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CORRELATION OF CARDIOVASCULAR AUTONOMIC FUNCTION TESTS, MAGNETIC RESONANCE BRAIN IMAGING AND CLINICAL FEATURES IN SUSPECT CASES OF MULTIPLE SYSTEM ATROPHY

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Nine patients presenting with parkinsonian features and no other clinical abnormalities were studied. These patients were evaluated for dopaminergic responsiveness, for cardiovascular reflex autonomic function, and underwent high field magnetic resonance scan. A 0 to 5 point probability score was used to evaluate the possibility that parkinsonian signs were the presenting symptoms of multiple system atrophy (MSA). Five patients were considered at risk for having MSA: three of them were classified as possible MSA cases (score 2-3), two of them were classified as probable cases of MSA (score 4-5). In patients at risk for MSA, no specific pattern of combination of clinical and laboratory data was found; all patients had different combinations of positive findings.

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As defined by Graham and Oppenheimer in 1969 (1), multiple system atrophy (MSA) includes different neurological syndromes resulting in various combinations of parkinsonian, cerebellar, pyramidal and autonomic features. MSA accounts for four different clinical conditions: pure autonomic failure, Shy-Drager's syndrome, striatonigral degeneration, and sporadic adult-onset olivopontocerebellar atrophy (2). The complete neuropathologic picture shows atrophy of many regions of the central nervous system in a variety of overlapping combinations. Cell loss and gliosis are mainly found in the substantia nigra, in the corpus striatum, in the cerebellum and in the brain stem, while Lewy bodies are not constantly present (3,4).

A definite diagnosis of multiple system atrophy can be achieved only with *post mortem* neuropathologic examination. Therefore criteria for assessing a putative clinical diagnosis *in vivo* are required. A recent clas-

sification has been proposed by Quinn (2), who divided the suspect cases into two main subgroups: those with predominant parkinsonian and those with predominant cerebellar signs. He also set criteria for classifying cases as possible or probable forms of MSA. As a general rule, in patients presenting with parkinsonism, MSA should be suspected if the response to dopaminergic therapy is poor, particularly when autonomic failure, pyramidal or cerebellar signs are also present. The clinical diagnosis of MSA is a difficult task in those cases presenting just with parkinsonian signs. Therefore, the present research was undertaken in order to evaluate the possibility that patients presenting with non typical parkinsonian features, but no other neurological abnormalities, could be affected by MSA. We detected the occurrence of brain image abnormalities and of signs of autonomic dysfunction, which, in addition to the clinical evolution, could support a diagnosis of MSA in such patients.

METHODS

Nine patients (4 women and 5 men) with atypical parkinsonian features (as defined below), a disease of recent onset (less than 4 years), and no cerebellar or pyramidal signs were selected in the out-patient clinic for movement disorders. Patients presenting with supranuclear ophthalmoplegia were excluded. Atypical parkinsonian features consisted in: (a) a rapid progression of parkinsonian signs, with patients scoring at least 2.5 (Hoehn and Yahr's scale) within 3 years from onset, or (b) a poor response to standard dopaminergic therapy, as observed in clinical practice.

The patients were aged from 44 to 69 (average 57.4); at the time of evaluation the disease duration averaged 3 years (from 1.5 to 4), and Hoehn and Yahr's staging averaged 2.8 (from 2 to 4).

After admission to hospital, the clinical response to antiparkinsonian drugs was evaluated in each patient by assessing the variations of motor conditions from a baseline after the administration of single increasing doses of apomorphine (1.5, 3 and 4.5 mg) and of a single dose of levodopa and carbidopa (250/25 mg). The method has been described by Hughes, Lees and Stern (5). In the case of no response to the acute test, levodopa in association with carbidopa (500/50 mg daily) or with benserazide (400/100 mg daily) was started; patients were followed up as out-patients and re-evaluated two months later.

The electrocardiogram and the blood pressure were recorded in each patient before, during and after the following cardiovascular reflex tests (6). (a) Lying to standing: after 15 min of lying, the patients were asked to stand up quickly and to remain quiet for 2 min. (b) Deep breathing: the patients were asked to breath deeply for 1 min at a frequency of 6 breaths per min while lying. (c) Maximal hyperventilation for 30 s. (d) Valsalva manoeuvre: the patients were asked to expire, after a deep inspiration, against a pressure of 40 mm Hg for 10 s by blowing through a mouthpiece attached to an aneroid manometer. (e) Sustained handgrip: an isometric contraction of the dominant hand at 30% of the maximal strength for 5 min. (f) Bilateral alternated carotid sinus massage. (g)

Atropine test: 0.02 mg/kg was given i.v.

Each patient also underwent a high field (1.5 Tesla) magnetic resonance (MR) scan. Both T₁- and T₂- weighted spin-echo pulse sequences were used. In each examination, 5 mm thick axial, sagittal and coronal sections of the entire brain were obtained. Both T₁- and T₂- weighted pulse sequences were used for the morphological observation; T₂-weighted pulse sequences were used for the identification of hypointensity in the basal ganglia.

RESULTS

Clinical tests of dopaminergic responsiveness showed a normal response in six patients, while all the others had no response to dopaminergic therapy.

