



Parkinsonism and dysautonomia: Multiple system atrophy?

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ARTICLE INFO

Keywords:

Multiple system atrophy

Amyloidosis

Autonomic nervous system

A 51-year-old-man, with unremarkable personal and family history for neurological conditions and a positive family history for coronary artery disease, developed parkinsonian signs in December 2015, when micrographia and bilateral symmetrical bradykinesia were first noticed. Levodopa treatment (up to 300 mg/daily) did not provide significant changes in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and was poorly tolerated due to hypotension. In July 2016, he had repeated episodes of postural hypotension and syncope, causing a progressive decline in self-autonomy. Fludrocortisone (0.1 mg daily) was prescribed. By Fall 2016, the dysautonomia also included urgency and urinary incontinence, impotence, chronic diarrhea, occasional bowel incontinence and weight loss. In October 2016, ¹²³I-Ioflupane scintigraphy showed a bilaterally reduced putaminal binding (Fig. 1). Brain MRI was normal.

The patient received a diagnosis of probable multiple system atrophy with parkinsonian presentation (MSA-P) by a general neurologist; this was based on current diagnostic criteria dictating “a sporadic, progressive adult-onset disorder including rigorously defined autonomic failure and poorly levodopa responsive parkinsonism or cerebellar ataxia” [1]. These clinical features concurred in the absence of either supporting or non-supporting features, namely classic pill-rolling tremor, clinically significant neuropathy, hallucinations, late age at onset, family history, dementia, or white matter disease.

We first saw this patient in January 2017. He presented with mild bilateral rigid-bradykinetic parkinsonism with postural instability and dysautonomia, along with hypometric saccades, hypomimia, hypophonic voice and dysphagia. Muscles were generally weak and hypotrophic, especially distally in the limbs. Deep tendon reflexes were

normal. Sensory examination showed limb hypoesthesia and paresthesia. Parkinsonism was bilateral and asymmetric. There were no spinocerebellar or pyramidal signs, no inspiratory stridor at night, no REM sleep behavior disorder [2]. Acute levodopa administration in the morning did not improve the parkinsonian motor features. Without treatment, alternating tapping on two buttons spaced 30 cm apart produced 52 taps in 15 s (using either hand); 60 min after acute administration of 150/62.5 mg levodopa/carbidopa, there was no change (51 taps on the right and 50 on the left); after 30 additional minutes, the taps were still unchanged (52 and 54, respectively). Orthostatic hypotension was severely disabling and prominent, not allowing the patient to perform orthostatism for a full 3-min interval after standing up. A head-up tilt test to 75° was stopped after 1 min due to a syncope; blood pressure had decreased from 115/80 mmHg to 65/non-measurable. The Valsalva maneuver was abnormal, with loss of phase IV overshoot. The Composite Autonomic Symptom Scale 31 [3] score was 26.

Autonomic testing confirmed the presence of severe autonomic dysfunction, indicating cardiovascular reflex impairment with relevant orthostatic hypotension and orthostatic intolerance. We noticed that dysautonomia had developed quite fast and was progressing quickly, whereas the non-responsive parkinsonian motor features were relatively stable. This was at odds with earlier observations that fast-progressing MSA cases are characterized by a rapid deterioration of motor signs [2]. Furthermore, some of the clinical clues were unusual for MSA. The patient had chronic diarrhea, which is far less common than constipation in MSA [2]. Although ¹²³I-Ioflupane scintigraphy was consistent with MSA-P, other neuroimaging findings were not corroborative of MSA: brain MRI was unremarkable, and the ¹²³I-

Abbreviations: AL- λ , lambda light chains amyloidosis; MIBG, ¹²³I- metaiodobenzylguanidine; MSA, Multiple system atrophy; UPDRS, Unified Parkinson's disease rating scale

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<https://doi.org/10.1016/j.parkreldis.2019.05.005>

Received 1 August 2018; Received in revised form 9 April 2019; Accepted 2 May 2019

