified 20 patients from a series of 298 consecutive parkinsonian outpatients. The following clinical pointers were analysed: (*a*) rate of disease progression; (*b*) symmetry of parkinsonian symptoms and signs; (*c*) occurrence of resting tremor during the first three years from onset. In addition, all patients underwent (*d*) acute and chronic challenge with dopaminergic drugs; (*e*) cardiovascular reflex autonomic function tests; (*f*) high field MRI.

Rapid progression of disease was seen in 45% of patients, onset was symmetric in 25%, tremor was absent at onset in 70%, response to dopaminergic drug challenges was inadequate in 40%, abnormal cardiovascular reflexes occurred in 50%, and some abnormal MRI finding occurred in 35% of cases. Each of these features was equally weighted by giving to each patient a 0 to 6 point score corresponding to the number of abnormal findings. Fifteen patients scoring higher than 1 were considered at risk for having MSA: five of them were classified as clinically possible (score 2), six as clinically probable (score 3–4), and four patients were classified as clinically definite multiple system atrophy (score 5). The six pointers considered were variably combined in each patient, none of them being universally abnormal in patients with high scores.

The patients were followed up for a mean 2·1 (SEM 0·65) years. All but one of the 10 patients prospectively classified as probable or definite MSA developed unequivocal clinical signs of fully symptomatic MSA. A receiver operator characteristic curve was plotted for the prospective score, based on follow up diagnosis. The best compromise for trade off between sensitivity and specificity was a cut off value at a score of 3.

The sensitivity and specificity of the individual pointers considered to predict fully symptomatic MSA varied considerably, and no single item could predict whether patients presenting with just parkinsonian signs went on during the two year follow up period to develop fully symptomatic MSA. Instead, the number of abnormalities offered a predictive value for the clinical prognosis of these parkinsonian patients.

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Multiple system atrophy (MSA) is a sporadic neurodegenerative disease resulting in assorted combinations of parkinsonian, cerebellar, pyramidal, and autonomic features. It is currently accepted that MSA is a clinicopathological entity that encompasses degeneration of the intermediolateral cell columns of the spinal cord, striatonigral degeneration, and olivopontocerebellar atrophy.[1] Characteristic glial and neuronal cytoplasmic inclusions have been found in MSA[2] but, unlike Parkinson's disease, Lewy bodies are not usually present.[3 4]

The disease may variably present with a parkinsonian syndrome, a cerebellar syndrome, progressive autonomic failure, or with a combination of these features. The clinical picture then commonly develops into one of involvement of multiple systems. As there is no diagnostic test for MSA, only a minority of patients are diagnosed before reaching the full blown stage. Based on the consideration that a definite diagnosis can be achieved only with postmortem pathological confirmation, Quinn[1] proposed clinical criteria to classify patients with suspected MSA as possible or probable. MSA of striatonigral degeneration predominance is probable when sporadic adult onset partly levodopa responsive parkinsonism without dementia or down gaze palsy occurs in association with cerebellar ataxia or severe symptomatic autonomic failure. An early clinical diagnosis of MSA is particularly difficult when parkinsonian signs occur in isolation.[5 6] Patients with MSA with a pure parkinsonian presentation (MSA-P) may have features such as poor response to levodopa,[7] rapid disease progression,[8] or focal reflex myoclonus.[9] The occurrence of such atypical features is not specific to MSA-P, however, as they may also be found in other atypical parkinsonian (parkinson-plus) syndromes, the

most common of which is Steele-Richardson-Olszewski disease (progressive supranuclear palsy).

In a retrospective study, we recently compared the incidence of some atypical parkinsonian features and of CT abnormalities in patients with pathologically established MSA presenting only with parkinsonian signs and in patients with Parkinson's disease and progressive supranuclear palsy.[8] Symmetric onset, absence of tremor, lack of response to levodopa, rapid clinical progression, and abnormal autonomic tests occurred more often in MSA than in Parkinson's disease. None of these pointers was specific for MSA, but the total number of abnormal features occurred more often in MSA than in Parkinson's disease. In the present study, we attempted to verify whether the same criteria, combined with abnormal MRI morphometry, may be used as prospective pointers to a clinical diagnosis of MSA. In this prospective study, as well as in the earlier retrospective evaluation, we focused on patients in the early stage of their disease who have only isolated parkinsonism. We also give a preliminary verification of the predictive value of these abnormalities, based on the evaluation of the patients over a subsequent two year follow up.

