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The Clinical Diagnosis of Multiple System Atrophy Presenting as Pure Parkinsonism

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Striatonigral degeneration was first described by Adams, van Bogaert, and van der Eecken in 1961 as a degenerative disease of the central nervous system, clinically resembling Parkinson's disease (PD) (1,2). Subsequently it became clear that striatonigral degeneration presents clinical features that overlap with the Shy–Drager syndrome and sporadic olivopontocerebellar atrophy. The term "multiple system atrophy" (MSA) was then coined to embrace three different neurologic syndromes that can present with different combinations of parkinsonian, cerebellar, pyramidal, and autonomic signs (16). Pathologically, MSA is characterized by a marked neuronal loss and gliosis in the basal ganglia, autonomic pathways, and cerebellum and by the lack of Lewy bodies (22). This pathologic picture is associated with the widespread occurrence of glial and neuronal cytoplasmic inclusions, which have been interpreted as a specific marker for this disease, thus supporting the inclusion of these different syndromes in a single nosologic entity (19).

Multiple system atrophy is not a rare disease: during the period from 1984 to 1992, 27 definite cases of MSA were collected by the PD society brain bank in London. This facility receives donor tissue from parkinsonian patients, most of whom had been examined at annual intervals by a panel of experienced neurologists. The MSA cases accounted for 13% of the 208 consecutive brains collected in the 8 years considered, and PD cases were 65% of the total (7). When these figures are extrapolated to the normal population, it can be reckoned that MSA may have a prevalence as high as 20 per 100,000 inhabitants.

Although a clinical marker for MSA is not available yet, a reliable diagnosis can be easily made on clinical grounds when a combination of parkinsonian, autonomic, cerebellar, and pyramidal signs occur sporadically in middle age. A set of diagnostic criteria has been proposed by Quinn, who classified MSA into two main subgroups: one with predominant parkinsonian features (striatonigral type), the other predominantly cerebellar (olivopontocerebellar type). Either type was clinically possible or probable, based on the combination of poor response to dopaminergic drugs, autonomic failure, and pyramidal, cerebellar, or parkinsonian features (25). Notwithstanding, it is rather difficult to recognize MSA in patients presenting with only parkinsonian signs, and in some cases the clinical picture may be indistinguishable from idiopathic PD until death (7,12). Recently, a number of associated signs have been described as possible pointers toward MSA, namely, focal reflex myoclonus, jerky tremor, unilateral facial dystonia, disproportionate anterocollis, and square-wave jerks (24,28,30). Unfortunately, these signs are not very common and may be difficult to recognize.

We performed a retrospective clinical–pathologic study to identify simple clinical criteria that could be inserted in a probability scale

to differentiate PD from striatonigral MSA when it initially presents with only parkinsonian signs. Furthermore, we prospectively attempted to verify whether the same criteria, in addition to brain magnetic resonance (MR) imaging, may be used as pointers for an early diagnosis of striatonigral MSA (4,7).

RETROSPECTIVE STUDY

Patients and Methods

Fifty-two cases who initially presented with only a parkinsonian syndrome and no other neurologic abnormality were retrospectively studied. Half-brains fixed in 10% neutral formalin were available for examination using standard neuropathologic methods (22). The final diagnosis was MSA in 16 cases, PD in 20 cases, and Steele–Richardson–Olszewski disease (SROD) in 16 cases. In 25% of MSA cases a clinical diagnosis of idiopathic PD, without any suspicion of MSA, was on record throughout life.

Based on previous suggestions (12,15,17,26, 33,34), we evaluated the occurrence of five parameters, referred to the first 3 years after disease onset. The following were selected as possible pointers to MSA: (a) rapid progression of the disease, with patients scoring at least 3 (Hoehn–Yahr scale) within 3 years from onset; (b) symmetric onset of symptoms; (c) absence of rest tremor; (d) poor or no response to L-DOPA after an adequate chronic challenge; (e) cardiovascular autonomic testing showing moderate or severe autonomic involvement, according to Ewing's criteria (11), in the absence of clinical autonomic symptoms. Data collected from MSA cases were compared to the corresponding features of pathologically confirmed PD cases and of pathologically confirmed SROD cases. Each of the following features was given the weight of 1 point score: rapid progression, symmetric onset, absence of tremor at onset, lack of response to L-DOPA, autonomic dysfunction. A total retrospective score was then assigned to each patient. Clinical data were compared using Student's t test for continuous variables and the Mann–Whitney U test for categoric or nonnormal data.

Results

Analysis of the clinical parameters in MSA patients 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 occurred in 11 cases (68.7%); onset was symmetric in seven cases (43.7%); L-DOPA produced no benefit in five cases (31.2%). The results are summarized in Table 1. Based on these findings, one case retrospectively scored 5 points, two cases scored 4, nine cases scored 3, four cases scored 2. No case received less than 2 points. The mean total score (±SD) of MSA cases was 2.9 (±0.8).