Available online 03 May 2019

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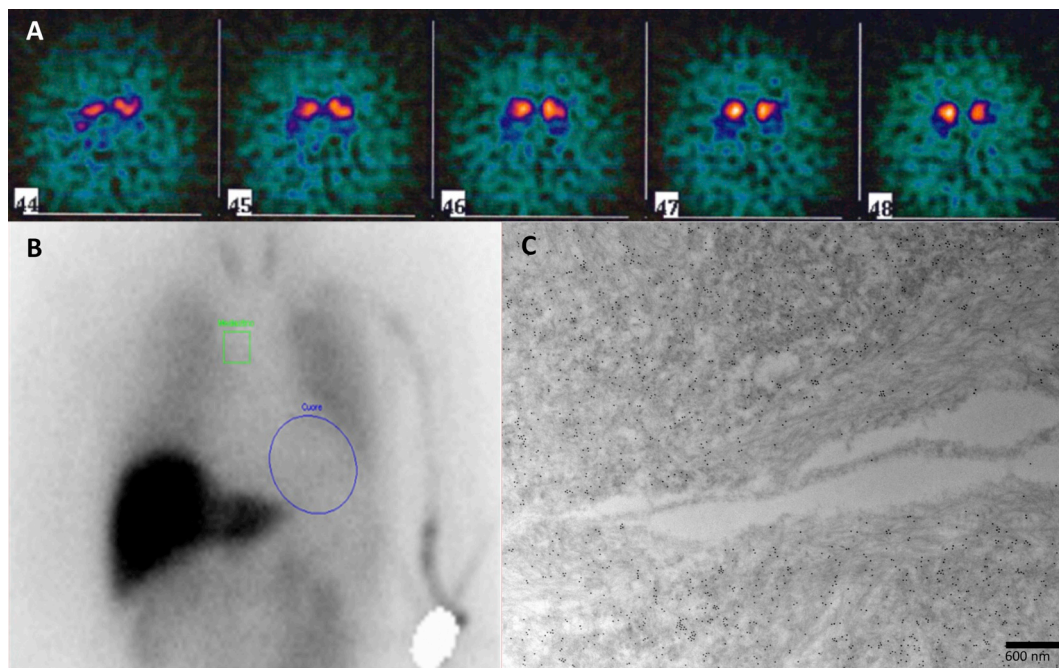


Fig. 1. The patient's DAT scan shows reduced presynaptic nigrostriatal dopaminergic binding (A). The MIBG scan shows absence of postganglionic sympathetic cardiac binding (B). A transmission electron microscopy of abdominal fat aspirate reveals abundant deposits of randomly disposed non-branched fibrils (8–10 nm in diameter) identified as amyloid fibrils distributed in the interstitium between adipocytes (C). Amyloid fibrils are intensely and specifically immunostained with a polyclonal anti-lambda light chains antibody. Immunoreaction is revealed by a secondary antibody conjugated to colloidal gold particles sized 15 nm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

metaiodobenzylguanidine (MIBG) scan showed severely reduced adrenergic cardiac binding (Fig. 1) [1,2]. Notwithstanding a disease course of more than 1.5 years, there were no supporting clinical diagnostic features for MSA, namely orofacial dystonia, anterocollis, camptocormia, contractures, snoring or inspiratory sighs, emotional lability, cold extremities, jerky tremor or polyminimyoclonus [1]. Since the patient started complaining of mild sensory symptoms in the lower limbs, we performed an EMG study that showed a diffuse axonal neuropathy. According to the current criteria, clinically significant neuropathy is not a supporting feature for a diagnosis of MSA [1].

Although the overall picture resembled that of an MSA-P, this patient was different from the spectrum of MSA presentation we had seen over the years. Neuropathy had never been a complaint, but we considered neurophysiological findings of sufficient clinical significance to meet the required criterion for a non-supporting feature (“clinically significant neuropathy”). An internal medicine workup then revealed a different diagnosis. Laboratory findings showed: coronary artery stenosis and infiltrative cardiomyopathy; renal failure with nephrotic syndrome; serum and urine monoclonal lambda (λ) light chains; elevated free λ light chain concentration in serum; anemia and reduced platelet count; elevated concentration of cardiac biomarkers NT-proBNP and troponin; echocardiographic signs of restrictive cardiomyopathy. The diagnosis of systemic amyloidosis was confirmed by an abdominal fat aspirate, showing the presence of λ -light chain deposits at immune-electron microscopy (Fig. 1). DNA analysis for mutations related to transthyretin amyloidosis was negative. A diagnosis of light chain amyloidosis (AL- λ) with cardiac, renal, peripheral and autonomic nervous system involvement was eventually made. The pattern of dysautonomia was type 1 according to a recent listing [4].

