

Case Report

Multiple system atrophy in a man misdiagnosed with parkinsonism

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ABSTRACT

Multiple system atrophy (MSA) is a rare sporadic, progressive, neurodegenerative disorder with autonomic deficits, with a yearly incidence of 0.000006%. MSA is often misdiagnosed as idiopathic Parkinson's Disease (PD). It may present with a combination of parkinsonian, autonomic, and cerebellar signs. From a prognostic point of view, accurate diagnosis is essential. Our patient was misdiagnosed as having PD, but after thorough workup was diagnosed as having MSA type Parkinson's. Because of this, the patient was put on supportive treatment for MSA. The authors strive to differentiate between the types of multiple system atrophy and its diagnostic criteria as well as differences between MSA and Parkinson's.

Keywords: Multiple system atrophy, Parkinson's disease

INTRODUCTION

Multiple system atrophy as an ailment was initially regarded as a singular disease with established subtypes. These subtypes are as follows: striatonigral degeneration (associated with parkinsonian symptoms), sporadic olivopontocerebellar atrophy (associated with cerebellar symptoms) and Shy-Drager syndrome (associated with autonomic dysfunction).¹ Following the second consensus statement regarding multiple system atrophy, the terminology was amended and standardized as follows: MSA with predominantly parkinsonian features (MSA-P) or predominantly cerebellar features (MSA-C).²

Multiple system atrophy is defined as a rare sporadic neurological disorder that is degenerative in nature and is characterized by progressive detrimental effects on the body's autonomic functions (namely bladder function, muscle control, blood pressure and breathing). The hallmark lesions of multiple system atrophy are glial cytoplasmic inclusions that are composed of α -synuclein.³ The cerebellar variant of MSA showcases the

inability of the afflicted to coordinate voluntary movements, whereas the Parkinson's variant of MSA showcases marked similarities to PD.^{2,3} Both variants will exhibit autonomic dysfunction, which manifests in the form of blood pressure dysregulation, urinary retention and random falls. The cause of MSA is unknown, with the median survival of afflicted individuals placed at 6 to 9 years following initial diagnosis.⁴

CASE REPORTS

A 54-year-old male presented to the emergency room with a bleeding facial laceration after a fall after reaching for an object which occurred at home. The patient had a history of recurrent falls during the preceding week. Medical history was significant for Parkinson's disease, urinary incontinence, recurrent urinary tract infections (UTIs) with extended-spectrum beta-lactamase (ESBL) producing infection, neurogenic bladder, and bilateral glaucoma. He reported six falls in the previous week, which occurred following rising from the sitting position. His blood pressure was reported to fluctuate while making recordings at home.

He received five stitches for his skin lesion, and the bleeding receded. The patient was adamant about being discharged. He was subsequently discharged against medical advice. Upon exiting the hospital, he sustained another fall, so he was readmitted, and thorough investigations were done.

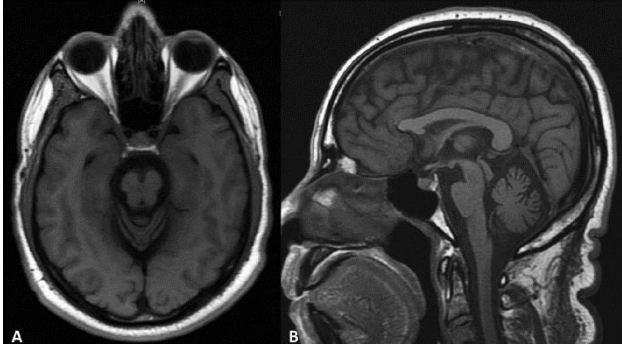


Figure 1: T1-weighted flair MRI revealed A. Pons and Vermis atrophy B. Moderate cerebellar/vermian folia atrophy with dilatation of the fourth ventricle.

History revealed a diagnosis of Parkinson’s back in his home country, for which he has been taking treatment for five years. However, he feels as though the medication has not had the same effect as when he first took the medication. On examination, he had mask-like facies, staccato speech, bradykinesia, and gait ataxia but with preserved motor strength in all limbs. However, on presentation he did not have pill rolling movements or resting tremor. He did however state that this does occur when he is at home. He also states that he does have dysphagia and is impotent. Blood pressure was 165/100 mmHg at the supine position, and 130/67 mmHg after sitting up for 10 minutes. Babinski’s sign was negative, and mental status examination was within normal limits.

Investigations

T1 weighted fluid-attenuated inversion recovery (FLAIR) MRI revealed moderate cerebellar atrophy with dilatation

of the fourth ventricle and cerebellar/vermian folia (Figure 1).

The atrophy did not correspond to the age of the patient. The ventricular system and subarachnoid spaces were typical. The gradient echo images demonstrated no intracranial hemorrhage, no mass effect or infarct was seen, and abnormal signal intensity was seen within the brain parenchyma. MR angiogram of the intracranial arterial circulation was normal. EKG and lab investigations were insignificant.