MR brain imaging allowed to visualise the basal ganglia and all other relevant brain centres. In two patients, non specific findings of vascular insufficiency were found. MR data were considered consistent with MSA when they showed a cerebellar or brain stem atrophy (7), or a hypointensity of the putamen on T₂-weighted images, as compared to the globus pallidum (8). A mild cerebellar atrophy was found in cases 8 and 9, while signal alterations in the putamen were never detected.

The probability of having MSA was evaluated with a 0 to 5 point score. Each patient received one point for each of the following conditions: (a) rapid progression of the disease; (b) abnormal autonomic function tests; (c) abnormal MR scan. Each patient received two points when poor or no response to dopaminergic drugs (as evaluated by means of the apomorphine and levodopa acute tests)

Table I - Probability score for multiple system atrophy.

Criteria	Score
Lack of dopaminergic responsiveness	2
Rapid progression of the disease	1
Autonomic failure	1
Abnormal MR picture	1

Total score: 0-1 no MSA; 2-3 possible MSA; 4-5 probable MSA.

was detected.

Patients with low scores (0-1) were artificially classified as not having MSA; in patients with scores of 2 or 3 the diagnosis was regarded as possible; patients who scored 4 or 5 were diagnosed as probable cases of MSA (Table I).

Based on this multifactorial scale, four patients were classified as not having MSA, three patients were classified as possible cases and two patients were given a diagnosis of probable MSA (Table II). The three patients classified as possible MSA cases scored 2 or 3 with various combinations of positive findings. Patient 5 had both features that were considered atypical for Parkinson's disease, but had normal autonomic tests and

MR scan; in patient 6 the disease progressed rapidly and autonomic tests were abnormal (Fig. 1), while the clinical response to drugs and MR scan were normal. Patient 9 responded to therapy; she scored 3 because all the other criteria were abnormal. Two patients received a diagnosis of probable MSA. In patient 7 both clinical criteria were fulfilled and autonomic tests were abnormal; since the MR scan was normal he scored 4. Patient 8 was found to have abnormalities in all the four items considered; therefore he scored 5.

It is interesting to remark that patients from 1 to 4 were included in the study since, as out-patients, they reported a poor response to dopaminergic therapy. In fact, upon ob-