Analysis of the same clinical parameters in the 20 pathologically confirmed PD cases showed that: (a) absence of tremor at onset was not uncommon, occurring in eight cases (40%); (b) the disease progressed rapidly in only two cases (10%); (c) orthostatic hypotension occurred in one case (5%); (d) onset was symmetric in five cases (25%); (e) L-DOPA produced a clinical benefit in all cases. Based on these findings, two cases retrospectively scored 3 points, two cases scored 2, six cases scored 1, and ten cases scored 0. The mean total score (±SD) of PD cases was 0.8 (±1.0).

In the 16 pathologically confirmed SROD cases it was reported that: (a) absence of tremor was a clinical feature in ten (62.5%); (b) the disease progressed rapidly in 15 (93.8%); (c) autonomic dysfunction (or proven orthostatic hypotension) never occurred in the eight cases on whom data were available; (d) onset was symmetric in 13 (81.3%); (e) L-DOPA produced no benefit in 12 (75%). Based on these findings, nine cases retrospectively scored 4 points, two cases scored 3, three cases scored 2, two cases scored 1. The mean total score (±SD) of SROD cases was 3.1 (±1.2). At variance with MSA and PD, SROD patients had clinical signs that were clearly atypical for idiopathic PD. Indeed, early in the course of the disease, 50% of SROD

TABLE 1. *Clinical parameters of 52 parkinsonian cases classified by histologic diagnosis*

Clinical feature	MSA	PD	SROD
Number of cases	16	20	16
Age at onset of disease (years ± SD)[a]	54.4 (±10.7)	62.2 (±7.0)	70.3 (±8.0)
Disease duration (years ± SD)[b]	7.1 (±2.6)	13.6 (±5.6)	6.7(±2.2)
Rapid progression	11 (68.7%)	2 (10%)	15 (93.8%)
Symmetric onset	7 (43.7%)	5 (25%)	13 (81.3%)
No tremor	14 (87.5%)	8 (40%)	10 (62.5%)
No response to L-DOPA	5 (31.5%)	0	12 (75%)
Autonomic dysfunction	11 (68.7%)	1 (5%)	0
Total score (mean ± SD)[c]	2.9 (±0.8)	0.8 (±1.0)	3.1 (±1.2)
Total score (median)	3	0.5	4

[a]Significance of differences: MSA vs. PD, $p < 0.001$; MSA vs. SROD, $p < 0.001$; PD vs. SROD, $p < 0.05$; all by Student's *t* test.

[b]Significance of differences: MSA vs. PD, $p = 0.002$; MSA vs. SROD, n.s.; PD vs. SROD, $p = 0.01$, all by Student's *t* test.

[c]Significance of differences: MSA vs. PD, $p < 0.001$; MSA vs. SROD, n.s.; PD vs. SROD, $p < 0.001$; all by Mann–Whitney *U* test.

cases presented also supranuclear ophthalmoplegia, 56.2% had axial dystonia, and 50% had a cognitive impairment of the frontal type (13,20).

PROSPECTIVE STUDY

Patients and Methods

A series of 298 consecutive parkinsonian outpatients were evaluated during a 3-year period. Among these, we selected 20 consecutive subjects (8 women and 12 men) who subjectively reported to have a poor response to standard dopaminergic therapy. They had neither cerebellar nor pyramidal signs, nor were they clinically symptomatic for autonomic dysfunction. Additional exclusion criteria were supranuclear down-gaze palsy, dementia (as defined by DSM-III-R), exposure to neuroleptic drugs or to known neurotoxins, abnormal copper metabolism.

As soon as they were selected for the study, the patients underwent the following clinical and laboratory evaluation.

1. Response to dopaminergic drugs. We evaluated the clinical response to antiparkinsonian drugs by assessing the variation of motor conditions from a baseline after the administration of single increasing subcutaneous doses of apomorphine (1.5, 3, and 4.5 mg) and of a single oral dose of L-DOPA and carbidopa (250/25 mg). A patient was considered to respond when standard criteria were met (6). Each patient was also treated chronically with L-DOPA and carbidopa (750/75 mg daily) or with L-DOPA and benserazide (800/200 mg daily) for 2 months. The patients were evaluated before and after this chronic treatment. Those who improved by at least 20% after the chronic regimen were also classified as responding to therapy.
2. Autonomic cardiovascular reflexes. Each patient underwent the following cardiovascular reflex tests under continuous electrocardiographic monitoring, as already reported (11): (a) blood pressure and heart rate response to standing up; (b) heart rate response to deep breathing; (c) Valsalva ratio; (d) blood pressure response to sustained hand-grip. Antiparkinsonian drugs were withdrawn or at least diminished to the lowest dosage that allowed appropriate cooperation during the tests. The global involvement of autonomic dysfunction was defined as early, definite, severe, or atypical, according to Ewing's criteria (11).
3. Brain morphology. All patients underwent a high-field (1.5 Tesla) MR scan. Both T_1- and T_2-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. We used both T_1- and T_2-weighted pulse sequences for the morphologic observation; T_2-weighted pulse sequences made it possible to identify hypointensities in the basal ganglia. The MR data were considered consistent with MSA when they showed cerebellar or brainstem atrophy (3,8,31) or when the putamen was found to be hypointense on T_2-weighted images, as compared to the ipsilateral globus pallidus (14,23).