Patients and methods

All the 298 consecutive parkinsonian outpatients seen at the movement disorder clinic during the period 1989 to 1992 were studied prospectively. Among these, we selected all the 20 who reported that they had not experienced the anticipated good response from standard dopaminergic treatment. Parkinsonian signs included resting tremor, akinesia, cogwheel rigidity, and impairment of postural reflexes on pull test: all patients had at least two of these clinical features in different combinations. They had neither cerebellar nor pyramidal signs, nor did they have symptoms of autonomic dysfunction (for example, orthostatic faintness, syncope, erectile dysfunction, etc). Mild autonomic signs that are common in Parkinson's disease (for example, changes in the skin or abnormal sweating) were accepted. Additional exclusion criteria were supranuclear down gaze palsy, dementia (as defined by DSM-IIIR[10]), exposure to neuroleptic drugs or to known neurotoxins, abnormal copper metabolism, parkinsonism in first or second degree relatives, and evidence of consanguinity.

CLINICAL AND LABORATORY DATA

As soon as selected for the study, each patient underwent the following clinical and laboratory evaluations.

Rate of disease progression

The patients were evaluated with the Hoehn and Yahr score in practically defined *off* after overnight withdrawal.[11] Those who had reached at least Hoehn and Yahr stage 3 within three years from onset of the disease were considered to have rapid progression.

Symmetric onset

Symmetric onset was considered to have occurred when the patients were unable to indicate clearly a side of onset for their parkinsonian symptoms and signs.

Resting tremor

The occurrence of resting tremor during the first three years after onset of disease was recorded. Disease onset was dated based on the first occurrence of a typical and unequivocal parkinsonian sign in one limb (for example, resting tremor, bradykinesia, loss of finger dexterity, rigidity).

Response to dopaminergic drugs

The variation of motor state from a baseline in the defined *off* condition was assessed objectively after giving single increasing subcutaneous doses of apomorphine (1·5, 3, and 4·5 mg) and of a single oral dose of levodopa and carbidopa (250/25 mg). Motor performance was measured just before and 15 minutes after each dose of apomorphine or just before and 60 minutes after the levodopa challenge. Each of these evaluations included unilateral hand tapping on two digital counters mounted 20 cm apart, the time taken to walk 20 m, and a clinical assessment by means of the motor score (part III) of the unified Parkinson's disease rating scale (UPDRS[12]). A patient was considered to respond to drugs when at least two of the following criteria were met in at least one evaluation: tapping improved by 15%, walking time improved by 25%, tremor score improved by two points, or total UPDRS motor score improved by 20%.[13] Each patient was also treated chronically with levodopa and carbidopa (750/75 mg daily) or with levodopa and benserazide (800/200 mg daily) for two months. The patients were evaluated before and after this treatment by means of the UPDRS motor score. Patients who improved by at least 20% after chronic treatment were also classified as responding to treatment.

Cardiovascular autonomic reflexes

Each patient underwent the following cardiovascular reflex tests under continuous electrocardiographic monitoring:

Blood pressure response to standing—After 15 minutes lying, patients were asked to stand up quickly; blood pressure was measured immediately, and every 30 seconds during the next two minutes.

Blood pressure response to sustained hand grip—An isometric contraction of the dominant hand (at 30% of its maximal strength) was performed for five minutes.

Heart rate response to standing—The subject is asked to lie quietly on a couch and then to stand up unaided as quickly as practicable. The characteristic heart rate response can be expressed by the 30:15 ratio, which is the ratio of the longest R-R interval around the 30th beat after standing up to the shortest R-R interval around the 50th beat.

Heart rate response to deep breathing—Patients were asked to breathe deeply for one

minute, at a frequency of six breaths per minute, while lying.

Valsalva ratio—Patients were asked to expire, after a deep inspiration, against a pressure of 40 mm Hg for 10 seconds, by blowing through a mouthpiece attached to a mercury manometer.