Chest X-ray revealed fluffy para-hilar airspace opacities suggesting aspiration which could be due to his dysphagia as seen in many cases of multiple system atrophy (Figure 2).

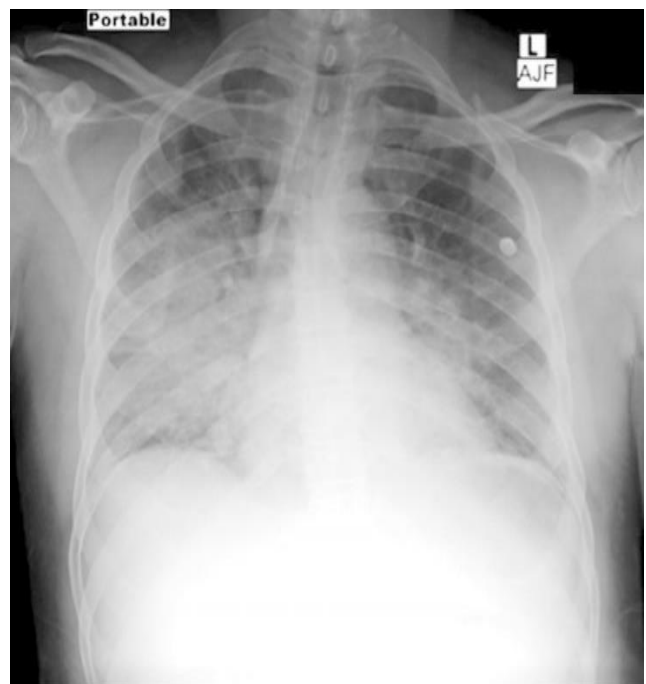


Figure 2: Chest X-ray showing bilateral fluffy perihilar infiltrates.

Table 1: Differential Diagnosis of MSA vs Parkinson's disease.

Characteristic	MSA	PD
Response to long term levodopa	Poor response due to loss of postsynaptic dopamine receptors. There will be an initial improvement in some patients but over 90% were subsequently unresponsive.	Good response
Effects on striatonigral transmission	Pre and postsynaptic	Pre-synaptic
Progression of symptoms and disability	Rapid	Slow
Abnormal speech and respiration	Affected speech in 30% of patients with dysarthria. Stridor, and abnormal aspiration can be seen in 60% of patients with MSA	Less commonly affected
Cytoplasmic inclusions	Glial inclusions; argyrophilic cellular inclusions in oligodendrocytes	Absent
Dopamine uptake on PET-caudate-putamen index	Decreased in putamen and caudate	Decreased in putamen and in caudate

Differential diagnosis

The most important differential diagnosis we faced was for Parkinson’s disease (Table 1).

It has been noted from studies that the accuracy of a clinical diagnosis of MSA is about 60-78 percent compared to autopsy findings.⁵ Based on our patient’s clinical features mainly his recurrent falls, orthostatic hypotension, recurrent UTIs due to autonomic failure, tremor and ataxia we had a high suspicion for MSA (Table 2).

Our patient however did not have the recognizable signs associated with MSA like the “hot cross bun sign” associated with the cerebellar variant or the slit like putaminal rim seen in parkinsonian variant. This absence of signs derailed our diagnosis at first but after further research we found that these signs are not specific nor were they necessary for a diagnosis according to the second consensus statement on the diagnosis of multiple

system atrophy by Gildmen et al. Following these diagnostic guidelines (Table 3) we diagnosed our patient as having probable MSA.

Table 2: Clinical Diagnostic Criteria.

Autonomous and urinary dysfunction	Orthostatic hypotension* urinary incontinence impotence dysphagia
Cerebellar dysfunction	Gait ataxia* Extremity ataxia
Parkinsons	Bradykinesia* Rigidity Tremor
Corticospinal tract dysfunction	Hyperreflexia Extensor plantar response
Posture	Anterocollis Camptocormia

*Are required for diagnosis

Table 3: Diagnostic criteria for definite probable, and possible multiple system atrophy (MSA) by Gilmen et al.

Definite	Neuropathological demonstration of α -synuclein-positive glial cytoplasmic inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures A sporadic and progressive adult onset (>30 y) disease characterized by the symptoms below
Probable	A sporadic, progressive, adult (>30 y)–onset disease characterized by: 1) Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mm Hg diastolic and 2) Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or a cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)
Possible	A sporadic, progressive, adult (>30 y)–onset disease characterized by: 1) Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or 2) A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and 3) At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and 4) At least one of the additional features shown in the red flags
Red Flags	1) Possible MSA-P or MSA-C o Babinski sign with hyperreflexia o Stridor 2) Possible MSA-P o Rapidly progressive parkinsonism o Poor response to levodopa o Postural instability within 3 y of motor onset o Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction o Dysphagia within 5 y of motor onset o Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum o Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum 3) Possible MSA-C a. Parkinsonism (bradykinesia and rigidity) b. Atrophy on MRI of putamen, middle cerebellar peduncle, or pons c. Hypometabolism on FDG-PET in putamen d. Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

Table 4: Classification of MSA-P vs MSA-C.