Clinical Score and Follow-up

The probability of having MSA was evaluated with a 0- to 6-point score. Each patient received one point for each of the following: (a) rapid progression of the disease; (b) symmetric onset of symptoms; (c) absence of tremor within 3 years from the disease onset; (d) poor or no response to dopaminergic drugs; (e) definite or severe involvement of autonomic function (as evaluated by cardiovascular reflex tests); (f) abnormal MR scan. Rapid disease progression was observed in 45% of patients, symmetric onset in 25%, tremor was absent in 70%, lack of response to dopaminergic drugs in 40% of cases, autonomic dysfunction occurred in 50%, and MR showed specific abnormalities in 35% of cases. Fifteen patients, who scored higher than 1 were considered at risk for having MSA: five of them were classified as possible MSA cases (score 2); six of them were classified as probable cases (score 3–4). Four patients were classified as clinically definite MSA cases (score 5). The six features considered in the probability score were variably combined in each patient; none of them was specifically altered in patients with high scores (4).

All patients were followed up until May1994 (mean 2.14 ± 0.65 years). Their diagnosis was periodically reevaluated based on the appearance of clinical signs of multiple system involvement. During this extension of the study, all but one of the ten cases prospectively classified as probably or definitely affected by MSA developed unequivocal clinical signs of multiple system involvement.

DISCUSSION

In keeping with earlier observations (7,12,25), the present data show that, in a significant percentage of cases, MSA may initially present with only parkinsonian features. A probability score for MSA may improve the reliability of the clinical diagnosis in such cases because there is no clinical or laboratory parameter that is pathognomonic for MSA. A lack of dopaminergic responsiveness can no longer be considered a landmark for the clinical diagnosis of MSA because some response to dopaminergic therapy occurs, at least initially, in MSA (18,27). This has been confirmed by our data showing that 68.8% of pathologically confirmed MSA cases had a response to L-DOPA during the first 3 years from disease onset. The variability of pharmacologic response in different patients affected by MSA probably depends on the relative degree of nigral, as compared to striatal, damage. When nigral damage is the main feature, and the putamen is relatively preserved, a better response to therapy is observed (12). In addition, the present study also indicates that an objective quantitative evaluation of the benefit produced by dopaminergic challenge is warranted before a patient is clinically classified as a poor responder to therapy. Indeed, 60% of the patients enrolled in our prospective study who subjectively reported a poor response to dopaminergic therapy were objectively found to have a detectable clinical response to the same drugs.

The present study also shows that some clinical features are significantly correlated with a high probability of having MSA, although none of them was invariably altered; they are useful pointers to differentiate MSA, when it initially presents with parkinsonian signs, from PD. The observation of the following signs in a parkinsonian patient clearly points to MSA: a rapid dis-

ease progression, a symmetric onset, no tremor at onset, a lack of response to L-DOPA (as measured objectively), and autonomic dysfunction (also if not overtly symptomatic). The suspicion is further supported when the occurrence of supranuclear gaze palsy, dementia, or axial dystonia, which are specific clinical markers for SROD (13,20) and are quite uncommon in MSA (25,29), are not observed.

The present study considered some clinical and laboratory features that can be easily evaluated by a neurologist with no particular expertise in movement disorders. Therefore, the multifactorial probability score used here may be adopted in general hospitals and in clinical practices as a simple means for a prognostic evaluation of parkinsonian patients. This score may be further improved by the use of newer imaging techniques such as single-photon-emission computed tomography (32) or positron emission tomography (5,10,14). In addition, electromyography of the external urethral and anal sphincters have been used to support the clinical diagnosis of MSA. A finding of neurogenic denervation is common in MSA patients and is rare in PD (9,21): this is because of a specific loss of anterior horn cells running from S2 to S4 (Onuf's nucleus), which occurs frequently in MSA. Unfortunately, these neurophysiological abnormalities appear not to be useful for the purpose of an early diagnosis of MSA, for they appear rather late during the course of the disease (25).

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