The criteria for evaluating these procedures have been already described in detail.[14] Antiparkinsonian drugs were withdrawn or reduced to the lowest dosage that allowed appropriate cooperation during the test. The global involvement of autonomic dysfunction was defined as early, definite, severe, or atypical, according to Ewing's criteria.[15] Sensitivity and specificity of each of the five items considered in autonomic cardiovascular testing were evaluated for patients with severe or definite autonomic dysfunction compared with those with normal responses or with early autonomic involvement. Sensitivity was defined as the ratio between the number of cases having a feature in the group affected by severe or definite dysfunction and the total number of cases in the same group. Specificity was defined as the ratio between the number of cases not having a feature in the group with normal function or with early dysfunction and the total number of cases in the same group.

Brain morphology

All patients underwent high field (1·5 Tesla) MRI. Both T1 and T2 weighted spin echo (SE) and inversion recovery pulse sequences were used. Axial, sagittal, and coronal sections (5 mm thick) of the entire brain were obtained in each examination. Axial SE images were obtained parallel to the intercommissural plane; coronal inversion recovery images were parallel to the floor of the fourth ventricle. T1 and T2 weighted pulse sequences were used, the second particularly to identify hypointensities in the basal ganglia. Data from MRI were considered consistent with MSA when they showed cerebellar or brain stem atrophy[16] or when the putamen was found to be hypointense on T2 weighted images, compared with the ipsilateral pallidum.[17 18] Morphometric measurements of the basal ganglia and of the pons were performed on axial SE images. Five variables were measured in each patient and compared with those collected from 18 age and sex matched controls with normal neurological examinations: (*a*) The largest sagittal diameter of the pons was measured in SE T1 sagittal sequences; (*b*) the maximal transverse diameter of the midbrain was measured in SE T2 axial sequences; (*c*) the distance between the substantia nigra pars reticulata and the red nucleus was measured in SE T2 axial sequences, giving an indirect measure of the pars compacta; (*d*) the maximal transverse diameter of the lentiform nucleus was measured in SE T2 axial sequences at the level of the anterior commissure; (*e*) the maximal transverse diameter of the head of the caudate nucleus was measured in SE T2 axial sequences at the level of the foramina of Monro. In (*c*), (*d*), and (*e*) average values of measures obtained from each side were used. Statistical analysis was by unpaired Student's t test; the significance level was taken as $P < 0{\cdot}05$.

CLINICAL SCORE AND FOLLOW UP

To assess the sensitivity and specificity of the clinical and laboratory pointers considered, each of them was given the same weight by allotting a 0 to six point score. Each patient received one point for each of: rapid progression of the disease; symmetric onset of symptoms; absence of tremor within three years from the onset of disease; poor or no response to dopaminergic drug challenges; definite or severe involvement of autonomic function; specifically abnormal MRI (table 1).

All patients were followed up until May 1994. Their diagnosis was periodically re-evaluated, based on the appearance of clinical signs of multiple system involvement. A diagnosis of MSA was made when patients met all the following criteria: (*a*) severe symptomatic autonomic failure with at least one postural syncope or pronounced urinary incontinence or retention not due to other causes; (*b*) progressive cerebellar ataxia or non-responsive (or poorly responsive) parkinsonism without evidence for a symptomatic origin of the disorder; (*c*) absence of parkinsonism in first and second degree relatives and no evidence of consanguinity; (*d*) absence of dementia according to DSM-IIIR criteria, generalised tendon areflexia, or predominant down gaze supranuclear palsy. The efficacy of chronic dopaminergic treatment was periodically evaluated by scoring the UPDRS at a standard time of the day, when patients were considered to be in an *on* condition, and comparing it with the UPDRS score in defined *off* condition.

The sensitivity and specificity of the prospective total score were analysed, based on follow up, by comparing the cases who had developed definite signs of multiple system involvement with those who had not. Sensitivity was defined as the ratio between the number of patients classified as MSA having a feature in the group and the total number of patients in the same group. Specificity was defined as the ratio between the number of patients not having a feature in the group considered not affected by MSA and the total number of patients in the same group.

