

ORIGINAL CONTRIBUTION

Some Specific Clinical Features Differentiate Multiple System Atrophy (Striatonigral Variety) From Parkinson's Disease

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Objective: The clinical recognition of multiple system atrophy (MSA) in patients presenting with parkinsonian signs is difficult. We attempted to verify the predictive value of some pointers that are used in clinical practice.

Design: Sixteen consecutive patients with pathologically confirmed MSA who presented with a parkinsonian syndrome over an 8-year period were studied retrospectively, and their clinical features were analyzed in detail.

Setting: Parkinson's Disease Society, Brain Tissue Bank, Institute of Neurology, London, England.

Patients: Sixteen patients with pathologically proven MSA who presented with parkinsonian syndrome in the first 3 years since disease onset.

Methods: Clinical features that were analyzed included the rapidity of disease progression, the relative

symmetry of symptom onset, the presence or absence of tremor at initial presentation, the therapeutic response to levodopa and the associated presence of autonomic dysfunction. Fourteen of the 16 patients also had a computed tomographic scan of the brain performed. The frequency of selected items in MSA was compared with that found in 20 pathologically confirmed cases of Parkinson's disease and 16 pathologically confirmed cases of progressive supranuclear palsy (Steele-Richardson-Olszewski disease).

Results: It was found that a probability scale based on five selected items discriminated MSA with a pure parkinsonian presentation from Parkinson's disease, but not from progressive supranuclear palsy. Patients affected by the latter disorder, however, commonly presented with additional clinical features (supranuclear vertical downgaze palsy, axial dystonia, and cognitive impairment), which helped to differentiate it from MSA.

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STRIATONIGRAL degeneration was originally described as a neurodegenerative disease that clinically resembles Parkinson's disease (PD).^{1,2} Subsequently, it became clear that striatonigral degeneration presents clinical features that overlap with the Shy-Drager syndrome and olivopontocerebellar atrophy. The term *multiple system atrophy* (MSA) was coined in 1969 by Graham and Oppenheimer³ to embrace these three different clinical syndromes. All are characterized pathologically by marked neuronal loss in the basal ganglia, autonomic pathways, and cerebellum, with gliosis and glial cytoplasm inclusions.⁴

A reliable diagnosis of MSA can be made on clinical grounds when patients present sporadically in middle age with a combination of parkinsonian, autonomic, cerebellar, and pyramidal signs. A significantly more difficult task is the clinical recogni-

tion of MSA in patients presenting only with parkinsonian signs. In some cases, the clinical picture may be indistinguishable from idiopathic PD up to the time of death.^{5,6} However, a number of associated signs, when present, may point toward MSA (eg, focal reflex myoclonus, jerky tremor, unilateral facial dystonia, disproportionate anterocollis, and square wave jerks⁷⁻⁹), and some patients also develop late pyramidal signs, autonomic failure, or cerebellar signs leading to revision of the diagnosis.⁵

A quite difficult clinical task is to accomplish an early diagnosis of MSA in the patients presenting only with parkinsonian signs. We¹⁰ recently proposed that some features, which have been reported to

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PATIENTS AND METHODS

Twenty-seven cases of pathologically proven MSA were collected from 1984 to 1992 by the PD Society Brain Tissue Bank in London, England. This facility receives donor tissue from parkinsonian patients, most of whom had been examined at annual intervals by a panel of experienced neurologists. These 27 MSA cases accounted for 13% of the 208 consecutive brains collected in the 8 years considered, being the second most common pathological diagnosis after PD. Half-brains fixed in 10% neutral formalin were available for examination using standard neuropathological methods. The diagnosis of MSA was made according to already published neuropathological criteria.⁶ All cases showed striatonigral involvement combined (in most instances) with some degree of olivopontocerebellar damage.

Based on the clinical records, we selected 16 cases with parkinsonian signs and no other neurological abnormality present during the first 3 years from disease onset. Of the 11 cases that were ruled out, three had early features suggestive of MSA (cerebellar and pyramidal signs or symptomatic autonomic involvement), and the remaining eight had inadequate clinical data. In the 16 cases selected, the following data were extracted from the patients' records: (1) age at disease onset; (2) duration of disease; (3) initial and late features of disease; (4) amount of response to levodopa in the early stages of disease, according to the following scale: nil to poor (improvement less than 30%), moderate (improvement from 30% to 50%), good (improvement

from 50% to 70%), or excellent (improvement over 70%); and (5) signs of initial autonomic dysfunction.

