A case of multiple system atrophy

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Abstract

The authors describe a case of multiple system atrophy in a 54 year-old man with dizziness, syncope and sexual dysfunction as the initial symptoms. Signs of Parkinsonism, dysautonomy and cerebellar dysfunction were shown on physical examination and autonomic function tests. Conservative treatment led to clinical improvement. A review of multiple system atrophy was made following this clinical case.

Key words: Multiple system atrophy, Parkinsonism, dysautonomy, cerebellar dysfunction.

Introduction

Multiple system atrophy (MSA) is a neurodegenerative disease which is characterized by extrapyramidal, dysautonomy and cerebellar symptoms. Each of these groups of symptoms may appear in isolation or in various combinations, leading to a highly variable presentation spectrum of the disease. The resulting diagnostic difficulty has led to underdiagnosis of MSA and overdiagnosis of the pathology that is most frequently confused with MSA: Parkinson's Disease (PD). Given that the clinical presentation, evolution and treatment are different for these two pathologies, recognition of MSA is important.

Clinical case

A white, 54 year-old male, an engineer, from Lisbon, was evaluated in November 2003 with dizziness, syncope and sexual dysfunction.

The patient presented clinically well until January 2001, when he began to report sporadic dizziness on effort, tiredness and decreased sweating on effort, and sexual dysfunction characterized by weak erection and absence of ejaculation. In July 2001, on a hot day, after eating a large meal accompanied by alcoholic drink, the patient had an episode of syncope while urinating in orthostatic position. In September 2001, after a long and tiring trip to an African country with a tropical climate, on arrival, he once again had syncope after urinating, also while standing. Around 6 months later he experienced dizziness on standing up.

About 3 months later, the patient began to experience increasing difficulty going down stairs, due to incessant, involuntary, rhythmic movements of the feet.

Personal antecedents include ischemic cardiopathy, and a coronary stent was inserted in 2000, following an episode of chest angina. His habitual medication consisted only of clopidogrel, at a dose of 75mg daily. The patient reports that he did not receive any other treatments, including beta-blockers.

The patient's family history was not relevant.

In the objective examination, patient presented a good general state, only the following aspects being altered: arterial hypertension marked in decubitus (200/102 mmHg), with a decrease to 104/52 mmHg, on assuming the orthostatic position. Heart rate (HR) in decubitus was 82 beats per minute (bpm), increasingly only to 89 bpm in orthostatism. Neurological examination showed no alterations in superior nervous functions (MMS score 30/30). The evaluation of cranial pairs revealed miotic and poorly reactive pupils. Both upper limbs showed resting tremor, increased muscle tonus and slight cogwheeling movement. In the motor coordination tests (finger-nose and heel-knee) bilateral cerebellar ataxia was evident; the rapid and alternating movements were small, irregular and disorganized. There was osteotendinous hyper-reflexia, which was more marked in the lower limbs, with an increased reflexogenous area and widespread clonus of the feet. Eye movements did not show any alterations.

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Received for publication on 06 February 06
Accepted for publication on 30 September 08

TABLE I

Laboratory results

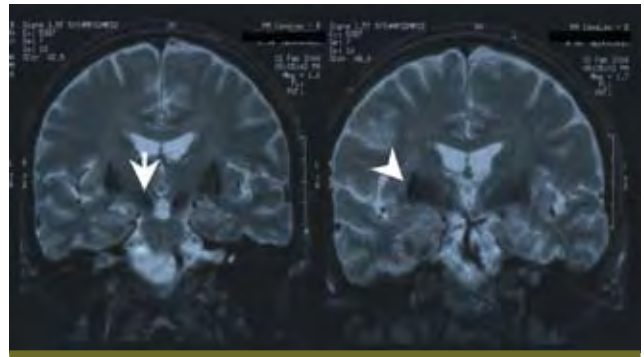
Glucose (mg/dL)	123
Urea (mg/dL)	35
Creatinine (mg/dL)	0.9
AST (U/L)	18
ALT (U/L)	19
Alkalyne phosphate (U/L)	44
Gama-GT	18
Sodium (mmol/L)	143
Potassium (mmol/L)	5.5
Chloride (mmol/L)	104
Calcium (mg/dL)	2.39
Phosphorus (mg/dL)	4.21
Magnesium (mg/dL)	2.2
Uric acid (mg/dL)	4.7
Serum iron (mcg/mL)	159
TIBC (mcg/mL)	412
Ferritin (ng/mL)	39.6
ß2-microglobulin (mg/L)	1.9
TSH (mcUI/mL)	1.2
fT3 (pg/mL)	3.5
fT4 (ng/dL)	2.0
Total proteins (g/dL)	68
Albumin (g/dL)	43,5
Globulins (g/dL)	24,5