Results

CLINICAL DATA

Patients selected for the study were 6·7% of the total population of 298 consecutive parkinsonian outpatients. They were aged 64·2 (SEM 2·3) (range 44–80) years, and had a mean disease duration of 4·25 (SEM 0·6) (range 1–10) years when they entered the study. Their mean Hoehn and Yahr stage (in defined *off* condition) was 2·95 (range 2–4). The remaining 278 patients were aged 65·5 (SEM 2·2) (range 27–88) years, they had a mean disease duration of 6 (SEM 0·8) years, and a mean Hoehn and Yahr stage of 2·25.

Table 1 Synopsis of normal and abnormal findings in 20 suspected cases of MSA. Scores of 0 or 1 indicate that a feature is absent or present respectively

Patient No	*Age/sex*	*Rapid progression*	*Symmetric onset*	*Absence of tremor*	*No response to treatment*	*Autonomic failure**	*MRI abnormalities†*	*MSA prospective score*	*Disease duration at prospective score (y)*	*Clinical MSA at follow up*	*Disease duration at follow up (y)*
1	60/F	0	0	1	0	0	0	1 No MSA	3	No	5
2	56/M	0	1	0	0	0	0	1 No MSA	5	No	7
3	53/M	0	0	0	0	0	0	0 No MSA	3	No	5
4	44/F	0	0	1	0	0	0	1 No MSA	5	Yes	7
5	69/M	1	0	0	1	0	0	2 Possible	3	No	5
6	66/F	1	0	1	0	1 S	0	3 Probable	4	Yes	8
7	53/M	1	0	0	0	0 E	0	1 No MSA	3	No	6
8	69/M	1	1	1	1	0 E	1 CA	5 Definite	4	Yes	6
9	48/F	1	0	1	0	1 S	1 CA	4 Probable	6	Yes	9
10	72/M	0	0	1	0	1 S	0	2 Possible	8	No	10
11	59/F	0	0	1	1	1 D	0	3 Probable	1	Yes	3
12	80/M	0	1	1	1	0 E	0	3 Probable	8	No	10
13	72/M	1	1	0	1	1 S	1 BSA	5 Definite	1	Yes	3
14	72/M	1	0	1	0	1 D	0	3 Probable	2	Yes	4
15	69/F	0	0	0	0	1 S	1 BSA	2 Possible	10	No	13
16	61/M	1	0	1	0	0 E	0	2 Possible	6	Yes	8
17	63/F	0	0	1	0	1 S	1 CA, BSA	3 Probable	5	Yes	6
18	66/M	1	0	1	1	1 S	1 CA, BSA	5 Definite	2	Yes	4
19	58/M	0	0	1	1	0	0	2 Possible	2	No	3
20	72/F	0	1	1	1	1 S	1 SI	5 Definite	3	Yes	4

*The score is in the left column; Ewing's criteria are in the right column: D = definite involvement; E = early involvement, S = severe involvement; †The score is in the left column; the following additional information is provided in the right column: BSA = brain stem atrophy; CA = cerebellar atrophy; SI = uneven signal appearance in the neostriatum.

INDIVIDUAL POINTERS

Most patients had abnormalities in the different pointers. Rapid disease progression was detected in nine patients (45%), symmetric presentation was seen in five (25%), tremor at onset was absent in 14 (70%), response to dopaminergic drugs was poor or absent in eight (40%), and autonomic dysfunction occurred in 10 (50%).

Dopaminergic challenge produced a clinical improvement in 11 patients and no response in the remaining nine. In patients who improved after the acute challenge, variations in motor scores recorded after apomorphine or levodopa/carbidopa were 28% and 23% respectively. Patient 7 had no improvement after the acute challenge, but had a 30% improvement after two months of treatment with levodopa and carbidopa. He was therefore considered as a responder to dopaminergic treatment.