The patient received three cycles of melphalan and dexamethasone that produced a partial hematologic response. Dysautonomia and parkinsonism improved, and he was able to stand and walk by himself without the need for hypertensive agents. Later he was put on bortezomib, which was soon withdrawn due to the occurrence of corneal ulcerations, and finally on lenalidomide, which aggravated postural

hypotension and was also withdrawn. When reassessed by us in August 2018, the patient had stopped treatment for amyloidosis. There was a mild bilateral non-tremulous parkinsonism; hypophonia and bradykinesia had improved; a lateral bending of the trunk and slight blepharospasm had appeared; there was no postural instability and there were no cerebellar signs. Cognition was normal.

The early presentation of non-responsive parkinsonian features and dysautonomia led to a premature diagnosis of MSA. Oversimplification of diagnosis may occur if there is insufficient expertise on MSA. Diagnostic criteria may need to be applied by a specialist in order to be accurate; a glossary detailing definitions of supporting and non-supporting features would facilitate wider use of current diagnostic criteria [1]. Indeed, a variety of conditions may mimic MSA (Table 1), which are identified by accounting for non-neurological features, disease course, and individual supporting and non-supporting features. Clinical details can provide relevant clues; for example, the combination of distal muscle weakness and limb hypoesthesia with preserved reflexes may point to small fiber neuropathy, a finding observed in amyloidosis. Rapid worsening of dysautonomia, but not of parkinsonism, is also consistent with an alternative diagnosis, having been reported in patients with systemic AL amyloidosis [5].

Systemic amyloidosis has not been previously reported in association with parkinsonian features, which is a remarkable coincidence. Although no direct link between systemic amyloidosis and parkinsonism has ever been reported, it is accepted that AL amyloidosis deposition may take place in the brain, particularly in areas with a “leaky” blood-brain barrier, such as the choroid plexus, the infundibulum, the area postrema, the pineal body and the subfornical organ [6,7]. Whether amyloid can reach the midbrain or the basal ganglia from there is a matter of speculation. This case may illustrate the very uncommon coincidence of a non-levodopa responsive atypical parkinsonism or the unreported occurrence of parkinsonism in systemic amyloidosis, a dilemma that could only be solved by brain autopsy. The peculiar clinical associations observed in this case warn us not to miss potentially treatable medical conditions when suspecting an MSA.

Table 1
Main clinical features observed in medical conditions that may mimic multiple system atrophy. Early or predominant features are shown in bold. Clinical features of multiple system atrophy are presented for comparison.