Five clinical parameters, related to the first 3 years from disease onset, were selected as possible pointers to MSA: (1) rapid progression of the disease, with patients scoring at least 3 (Hoehn-Yahr's scale) within 3 years from the onset of symptoms; (2) symmetrical onset of symptoms; (3) absence of rest tremor; (4) poor or no response to levodopa, using the criteria defined above, with a daily levodopa intake not lower than 800 mg (in addition to peripheral decarboxylase inhibitors); and (5) cardiovascular autonomic testing showing moderate or severe autonomic involvement, according to Ewing's criteria.¹¹ In cases lacking laboratory evaluation, autonomic dysfunction was considered present if there was a postural systolic blood pressure drop greater than 30 mm Hg. In most patients (14 of 16), a computed tomographic (CT) scan of the brain was also available.

Data collected from MSA cases were compared with the corresponding features of 20 consecutive cases of pathologically confirmed PD and of 16 consecutive cases of pathologically confirmed PSP, which were also obtained from the PD Society Brain Tissue Bank. The specific sensitivity of the selected clinical features were tested in each group by using a retrospective score assigned to each patient. One point was given for each of the following features: rapid progression, symmetrical onset, absence of tremor at onset, lack of response to levodopa, and autonomic dysfunction. Clinical data were compared using the Student *t* test for continuous variables and the Mann-Whitney *U* test for categorical or nonnormal data.

occur infrequently in PD, may be assembled into a scale to rank the probability that a parkinsonian patient may later develop clinically definite MSA. To be accessed also by neurologists with no special expertise in movement disorders, such a scale should be unambiguous and easy to use. In the present study, some index items, which could be inserted in a probability scale, were evaluated retrospectively in a series of pathologically proven cases of MSA, PD, and Steele-Richardson-Olszewski disease (progressive supranuclear palsy [PSP]).

RESULTS

The 16 patients with MSA had a mean ($\pm$ SD) age at disease onset of 54.4 ($\pm$ 10.7) years and a mean ($\pm$ SD) disease duration of 7.1 ($\pm$ 2.6) years; 10 patients were female and six were male. The clinical diagnosis at death was PD in four cases (25%) and MSA in 12 cases (75%). In two cases, a family history of parkinsonism was on record. An akinetic-rigid presentation occurred in all patients, with associated tremor in two (patients 5 and 9). In the first of the two, a mild postural tremor of the left hand and foot was detected; the second patient had a moderate, typical, rest tremor of the left hand. A mild supranuclear upward gaze palsy was present in one patient (patient 1). Two patients (patients 8 and 16) developed dementia in the late stage of the disease.

Analysis of the clinical parameters in patients with MSA showed that absence of tremor at onset was the most common indicator, occurring in 14 cases (87.5%); the disease

progressed rapidly in 11 cases (68.7%); autonomic dysfunction (or proven orthostatic hypotension) occurred in 11 cases (68.7%); onset was symmetrical in seven cases (43.7%); levodopa produced no benefit in five cases (31.2%); and radiological changes consistent with MSA (eg, marked brainstem or cerebellar atrophy¹²) were detected on the CT scan in just two cases (12.5%). The CT scan usually revealed a nonspecific pattern of diffuse atrophy (seven cases [43.7%]) or a normal picture (five cases [31.2%]). Based on these findings, one case was retrospectively scored 5, two cases were scored 4, nine cases were scored 3, and four cases were scored 2. No case received a score less than 2 (**Table 1**). The mean total score ($\pm$ SD) of MSA cases was 2.9 ($\pm$ 0.8).

Analysis of the same clinical parameters in the 20 pathologically confirmed PD cases showed that (1) absence of tremor at onset was not uncommon, occurring in eight cases (40%); (2) the disease progressed rapidly in only two cases (10%); (3) orthostatic hypotension occurred in one case (5%); (4) onset was symmetrical in five cases (25%); and (5) levodopa determined a clinical benefit in all cases. Based on these findings, two cases were retrospectively scored 3, two cases were scored 2, six cases were scored 1, and 10 cases were scored 0. The mean total score ($\pm$ SD) of PD cases was 0.8 ($\pm$ 1.0).