Testing of autonomic function showed severe involvement in eight patients and definite involvement in two. Of the remaining 10, six had mild signs of autonomic dysfunction, comparable with those found in normal aging,[15] and four had normal autonomic function (table 1). The breakdown of individual items was as follows: heart rate response to deep breathing and to standing scored abnormal in 14 patients (70%) and nine patients (45%) respectively; the Valsalva ratio scored abnormal in eight patients (40%); blood pressure responses to standing and to sustained hand grip were abnormal in six patients (30%). Sensitivity and specificity were computed for each test. Heart rate response to deep breathing had a sensitivity of 100%; this value declined progressively when the heart rate response to standing (80%), the Valsalva ratio (70%), and blood pressure response to standing (60%) or to sustained hand grip (50%) were considered. Blood pressure response to standing had a specificity of 100%; blood pressure response to sustained hand grip, heart rate response to standing, and the Valsalva ratio all had a specificity of 90%; heart rate response to deep breathing had a specificity of 60% (table 2).

High field brain MRI imaged the basal ganglia, the brain stem, and the cerebellum. In three patients, non-specific periventricular changes in white matter were found. Mild cerebellar atrophy occurred in two patients (8 and 9); mild to moderate focal atrophy of the cerebral peduncles was seen in two other patients (13 and 15). Severe pontine and cerebellar atrophy occurred in patients 17 and 18. Patient 18 also had signal abnormalities in the neostriatum, which were found only in this patient and in patient 20.

Morphometry showed no variations either when patients were compared with controls or when patients with a low total score (score < 3) were compared with those with a high score (score ⩾ 3) (table 3).

Table 2 Per cent of patients with cardiovascular reflex test abnormalities

Autonomic test	*Abnormal findings*	*Sensitivity*	*Specificity*
Cardiovascular sympathetic function:			
BP response to standing up	30	60	100
BP response to sustained hand grip	30	50	90
Cardiovascular parasympathetic function:			
HR response to deep breathing	70	100	60
HR response to standing	70	80	90
Valsalva ratio	40	70	90

Sensitivity and specificity are computed for cases with severe or definite autonomic dysfunction (n = 10) compared with cases with no or early involvement (n = 10). BP = Blood pressure; HR = heart rate.

Table 3 Morphometric measurements (mean mm (SEM)) performed on MRI sequences through the brain in control subjects and in patients

Brain region	*Controls (n = 18)*	*All patients (n = 20)*	*Score < 3 (n = 10)*	*Score ⩾ 3 (n = 10)*
Pons	24·25 (0·32)	25·15 (0·79)	26·50 (0·98)	24·00 (1·07)
Midbrain	39·72 (0·66)	40·07 (0·67)	39·00 (0·69)	41·00 (1·04)
Substantia nigra	3·14 (0·13)	2·80 (0·14)	2·87 (0·18)	2·74 (0·21)
Lentiform nucleus	17·95 (0·50)	17·60 (0·58)	18·00 (0·95)	17·25 (0·73)
Caudate nucleus	10·06 (0·26)	10·09 (0·20)	10·17 (0·31)	10·03 (0·87)

Measurements performed on patients have also been analysed according to the MSA prospective score. There were no significant differences.

SUMMED SCORES

Patients with low total scores (0–1) were arbitrarily classified as non-MSA patients; in patients who scored 2 the diagnosis was regarded as clinically possible. Patients who scored 3 or 4 were diagnosed as clinically probable, and those who scored 5 or 6 as clinically definite MSA.

Possible MSA

Five (25%) of the 20 patients were considered to have possible MSA, scoring 2 with various combinations of positive findings (table 1). Patient 5 had two features that were considered atypical for Parkinson's disease, but had normal autonomic testing and MRI; by contrast, patient 10 presented akinesia and rigidity without tremor, together with autonomic failure, but no other atypical feature.

Probable MSA

Six (30%) of the 20 cases were considered to have probable MSA. In patient 6, the disease progressed rapidly, no resting tremor was detectable, and autonomic tests were severely affected; clinical response to drugs and the MRI were normal. Patient 9 responded to treatment and presented with non-symmetric onset: she scored 4 because all the other pointers were abnormal. In patient 11, two clinical criteria for MSA and autonomic testing were rated abnormal.

Definite MSA

Four (20%) patients (8, 13, 18, and 20) were considered to have clinically definite MSA. They had abnormalities in five out of the six pointers considered, although in differing combinations. Patient 8 met all the clinical criteria for MSA (rapid progression, symmetric onset, no tremor and lack of dopaminergic response) and was also found to have cerebellar atrophy; however, his autonomic testing was normal. Patient 18 had an asymmetric parkinsonian picture at onset, but met all the other criteria for MSA. Interestingly, no patient scored abnormal for all the pointers considered.