Condition	Dysautonomia	Parkinsonism	Cerebellar dysfunction	Other features
Predominant autonomic involvement				
Pure autonomic failure	Orthostatic hypotension , anhidrosis, constipation, fixed pulse rate , erectile dysfunction.	Not observed until late stages (MSA-A).	Not observed until late stages (MSA-A).	REM behavior sleep disorder, hyposmia.
AL amyloidosis	Anhidrosis, orthostatic hypotension , urinary symptoms, sexual dysfunction, constipation or diarrhea (also alternating), gastroparesis.	Reported in this case.	Not reported.	Solid organ involvement (cardiac, renal, gastrointestinal), peripheral neuropathy .
Predominant parkinsonian involvement				
MSA presenting with parkinsonian features (MSA-P)	Urinary symptoms, orthostatic hypotension , erectile dysfunction , constipation, nocturnal hypertension, vasomotor and thermoregulatory failure.	Poorly levodopa responsive parkinsonism , usually rigid-akinetic, with early postural abnormalities. Rest tremor usually not pill-rolling.	Gait ataxia , limb ataxia.	REM behavior sleep disorder, orofacial dyskinesia, dystonia, disproportionate anterocollis, postural trunk abnormalities, respiratory stridor, sleep apnea, pyramidal tract signs, dysarthria, dysphagia, pseudobulbar signs.
Parkinson disease	Constipation , postural hypotension, urinary urgency, erectile dysfunction, excessive sweating .	Levodopa responsive parkinsonian motor features, rest tremor (often pill-rolling), rigidity, bradykinesia, fluctuations, dyskinesias.	Not reported.	REM behavior sleep disorders, hyposmia, executive dysfunction, fatigue.
Dementia with Lewy bodies	Constipation , urinary symptoms, orthostatic hypotension.	Bradykinesia, gait impairment.	Not reported.	Cognitive impairment , visual hallucinations , fluctuations of attention and wakefulness, REM behavior sleep disorder, sensitivity to neuroleptics, hyposmia.
Gaucher disease	Orthostatic hypotension, impaired cardiovascular reflex testing.	Tremor , bradykinesia , often responsive to levodopa, motor fluctuations.	Not reported.	Cognitive decline, pain , peripheral neuropathy, hyposmia.
Perry syndrome	Constipation, orthostatic hypotension, erectile dysfunction, urinary symptoms, anhidrosis.	Motor parkinsonism (often symmetrical), variable levodopa responsiveness.	Not reported.	Psychiatric features, weight loss, central hypoventilation .
Predominant cerebellar involvement				
MSA presenting with cerebellar features (MSA-C)	Urinary symptoms, orthostatic hypotension , erectile dysfunction , constipation, nocturnal hypertension, vasomotor and thermoregulatory failure.	Motor parkinsonism with poor response to levodopa.	Gait ataxia , limb ataxia, action tremor, nystagmus.	REM behavior sleep disorder, orofacial dyskinesia, dystonia, disproportionate anterocollis, postural trunk abnormalities, respiratory stridor, sleep apnea, pyramidal tract signs, dysarthria, dysphagia, pseudobulbar signs.
Spinocerebellar ataxias (mainly SCA 2, 3, 6 and 17)	Urinary symptoms, orthostatic hypotension, gastrointestinal symptoms.	Motor parkinsonism, variable levodopa responsiveness, parkinsonian tremor.	Gait ataxia , limb ataxia , other cerebellar features.	Pyramidal tract signs, peripheral neuropathy, REM behavior sleep disorder, cognitive decline. Positive family history.
Fragile X-associated tremor ataxia syndrome	Urinary symptoms, bowel incontinence, erectile dysfunction.	Motor parkinsonism (often unresponsive to levodopa), isolated rest tremor.	Gait ataxia , limb ataxia, postural tremor .	Peripheral neuropathy, cognitive decline (short-term memory loss, executive dysfunction), proximal muscle weakness in lower limbs. Positive family history.
Late onset Friedreich ataxia.	Vasomotor abnormalities, dyshidrosis.	Not reported.	Gait ataxia (cerebellar and sensory), limb ataxia, dysarthria, nystagmus, square wave jerks, dysmetria saccades.	Peripheral neuropathy, pyramidal signs, skeletal abnormalities, diabetes, cardiomyopathy. Positive family history.
Mitochondrial disease (e.g. POLG).	Urinary dysfunction, orthostatic intolerance, gastrointestinal dysmotility.	Parkinsonism.	Gait ataxia, limb ataxia, dysarthria.	Cognitive impairment, neuropathy, myoclonus, deafness, ophthalmoparesis, diabetes.

Abbreviations: MSA-A, Multiple system atrophy with autonomic presentation; MSA-P, Multiple system atrophy with parkinsonian presentation; REM, Rapid eye movement.

Financial disclosures

There are no relevant financial disclosures related to this manuscript.

Funding sources

None.

Acknowledgement

The authors are grateful to Dr. Laura Verga, who performed the histological analysis. No video accompanies this article, as the patient did not give consent to video recording.

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