In the 16 pathologically confirmed PSP cases, it was reported that (1) absence of tremor was a clinical feature ($n=10$, 62.5%); (2) the disease progressed rapidly ($n=15$, 93.8%); (3) autonomic dysfunction (or proven orthostatic hypotension) never occurred in the eight cases in whom data were available; (4) onset was symmetrical ($n=13$,

Table 1. Clinicolaboratory Features of Pathologically Proven Cases of MSA Included in the Study*

Patient No.	Rapid Progression	Symmetrical Onset	No Tremor	Lack of Response to Levodopa	Autonomic Tests	CT Scan
1	Yes	Yes	Yes	Yes	Abnormal	Normal
2	No	No	Yes	Yes	Abnormal	Normal
3	No	No	Yes	No	Abnormal	Supratentorial atrophy
4	Yes	No	Yes	Yes	Normal	Normal
5	Yes	Yes	No	No	Abnormal	Cerebellar atrophy
6	Yes	No	Yes	No	Abnormal	Generalized atrophy
7	Yes	Yes	Yes	No	Orthostatic hypotension	
8	Yes	No	Yes	Yes	No orthostatic hypotension	Supratentorial atrophy
9	Yes	No	No	No	Abnormal	Atrophic changes
10	No	No	Yes	No	Orthostatic hypotension	Brain-stem and cerebellar atrophy
11	Yes	Yes	Yes	No	No orthostatic hypotension	Generalized atrophy
12	No	Yes	Yes	No	No orthostatic hypotension	
13	Yes	No	Yes	No	Abnormal	Normal
14	Yes	Yes	Yes	No	No orthostatic hypotension	Normal
15	Yes	Yes	Yes	No	Orthostatic hypotension	Generalized atrophy
16	No	No	Yes	Yes	Abnormal	Generalized atrophy

*MSA indicates multiple-system atrophy; CT, computed tomography.

81.3%); and (5) levodopa produced no benefit ($n=12$, 75%). Based on these findings, nine cases were retrospectively scored 4, two cases were scored 3, three cases were scored 2, and two cases were scored 1. The mean total score ($\pm$ SD) of PSP cases was $3.1 (\pm 1.2)$. At variance with patients with MSA and PD, those affected by PSP had clinical signs that were clearly atypical for idiopathic PD. Indeed, early in the course of the disease, 50% of PSP cases also presented with supranuclear ophthalmoplegia, 56.2% had axial dystonia, and 50% had a cognitive impairment of frontal type.

When the clinical scores of the three different groups were compared, it was found that the mean age at disease onset was lower in MSA cases (54.4 ± 10.7 years) than in PD cases (62.2 ± 7 years) and in PSP cases (70.3 ± 8 years); the disease duration of MSA cases (7.1 ± 2.6 years) did not differ from that of PSP cases (6.7 ± 2.2 years), but both differed from that of PD cases (13.6 ± 5.6 years). The mean total score of MSA cases was significantly different from that of PD cases ($P < .001$), but not from that of PSP cases (**Table 2**). Statistical analysis of individual items included in the probability score showed that the mean score of two items, ie, rapid progression and autonomic dysfunction, was significantly higher in patients with MSA than in patients with PD. On the other hand, symmetry of onset, lack of response to levodopa and lack of tremor did not statistically differ in the two groups.

COMMENT

Multiple system atrophy is a clinical pathological term encompassing striatonigral degeneration, olivopontocerebellar atrophy, and some entities of autonomic failure with or without added neurological signs. Early in the course of the disease, patients can be separated into subgroups; however, as the disease progresses, considerable clinical overlap occurs.⁵ Multiple system atrophy may present only with parkinsonian features⁶; in the present series, 25% of MSA patients had a clinical diagnosis of idiopathic PD without ever being suspected in life to have MSA. Besides autonomic, pyramidal, and cerebellar fea-

tures, early instability with falls, absence of rest tremor, rapid progression, and a poor or not sustained response to levodopa already have been reported to point to MSA.^{2,5,6}

A probability score for MSA may improve the reliability of the clinical diagnosis, as there is no single clinical or laboratory parameter that is pathognomonic for MSA. Our observation that none of the selected parameters was invariably altered in MSA is in keeping with this view. However, our study showed that some clinical features are significantly correlated with a high probability of having MSA. Thus, the observation of a parkinsonian picture associated with the clinical features of a rapid progression, a symmetrical onset of symptoms, no tremor at onset, a lack of response to levodopa, and autonomic dysfunction (also if not symptomatic) must raise the suspicion that the patient is affected by MSA. The present study is based on information commonly available in carefully kept neurological case records. It cannot be ruled out, however, that there may be other neurological features that could be used to differentiate MSA from PD and from PSP. The items considered in this article are those that can be easily evaluated by neurologists without a particular interest in abnormal movement disorders.