FOLLOW UP

The patients were followed up for an average of 2·1 (SEM 0·65) years (from eight months to four years). Nineteen of them are still alive; we were unable to obtain necropsy specimens of patient 11, who died of a myocardial infarction three years after the onset of her parkinsonian syndrome.

Table 4 Per cent of abnormal findings in the MSA prospective score

Item	*Abnormal findings*	*Sensitivity*	*Specificity*
Rapid progression	45·0	63·6	77·8
Symmetric onset	25·0	27·3	77·8
No tremor	70·0	90·9	55·6
No response to dopaminergic drugs	40·0	45·5	66·7
Autonomic dysfunction	50·0	72·8	77·8
Abnormal MRI	35·0	54·6	88·9

Sensitivity and specificity are computed for cases who had developed clinical MSA (n = 11) compared with those who had not (n = 9) at follow up.

Of the five patients who were initially classified as not having MSA, only patient 4 later developed atypical parkinsonian signs, four years after she was given a score. Seven years after onset of parkinsonian signs her neurological picture showed brisk tendon reflexes, left extensor plantar response, and the occurrence of focal reflex myoclonus in the left arm. Despite these features, her parkinsonian picture deteriorated slowly.

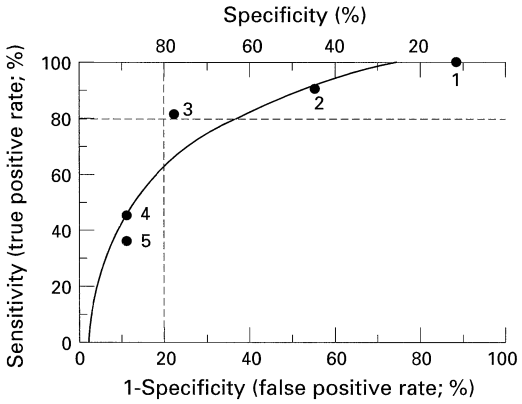
Of the five subjects who were initially classified as possible MSA, only patient 16 developed further atypical features during follow up. Six years after disease onset, he was found to have brisk tendon reflexes, left Babinski's sign, severe dysarthria, and urinary incontinence.

Of the six patients classified as probable MSA, five (6, 9, 11, 14 and 17) had developed clinical features at follow up clearly related to multiple system involvement. Patients 6 and 9 developed symptomatic autonomic failure and pyramidal signs three and four years after disease onset respectively; patient 9 also had limb ataxia. Thus they became patients with fully symptomatic MSA about eight months after they were given a score. Two years after onset of disease (1·5 years after she was given a score), patient 11 showed very rapid progression of her right sided unilateral parkinsonism, that did not improve with dopaminergic drugs. She then developed severe dysarthria, brisk tendon reflexes (particularly on the right), right Babinski's sign, focal reflex myoclonus in the right arm, urinary incontinence, and stereotyped facial movements. She died of myocardial infarction three years after onset of the disease. Six years after disease onset (two years after he was given a score), patient 14 was severely akinetic (Hoehn and Yahr stage 5); he also had retrocollis, stimulus sensitive focal myoclonus in the arms, and urinary retention. Three years after disease onset (one year after she was given a score), patient 17 had symptomatic postural hypotension and stimulus sensitive focal myoclonus.

All four patients classified as clinically definite MSA later developed clinical symptoms or signs clearly related to multiple system involvement. Patient 8 is now severely akinetic (Hoehn and Yahr stage 5) and has a neurogenic bladder and bilateral Babinski's sign. Patients 13, 18, and 20 now have symptomatic postural hypotension treated with fludrocortisone, and patient 20 also had rapid progression of her parkinsonian signs.

Stretch sensitive focal reflex myoclonus, described as a common feature of MSA,[9] was found on follow up in seven out of 20 patients (35%). Focal reflex myoclonus occurred in four of the six patients (67%) who were classified as probable, and in three of the four patients (75%) who were classified as clinically definite MSA.