Routine laboratory exams were normal *(Table I)*.

Functional evaluation of the Autonomous Nervous System (ANS) showed moderate dysfunction of the Parasympathetic Nervous System (PNS), adrenergic sympathetic dysfunction with a pathological drop in arterial pressure with orthostatism and cholinergic sympathetic dysfunction with a decrease in density of the sweat glands *(Table II)*.

The Tilt test showed a pathological drop in arterial pressure, heart rate and cardiac debit, with rapid passage from the orthostatic to the decubitus position.

Anal electromyography showed chronic loss of motor units in anal sphincter, compatible with denervation of these muscle fibers.



Cranial-Encephalic NMR. Arrow: Putamin and nigra substance hypointensity in T2 (SE), suggesting the deposit of paramagnetic substances (ferritin). Arrow head: Hypersignal range in the external edge of the putamin, suggestive of striatonigral degeneration.

FIG. 1

Magnetic resonance (NMR) showed images suggestive of deposits of paramagnetic substances (ferritin) in the putamen and nigra substance, and striatonigral degeneration *(Fig. 1)*.

The multiple neurological signs and symptoms can be organized into groups:

The dizziness, episodes of syncope, erectile dysfunction and hypohidrosis described by the patient, associated with hypoactive pupils and a pathological drop in Arterial Pressure with orthostatism (with small compensation of HR), all suggest a condition of autonomic dysfunction.

The difficulty reported by the patient in going downstairs reflects an extremely marked achilean clonus, which was subsequently also shown in the objective exam. This, together with the hypereflexia, is evidence of impairment of the pyramidal tracts.

The ataxia and the difficulty performing rapid and repeated movements (adiadochokinesia) are attributable to a cerebellar dysfunction.

The tremor, stiffness and cogwheel movement of the limbs are a set of symptoms which characterize Parkinsonism.

The only pathology that could be responsible for the simultaneous impairment of the autonomous nervous system (ANS), central and cerebral nervous system, and presents radiologically as the standard described in the NMR carried out on the patient, is multiple system atrophy.

TABLE II

Functional evaluation of SNA

	Reference values*	Patient values
Evaluation of adrenergic SNS		
ΔPO (mmHg)	-20	-63,3
ΔPE (mmHg)	+5 a +17	+3,3
Evaluation of cholinergic SNS		
Density of sweat glands in the hand (gl/cm^2)	200	140
Density of sweat glands in the feet (gl/cm^2)	160	88
Evaluation of SNPS		
R6	9	8,2
30:15	1,05	1,125
RV	1,3	1,05

ΔPO= AP variation with active orthostatism; ΔPE= PA variation with isometric effort; gl/cm^2= number of glands per square centimeter of skin; R6= variation in heart rate with deep breathing; 30:15= variation in heart rate with active orthostatism; RV= variation in heart rate with Valsalva maneuver
*For the patient's age range

The patient began symptomatic therapy with a diet high in water and salt, with the bed head raised 30° (for control of hypertension in decubitus), and fludrocortisone at a dose of 0.15 mg daily and amantadine, 100 mg every 12 hours.