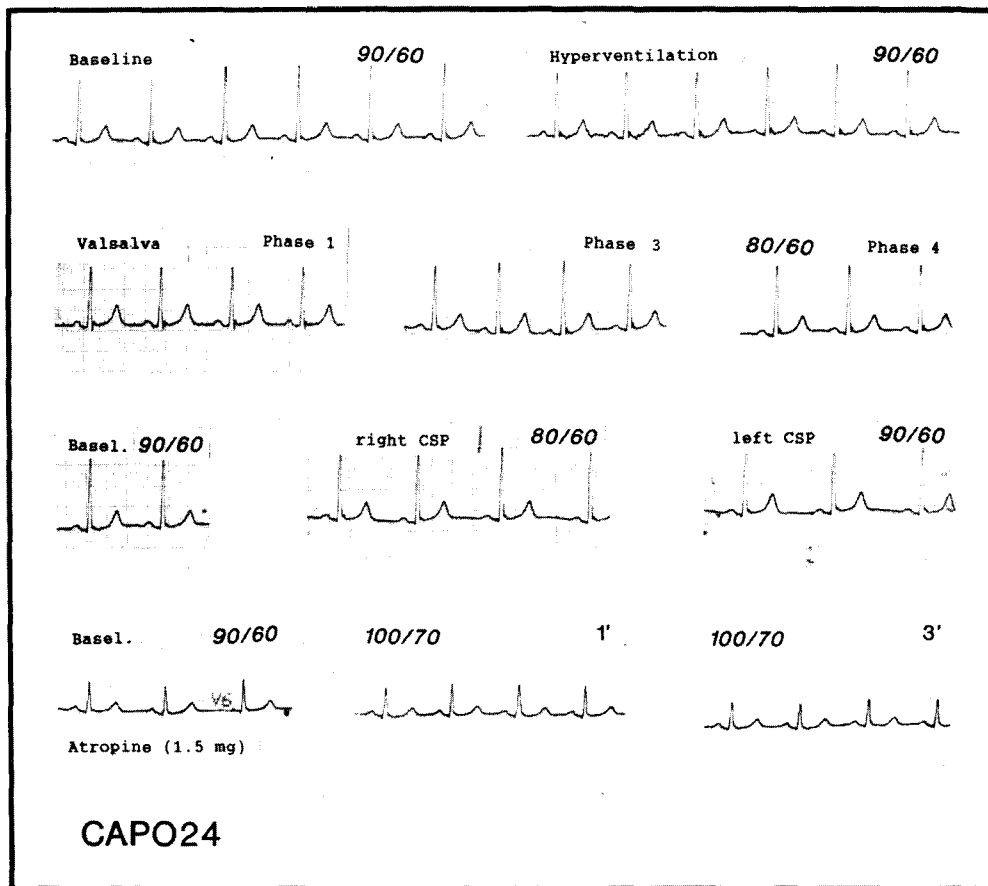


FIG. 1 - Cardiovascular autonomic function tests of patient 6 show no response to either sympathetic or vagal responses. Upper row: baseline electrocardiographic recording on the left, electrocardiographic recording after hyperventilation on the right. Middle-upper row: electrocardiographic recording during Valsalva manoeuvre. Middle-lower row: base-line electrocardiographic recording on the left, electrocardiographic recording after compression of the right (middle) and of the left carotid sinus (right). Lower row: baseline electrocardiographic recording on the left, electrocardiographic recording 1 min (middle) and 3 min (right) after the administration of atropine (1.5 mg i.v.). Blood pressure values are indicated by numbers. It is evident that none of these manoeuvres brings about variations of the electrocardiogram. (From *Fisiologia Clinica*, 21.06.90)

Table II - Synopsis of clinical findings.

Patient number	Age	Sex	Progression	Response to therapy	Autonomic failure	Magnetic resonance	Total score	MSA
1	60	F	-	-	-	-	0	No
2	56	M	-	-	-	-	0	No
3	53	M	-	-	-	-	0	No
4	44	F	+	-	-	-	1	No
5	69	M	+	+	-	-	3	Possible
6	66	F	+	-	+	-	2	Possible
7	52	M	+	+	+	-	4	Probable
8	69	M	+	+	+	+	5	Probable
9	48	F	+	-	+	+	3	Possible

+ indicates abnormal feature, - indicates a normal feature.

jective quantitative evaluation, they all resulted to be good responders to dopaminergic therapy. Since findings of autonomic tests and of MR scan were normal, the diagnosis of MSA was ruled out.

DISCUSSION

The definition of a probability score of MSA, which is based on clinical and laboratory items, stems from the observation that there is no specific clinical or laboratory parameter allowing to support a clinical diagnosis of MSA and to differentiate this disease from other parkinsonian syndromes. This choice was indirectly confirmed by the observation that none of the parameters considered in the diagnostic scale was consistently found in all patients receiving a diagnosis of possible or probable MSA.

First, a rapid progression of the disease can also be observed in patients affected by Parkinson's disease. Lack of response to dopaminergic therapy is also a non-specific feature of MSA presenting with parkinsonian symptoms. Indeed, patient 6, a 66-year-old woman who responded well to dopaminergic therapy, scored 2 on the basis of the rapid disease progression and of the finding of significantly abnormal cardiovascular reflexes (Fig. 1). Eight months after the study, this lady developed a symptomatic autonomic failure. As shown in two recent reviews of pathologically proven cases of MSA, between 33 and 40% of patients responded to levodopa

(9,10). Thus, although lack of response to dopaminergic therapy is very uncommon in Parkinson's disease (and has been therefore given the weight of a double score in this scale), it is not sufficient *per se* to rule out the diagnosis of the idiopathic disease. These observations indicate that an objective quantitative measurement of the responsiveness to dopaminergic drugs is always necessary before stating that a patient does not respond to dopaminergic therapy. With reference to autonomic failure, it must be considered that it is almost invariably found in MSA, but is not univocally associated with this clinical condition (11).

Analysis of the MR scan is a useful complement to clinical evaluation. The finding of putamen hypointensity in T₂-weighted scans was regarded as a specific feature of MSA by Olanow et al. (8). This feature has never been observed in our series. In two patients with no clinical signs of cerebellar dysfunction MR revealed a mild cerebellar atrophy. Patient 8 scored 5, because cerebellar atrophy was associated with the occurrence of all the features considered in the probability score. Thus, he was diagnosed as probably having MSA even though MR scan revealed no abnormalities in the basal ganglia. It is not yet clear whether putamen hypointensity occurs in all patients affected by MSA. Our data allow to hypothesise, however, that this feature is undetectable in the early stages of the disease and cannot, therefore, be used for the purpose of an early diagnosis. We are now performing a mor-

phometric study of the basal ganglia and cerebellum, in order to ascertain whether a reduction in the size of these brain nuclei correlates with the probability of having MSA.

The score used here is aimed at reaching a diagnosis of probability for MSA in patients presenting only with non typical parkinsonian signs. The main innovative feature of this probability score consists in its multifactorial nature. Recently, Quinn (2) proposed to classify suspect cases of MSA as possible or probable on pure clinical examination. In his view, probable cases were those in which cerebellar and pyramidal signs were combined with parkinsonian features. The present score is aimed, instead, at evaluating the probability of having MSA by using clinical and laboratory data for those patients who have no clinical signs of multiple system involvement.

The sensitivity of this probability score may be further improved. It has been reported recently that electromyography of the urethral and external anal sphincters is a useful tool for supporting the clinical diagnosis of MSA. Indeed, findings of muscular denervation are common in MSA patients and are not found in Parkinson's disease (12). We are currently evaluating whether this laboratory test may represent a new item to be considered in the probability score. The validation of this score will depend on the retrospective analysis of cases proven with autopsy findings. We figure that, after collecting about 20 patients and at least 10 autopsy reports, we will be able to quantify the reliability of this probability score.

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