Correlation based on the follow up diagnosis showed that the pointers considered had different degrees of sensitivity: absence of tremor had a sensitivity of 91%, autonomic dysfunction of 73%; sensitivity decreased to 64% for rapid progression, to 55% for MRI



This receiver operator characteristic curve represents the predictive accuracy of the prospective total score as a diagnostic test for clinically symptomatic MSA. Cut off values for scores from 1 to 5 are plotted together with the logarithmic curve fit. A cut off value of 3 is very close to the crossing point for 80% sensitivity and 80% specificity (dashed lines).

abnormality, and to 45% for lack of drug response. Symmetric presentation had a sensitivity as low as 27%. By contrast, all the pointers had a reasonably high specificity: abnormal MRI had the highest value (89%); rapid progression, symmetric onset, and autonomic dysfunction were ranked 78%; lack of response to levodopa had a specificity of 67%; and absence of tremor had a specificity of 56% (table 4).

When a receiver operator characteristic curve[19] was plotted, sensitivity decreased and specificity increased, as expected, as a direct function of the total score. With a cut off at 1, sensitivity was 100%, specificity was 11%; with a cut off at 2 they were 91% and 44%, respectively; with a cut off at 3 they were 82% and 78%; with a cut off at 4 they were 45% and 89%; finally, with a cut off at 5 sensitivity dropped to 36% and specificity was 89%. No patient scored 6, as already reported. The cut off value at score 3 seemed to be the best compromise for trade off between sensitivity and specificity; this was close to the crossing point for 80% sensitivity and 80% specificity (figure).

Discussion

Multiple system atrophy is a clinicopathological entity in which clinical diagnosis bears a degree of uncertainty. In the present series, none of the patients has had a necropsy. Hence the follow up validation of our prospective data currently relies on the finding of a fully symptomatic clinical picture. Although variable, the average survival of necropsy confirmed patients with MSA is 7·1–7·3 years.[8 20] The average disease duration of our patients on enrolment was 4·25 years; in addition they were followed up for an average 2·1 years, which brings the total observation period to an average of 6·35 years. Although the follow up time of this series is reasonably long, it may not be enough to detect a fully symptomatic clinical picture in all the patients with MSA under study. Moreover, some patients never develop evidence of multisystem involvement, yet have MSA at necropsy. By contrast, due to strict criteria, the possibility that patients labelled as having clinically definite MSA may be affected by a different neurological disease, although theoretically possible, is less likely. This is also supported by the finding that none of our patients had developed dementia or down gaze supranuclear palsy at follow up. In summary, the combination of stringent clinical inclusion criteria for cases with typical parkinsonism, yet reporting a disappointing clinical response to medication (allowing inclusion of only 6·7% of the total consecutive population), and of thorough clinical follow up criteria for MSA may have led to an underrepresentation of MSA. Hopefully, neuropathological verification will allow us to identify the true incidence of MSA in the present series.

Data previously collected from our retrospective clinicopathological study showed that some clinical and laboratory variables occur more commonly in MSA-P than in Parkinson's disease.[8] The present study provides a prospective evaluation of these pointers that is based on more reliable data than can be provided by the retrospective examination of patient records. The results, which are in keeping with our previous retrospective study, show that each patient has different combinations of normal and abnormal features, none of which is individually specific to MSA. Based on this finding a numerical total score, similar to the one assembled in the previous study, that measures with equal weight the number of abnormal findings was assembled for each patient. Those who had a higher number of abnormal features were assumed to have more chances of being affected by MSA-P.

Lack of response to dopaminergic drugs is commonly considered not to occur in idiopathic Parkinson's disease, as histologically established cases of Parkinson's disease typically respond to an adequate trial of levodopa.[21] In two series of pathologically established cases of MSA it was found that 33% to 40% of patients responded to levodopa[21 22]; this was confirmed by a more recent study reporting benefit from dopaminergic drugs in 37% of patients with a clinical diagnosis of MSA and in 65% of patients with a pathological diagnosis of MSA.[7] Our data are in keeping with these findings, as they show that 66·7% of patients, with predicted clinically probable MSA, and 60% of those with predicted clinically possible MSA, responded to a dopaminergic challenge (either acute or chronic).