The patient was also asked to use elastic stockings, but refused.

Three months after the start of therapy, the patient only had sporadic dizzy spells, and no tremor or new episodes of syncope. Since then, no progression of the disease has been observed that could be seen through the symptoms or examination of the patient.

THEORETICAL REVIEW

Introduction

Dejerine and Thomas were the first to use the term *olivopontocerebellous atrophy* (OPCA), in 1900, to refer to a degenerative disease that presented as cerebellous dysfunction and Parkinsonism.[1] 60 years later, Shy and Drager described a "syndrome characterized by the presence of multiple neurological deficits, particularly dysautonomy, ataxia and parkinsonism", with progressive and inexorable progression of an idiopathic nature.[2]

The knowledge acquired over time, in relation to the histopathology underlying this entity, has led to the designation of multiple system atrophy to include what was formerly known as *Shy-Drager syndrome*, OPCA, and *striatonigral degeneration (SND)*, which it is now known are merely clinical subtypes of the same underlying pathological process.

MSA is currently defined (by a panel of consensus led by the American Autonomic Society) as a "sporadic progressive disease in adults, characterized by dysautonomy, Parkinsonism and ataxia in any combination, and which is not explained by medicamentous effects or by known pathologies."[3]

When Parkinsonism is predominant, the term striatonigral degeneration (SND) is used. When there are abundant cerebellar manifestations, the term "sporadic olivopontocerebellar atrophy" is used. Finally, when autonomic dysfunction is predominant, the term Shy-Drager syndrome is used.

In clinical practice, the difficulty of making a differential diagnosis is common, as it is a disease that can present and evolve in different forms, according to the areas of the nervous system predominantly affected.

The need to distinguish between MSA and Parkinson's disease (PD) has been the object of particular attention, since a significant proportion of patients diagnosed as PD may present other non-extrapyramidal signs on neurological examination, and in autopsy, typical alterations of MSA.

Epidemiology[4]

MSA mainly affects men (1.4:1) and has a higher incidence in the 5th and 6th decades of life, occurring at the age of 53 years, on average.

In fact, various studies have revealed that 10 to 20% of patients diagnosed with PD have various non extra-pyramidal manifestations, and on autopsy, histopathological marks typical of MSA and not PD are seen.

Thus, the estimated prevalence of MSA in developed countries is 3 to 15 per 100000 people, reaching 29 per 100000 in the population aged over 55 years.

Etiology and Physiopathology

The etiology of MSA is currently not defined. There are only epidemiological data, which associates exposure to certain substances, such as organic solvents, plastic additives, pesticides and metals, with a higher risk of developing MSA, and smoking with a lower risk.

On macroscopic observation the cerebrum may be normal, but when there is severe olivopontocerebellar system degeneration, a decrease is seen in brain volume, cerebellar peduncules, bulb and protuberance, and discoloration of the pallidus, putamen and nigra substance.[5]

It was the description of the histopathological alterations in the nerve tissue of these patients that enabled the concept of nosological unit to be established for a set of syndromes (Shy-Drager, OPCA, SND) previously considered independent. On the other hand, it also enabled MSA to be understood as a separate pathology from other degenerative diseases of the SNC, such as Pure Autonomic Failure, progressive supranuclear palsy, Parkinson's Disease, and Alzheimer's Disease.

Histopathologically, MSA is characterized by neuronal and gliosis loss (non specific to degenerative alterations) and typical inclusions in the oligodendrocytes, in the absence of Lewy bodies or neurofibrillar aggregates.[6] The oligodendrocytic cytoplasmic inclusions (diagnostic mark of the disease) are eosinophilic and argyrophilic, and can be identified by immunological methods, as they are positive for ubiquitan and α-synuclein.[7]

These alterations are disseminated throughout the SNC in affected patients, but are predominant in some regions, which determine the dominant clinical approach.