Our study shows that a rapid progression of the disease occurs more frequently in MSA than in PD; the mean disease duration of MSA was significantly shorter than the duration of PD. A rapid disease progression is, therefore, a useful pointer to MSA, although the progression speed may be difficult to judge during the first years of illness.

The possible predictive value of symmetrical onset was suggested by a recent clinical pathological study of 100 patients in whom idiopathic PD was diagnosed.¹³ In our survey, symmetrical onset was not a very common feature of MSA, occurring in only 43.7% of the cases. This item appears not to be one of the most helpful clinical pointers for MSA, as it occurs more often in PSP than in MSA or PD.

The absence of tremor has been repeatedly proposed as a clinical marker for atypical parkinsonism.⁵ In

Table 2. Clinical Parameters of 52 Parkinsonian Cases Classified According to the Histologic Diagnosis*

Clinical Feature	MSA	PD	PSP
No. of cases	16	20	16
Age at onset of disease,† y (±SD)	54.4 (±10.7) ^a	62.2 (±7.0) ^b	70.3 (±8.0) ^c
Disease duration,† y (±SD)	7.1 (±2.6) ^d	13.6 (±5.6) ^e	6.7 (±2.2) ^f
Rapid progression, No. (%)	11 (68.7)	2 (10)	15 (93.8)
Symmetrical onset, No. (%)	7 (43.7)	5 (25)	13 (81.3)
No tremor, No. (%)	14 (87.5)	8 (40)	10 (62.5)
No response to levodopa, No. (%)	5 (31.2)	0	12 (75)
Autonomic dysfunction, No. (%)	11 (68.7)	1 (5)	0
Total score,‡ mean (±SD)	2.9 (±0.8) ^x	0.8 (±1.0) ^y	3.1 (±1.2) ^z
Total score, median	3	0.5	4

*MSA indicates multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; and NS, not significant.

†P values, using Student's t test statistics, show the following relationships: a-b, $P < .001$; a-c, $P < .001$; b-c, $P < .05$; d-e, $P = .002$; d-f, NS; and e-f, $P = .01$.

‡P values, the using Mann-Whitney U Test, show the following relationships: x-y, $P < .001$; x-z, NS; and y-z, $P < .001$.

1988, van Leeuwen and Perquin¹⁴ reviewed the literature on the clinical and neuropathological features of 33 cases of striatonigral degeneration. Tremor occurred as the initial symptom only in 6% of cases, while it occurred in 63% to 70% of cases of idiopathic PD.¹⁵ This observation is in keeping with our study, which showed that tremor was present from the beginning in only 12.5% of MSA cases, compared with 60% of pathologically confirmed PD cases and with 37.5% of pathologically confirmed PSP cases. It can be concluded, therefore, that while the absence of tremor is not specific for the striatonigral variety of MSA, its occurrence is rather typical for PD.

Lack of response to dopaminergic therapy has been claimed to represent a specific feature of MSA presenting only with parkinsonian signs.¹⁶⁻²⁰ In a more recent series of patients with a presumptive clinical diagnosis of MSA, it was found that a significant response to acute doses of levodopa occurred in 37% of the patients.²¹ Two reviews^{6,22} of pathologically proven series of MSA also confirmed that 33% to 40% of the patients responded to levodopa. In keeping with this, it is clear from our data that levodopa produces motor improvement in a significant percentage of patients with MSA. An initial response to levodopa was observed in 68.8% of the patients. In many of them a partial or complete loss of therapeutic efficacy occurred as the disease progressed.