We used the simple inclusion criterion of a clinically typical parkinsonian presentation associated with a lack of the expected benefit from antiparkinsonian drugs, as reported anecdotally. The response to dopaminergic drugs was then verified objectively and this measure was included in the set of data. The anecdotal report and the objective evaluation did not always agree. In the present study, the response to dopaminergic drugs was tested with both acute and chronic challenge at a time when clinical features were mild and of recent occurrence. A very high concordance between the acute and the chronic treatment was found. Just one patient improved after

chronic treatment with levodopa and bromocriptine but not with the acute standard challenge. This confirmed that the degree of responsiveness to dopaminergic drugs cannot always rely on the patient's impression alone. In this series 55·5% of the patients who reported a poor response to dopaminergic drugs were, in fact, subsequently objectively classified as responders. In some of those who originally had a good response to dopaminergic drugs, this was gradually lost. Our follow up data showed that 45·5% of the patients who subsequently developed clinical evidence of multisystem disease still maintained a good response to chronic treatment with dopaminergic drugs at follow up. We expect this proportion to decrease with time, as in a recent survey it has been reported that levodopa response was maintained in only 13% of patients with MSA who had a good or excellent response at some stage.[23] As loss of sustained response in patients initially treated with levodopa is believed to reflect a progressive extension of neurodegeneration to the putamen[22] and other structures, our finding of a gradual loss of therapeutic benefit may provide an indirect estimate of this process.

The finding of putaminal hypointensity has been reported to be a feature of parkinson-plus syndromes or of MSA.[17 24–30] This feature was found in only one of our selected parkinsonian patients. It has also been proposed that a putaminal hypointensity, relative to the pallidum, may be a more specific finding in patients affected by MSA.[17] Our data indicate, however, that this is not the case when patients are studied early in the disease when their picture is mild. The combined occurrence of low sensitivity and high specificity in MRI data show that these are not useful in patients with MSA-P for the purpose of an early diagnosis. This may also explain why we did not find the putaminal slit hyperintensity that has been reported in a high proportion of patients with clinically definite MSA.[31] In four of our patients with no clinical signs of cerebellar dysfunction, MRI suggested mild cerebellar atrophy (associated with pontine atrophy in two cases). There is no agreement on the incidence of imaging evidence of cerebellar and brain stem atrophy in patients with a diagnosis of MSA who clinically have no definite cerebellar signs. Our data are in keeping with a study reporting that only 50% of 18 patients with MSA who had cerebellar symptoms or signs had MRI evidence of cerebellar and brain stem atrophy,[32] but are at odds with another series reporting that 73% of patients with MSA without cerebellar signs had some degree of cerebellar atrophy.[7] In our study, no narrowing of the substantia nigra pars compacta was found; this is an interesting difference from idiopathic Parkinson's disease, where there is a significant reduction in width of the substantia nigra.[33 34] Interestingly, it has been recently reported that when narrowing of the substantia nigra occurs in patients with full blown MSA it does not correlate with the severity of the parkinsonian picture.[35]

At a time when no biological marker can reliably differentiate MSA-P from other parkinsonian syndromes, the use of multiple clinical pointers is required to improve diagnostic accuracy. Such a requirement is supported by the findings that: (1) no specific item or combination of items was consistently found to be abnormal in patients with high scores, (2) none of the items considered was consistently abnormal in patients who later developed full blown MSA, and (3) the same features were also seen in cases of pathologically established MSA studied retrospectively.[8] This means that patients with MSA-P do not have any one specific feature in common, but rather are more likely to present a selection of atypical features. The receiver operator characteristic curve for the prospective total score that we have assembled here showed that the loss in specificity is negligible for scores higher than 3. Thus this series of pointers may be used as a simple scoring method to predict the clinical outcome of patients with MSA-P.

Also, the possibility of adding other pointers not considered in the present study should be examined. To be of value, their inclusion should improve the overall sensitivity and specificity thus providing a larger area under the receiver operator characteristic curve. To this end, newer imaging techniques such as PET,[36] SPECT,[30 37] or EMG of the urethral and external anal sphincters[38 39] may prove useful. Their diagnostic value in MSA-P should be assessed retrospectively and their predictive value then validated prospectively.

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