Thus, degeneration in locations such as the putamen and nigra substance determine the extrapyramidal semiology (parkinsonism), degeneration of the intermediolateral medullary nuclei, Onuf's nucleus, and locus coeruleus lead to dysautonomy, and atrophy of the olivar, pontiac and cerebellar nuclei result in ataxia.[2] Other nuclei of the SNC, such as the pyramidal, may be affected, leading to more florid neurological semiology. The associative cortex is little affected.

The relationship of cause and effect between the typical histological alterations (notably the oligodendrocritic inclusions of α-sinuclein) and neuronal degeneration or reactive gliosis, is unknown, and there is some debate as to whether they are the cause, consequence or epiphenomenon. However, oligodendrocytic inclusions appear to precede neuronal alterations.

Clinical presentation

The disease is more common among middle aged or elderly individuals, manifesting as a variable combination of parkinsonism, dysautonomy and cerebellar and corticospinal dysfunctions.[8]

Characteristically, the signs of dysautonomy appear less than two years before the motor signals.

Some special characteristics of Parkinsonism of MSA may help in the differential diagnosis with PD in which bradykinesia and stiffness are predominant. Also, tremor is not very abundant, and the response to L-Dope is weak or transitory.[9] These findings, together with the presence of dysautonomy or other neurological non-extrapyramidal signs, strongly suggest a diagnosis of MSA.

During the course of the disease, symptoms of orthostatic hypotension, vesicle dysfunction, obstipation, anhydrosis, xerostomia and xerophalmia accumulate, resulting in anatomical dysfunction. Manifestations may also include imbalance, intention tremor and disartry by cerebellar dysfunction, and incontinence, spastic paralysis, dysphagia and dysphonia by pyramidal lesion. Finally, muscular atrophy and fasciculations may also remain, as a result of the peripheral neuropathy.

In the terminal phases, laryngeal dysfunction is responsible for marked morbidity and significant mortality, when it is complicated by pneumonia, asphyxia, sleep apnea or sudden death.

The associated superior cortical functions are normally preserved, therefore reactive depressive symptoms are common.[2,10]

Complementary tests

Some vegetative function tests enable the dysautonomies to be documented and prognostics to be established, given that the severity and distribution of vegetative deficits are predictive of the rate of pro-

gression of the disease.

Various autonomic tests, such as serum dosing of noradrenalin and other neurotransmitters, and their variations with postural alterations, are of diagnostic interest. Also the Tilt test, which evaluates the heart rate and arterial pressure with the postural alterations or physical activity, can be valuable for the diagnosis. Finally, the quantification of cholinergic secretions, through the sudomotor and lachrymal function tests (Schirmer test), and urodynamic tests, can also provide data.[2,10]

Magnetic resonance (MR) can show images which are characteristic of MSA, such as hypointensity of the putamen in T2 weighting, atrophy of the cerebral stem, and alterations in medium cerebellar peduncles signal.[11] These findings are very important for the differential diagnosis with PD. Also, positrons emission tomography (PET) with endovenous administration of F-dopamine shows long-term alterations in MSA, with a reduction in inflow rate in the caudate nucleus and putamen.[2]

Electrophysiological studies, such as electromyography of the anal sphincter, and the potentials evoked, also help in the diagnosis of this pathology, as they enable the pyramidal involvement to be documented, some of the upper tracts to be reached, such as the olivopontocerebellar tract, and preservation of associative cortical functions.[12]

Therapeutic

There is no intervention capable of modifying the natural history of the disease, therefore treatment is based only on symptomatic and general measures. The orthostatic hypotension can be improved by water and salt supplements,[13] pre-prandial coffee, external pressure prostheses, peripheral vasoconstrictor drugs, such as ephedrine and midodrine, or volemia retaining drugs such as desmopressin and fludrocortisone.[14] In patients who develop dysphagia, it is beneficial to adopt a soft diet with food supplements and possibly feeding by nasogastric probe. Finally, obstipation is also a recurrent and severe problem in this pathology, for which the therapy also includes general measures, such as a diet high in fiber, lactulose or microenemas and even intermittent manual extraction.[15]

The therapy for parkinsonism (L-DOPA) has only a slight response overall, in patients with MSA.