Poor response to dopaminergic drugs is thought to be due to striatal damage and the ensuing loss of post-synaptic receptors. The variability of response in different patients probably depends on the relative degree of nigral vs striatal damage. When nigral damage is the main feature, a better response to therapy is observed. This has been confirmed by Fearnley and Lees,⁶ who found that a relative preservation of the putamen correlates directly with responsiveness to levodopa. However, a re-

cent positron emission tomography study²³ showed that only two of 10 patients with striatonigral degeneration had a marked reduction of striatal ¹¹C-raclopride binding, an index of dopamine D₂ receptor function. Thus, the variable response to treatment of patients with MSA cannot be due to loss of dopaminergic sites alone, but must reflect loss of other connections in the basal ganglia involving different neurotransmitters.

Based on these data, it appears that in MSA a response to levodopa occurs more often than is generally believed, depending on duration and stage of the illness, although the magnitude and the nature of response differ from that usually seen in PD. An acute challenge with both levodopa and apomorphine and subsequent frequent follow-up in the first months of therapy are warranted in all de novo cases of parkinsonism.²⁴ This may help to characterize more precisely the type, magnitude, and characteristics of the dopaminergic response in MSA.

Autonomic dysfunction is a very common feature of MSA, which may also occur with Lewy body pathology.²⁵⁻²⁸ It was observed in 11 of our patients; considering that the number of positive cases could have been reduced by the incomplete evaluation of autonomic function in four patients who were considered normal, it must be concluded that autonomic dysfunction is very common, indeed, in MSA. On the contrary, autonomic test results were rarely found to be abnormal in the early stages of PD; the difference cannot be attributed to age, since patients with MSA had a lower mean age at disease onset than did patients with PD.

A comparison between the scores collected from MSA cases and from PD and PSP cases showed highly significant differences with the former, but not with the latter. This means that the use of such clinical criteria may be helpful in distinguishing the striatonigral variety of MSA from PD, but not from PSP. However, it must be considered that 50% of PSP cases also had early supranuclear up- and down-gaze palsy, which is the clinical hallmark of the disease and a necessary feature for the diagnosis.^{29,30} Supranuclear vertical down-gaze palsy, as well as axial dystonia, which occurred in 56.2% of our PSP cases, is only occasionally found in MSA; therefore, these features can easily be used as useful exclusion criteria for the clinical diagnosis of MSA.

Finally, our study also confirmed that dementia is uncommon in MSA. In a recent study,³¹ evidence of a mild cognitive dysfunction was reported using tests sensitive to frontal lobe damage; however, no consistent evidence of either memory deficits or learning impairment or generalized intellectual deterioration were found. Based on these data, dementia may also be considered as an exclusion clinical criterion for MSA. In contrast, "fronto-limbic" dementia is a relatively common early feature of PSP.^{29,30} To this regard, it is relevant to note that a significant degree of early cognitive impairment was present in 50% of cases in our series.

This study also pointed out that the CT scan is not a useful ancillary diagnostic tool, since only two patients presented with brain-stem and cerebellar atrophy. This was not surprising, as the CT scan cannot visualize the structures located in the posterior fossa with sufficiently high resolution. It is interesting to note that

patient 11 had only mild diffuse atrophic changes on CT scan; postmortem examination, performed 2 months later, revealed instead a significant atrophy of the cerebellar vermis and a significant shrinkage of the folia. Such discrepancies may also explain why a low occurrence of cerebellar and brain-stem atrophy was found in our series but not in other studies (eg, in the article by Fulham et al³²). Furthermore, it must also be considered that in the present study MSA cases with clinically detectable cerebellar or autonomic features were excluded. Newer imaging techniques, such as magnetic resonance imaging^{10,32-34}; single-photon emission computed tomography with ¹³¹I-iodobenzamide³⁵; or positron emission tomography with ¹⁸F-dihydroxyphenylalanine, ¹⁸F-fluorodeoxyglucose, or ¹¹C-raclopride,^{23,32,36} may hold greater promise.

In summary, we conclude that the five items listed in Table 2 have been verified pathologically and can be adopted in clinical practice to provide a probability score for MSA in patients presenting with a pure parkinsonian picture and no supranuclear down-gaze palsy, axial dystonia, or frontolimbic dementia.

Patients matching no more than one of these clinical features would fall below 2 SDs from the mean; they can, therefore, be considered on clinical grounds as not having MSA. Patients matching two of these clinical features would fall below approximately 1 SD from the mean; they can, therefore, be considered as patients with possible MSA. Patients matching three or more clinical criteria would exceed the mean score found in this study; therefore, they can be considered as patients with clinically probable MSA.

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