Support at the social, family and psychological levels is essential, as these patients gradually lose their functional capacities, so that they are no longer able to walk, eat or communicate, though their consciousness remains intact.[16]

Prognosis

The natural history of the disease is one of inexorable progression towards the accumulation of dysfunctions in multiple areas of the nervous system, and gradual functional incapacity of the patient. The appearance of dysartria and dysphagia are specific examples of signs of poor prognosis.[17] Total dependence occurs, on average, 5 to 8 years after the appearance of the first symptoms, and death follows soon afterwards[18] by laryngeal dysfunction, which predisposes to pneumonia and sudden death during sleep, or death by fatal arrhythmias (due to hypersensitivity and denervation). ■

References

1. Déjerine J, Thomas AA: L'atrophie olivo-ponto-cérébelleuse: Nouv Iconog Salpetriére 1900, 13:330-370.

2. Low P, Bannister R. Multiple system atrophy and pure autonomic failure. In: Low P. (Ed) Clinical autonomic disorders: evaluation and management. Philadelphia: Lippincott Raven. 1997:555-575.

3. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology 1996; 46:1470.

4. Vanacore N. Epidemiology of multiple system atrophy. Neurological Sciences 2001; 22:97-99.

5. Dickson DW, Lin W, Liu WK et al. Multiple system atrophy: a sporadic synucleinopathy. Brain Pathol 1999; 9:721-732.

6. Jaros E, Burn DJ. The pathogenesis of multiple system atrophy: past, present, and future. Mov Disord 2000; 15:784-788.

7. Spillentin MG. Filamentous alpha synuclein inclusions link MSA with Parkinson and dementia with Lewy bodies. Neur Sci Lett 1998; 251:205-208.

8. Wenning GK., Seppi K, Scherfler C et al. Multiple system atrophy. Semin Neurol. 2001; 21:33-40.

9. Colosimo C, Albanese A, Hughes AJ et al. Some specific clinical features differentiate multiple system atrophy (striatonigral variety) from Parkinson's disease. Arch Neurol 1995; 52:294-298.

10. Bannister R, Mathias CJ. Clinical features and evaluation of the primary chronic autonomic failure syndromes. In: Mathias, C.J., Bannister, R.(Eds). Autonomic failure: a textbook of clinical disorders of the autonomic nervous system. Oxford: Oxford Medical Publishers. 1999:307-316.

11. Bhottacharya K, Saadia D, Eisenkraft B et al. Brain magnetic ressonance imaging in multiple system atrophy and Parkinson disease: a diagnostic algorithm. Arch Neurol 2002; 59:835-842.

12. Gilad R, Giladi N, Korczyn AD et al. Quantitative anal sphincter EMG in multisystem atrophy and 100 controls. J Neurol Neurosurg Psychiatry 2001; 71:596-599.

13. Shannon JR, Diedrich A, Biaggioni I et al. Water drinking as a treatment for orthostatic syndromes. Am J Med 2002; 112:355-360.

14. Onrot J, Goldberg MR, Hollister AS et al. Management of chronic orthostatic hypotension. Am J Med 1986; 80:454-464.

15. Winge K, Rasmussen D, Werdelin LM. Constipation in neurological diseases. J Neurol Neurosurg Psychiatry 2003; 74(1):13-19.

16. Christine C, Aminoff M. Clinical differentiation of parkinsonian syndromes: prognostic and therapeutic relevance. Am J Med 2004; 117(6):412-419.

17. Muller J, Wenning GK, Verny M et al. Progression of dysarthria ans dysphagia in postmortem confirmed parkinsonian disorders. Arch Neurol 2001; 58:259:264.

18. Watanabe H, Saito Y, Terao S et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002;125:1070-1083.