MSA-P	Predominantly parkinsonian symptoms	Difficulty in moving, shuffling gait, resting tremor, rigidity, increased pitch and quiver in speech, and lack of facial expression	Degeneration on MRI Putamen, middle cerebral peduncle, cerebellum Can see “Slit like Putaminal Rim”
MSA-C	Predominantly cerebral symptoms	Difficulty coordinating walking and hand movements, cerebellar scanning speech, and eye movements	Degeneration on MRI ventral pons, olives, cerebellum can see “Hot Cross Bun” sign

Differentiating between the two types of MSA was yet another challenge in diagnosis as there are many similarities between both. However, since our patient had more parkinsonian symptoms, we felt he should be diagnosed as MSA-P based on clinical observations (Table 4).

The other major differential we faced was supranuclear palsy as it is very difficult to distinguish between it and MSA during life.⁶ However guidelines state that vertical

Treatment

He continued his home treatment on carbidopa-levodopa 25-100 mg tablets even though he stated that he was feeling a decreasing effect from it as compared to prior, and cefpodoxime prophylactically for his recurrent ESBL UTIs. Alfuzosin 5 mg with fludrocortisone acetate 10 mg was given for his autonomic symptoms. His glaucoma home regimen of latanoprost eye drops and dorzolamide/timolol eye drops were continued.

Outcome and follow-up

General education for avoiding repetitive falls was provided, and physical rehabilitation was recommended. The patient was advised a helmet and a wheelchair to prevent further injury from falling. As undiagnosed depression is prevalent in a majority of cases of MSA the patient was advised for an outpatient appointment with a psychiatrist.

The patient continued to follow up with his primary care provider for a year. His tremor has worsened but other symptoms have remained stable.

DISCUSSION

Multiple system atrophy is a sporadic progressive neurological disease with no established genetic or environmental cause.⁷ In cases where parkinsonian symptoms predominate, it is referred to as MSA-P, and when cerebellar symptoms predominate, the disorder is referred to as MSA-C. Clinical features can manifest as a combination of cerebral signs, autonomous nervous system dysfunction, Parkinson's, and corticospinal tract involvement.⁸

MSA affects multiple systems hence the name, but the most common presenting symptoms are lightheadedness, dizziness, and recurrent falls. Some patients will also eventually present with difficulty in initiating movement, rigidity, and urinary incontinence. The symptoms can change during the course of the disease, therefore, the determination of either MSA-P or MSA-C is based on the predominant symptom at the time of diagnosis.⁹ The diagnosis of MSA is not based on imaging but rather on its clinical presentation, so a high degree of suspicion is needed. Levodopa should be tried if early onset Parkinson's to check responsiveness. Imaging can be used to support the diagnosis, as well as urethral or anal sphincter electromyography.¹⁰

In a meta-analysis of 433 cases of MSA the mean age of onset was 54 years.¹¹ In Asian patients, the predominant type is MSA-C, while European patients have MSA-P.¹² Gilman et al., a second consensus conference on MSA, which was held in 2007, revised the diagnostic criteria making the diagnosis of probable MSA simpler, and requiring at least one feature suggesting autonomic dysfunction. There was an addition of other factors for the diagnosis of possible MSA, and red flags were introduced as other factors helpful in the diagnosis of MSA.¹³

The prognosis of MSA is rather dire as the standard progression of the disease is much faster than that of Parkinson's usually taking between 1 to 18 years.¹⁴ In retrospective studies the median times to disease onset to disability are only a few years. From onset of disease to autonomic dysfunction is 2.5 years, needing a walking aid is 3 years, wheelchair bound is up to 5 years and bed ridden is up to 8 years.¹⁵ The median onset of death is 6 to 10 years but survival can vary from each individual as some live 15 years and beyond.¹⁶

The treatment of MSA is mainly symptomatic as there are no disease modifying or neuroprotective medications available. A major problem in MSA patients is depression and thus should be appropriately treated as well. Physical and occupational therapy is also needed for most patients. Even Though the levodopa response is varied many authors agree that there should be a trial done to check for responsiveness.¹⁷ Fludrocortisone acetate is the treatment of choice for orthostatic hypotension due to autonomic dysfunction.¹⁸ There are

currently methods in clinical trials such as sertraline, a vaccination against an epitope similar to alpha-synuclein and the drug Verdiperstat.¹⁹

Parkinson's and MSA are quite similar, which can lead confusion among physicians trying to make a diagnosis clinically. MSA typically shows a younger age of onset, and most patients are likely diagnosed with Parkinson's first, but over time, the severity and extent of change of symptoms can allow for a change in diagnosis to MSA. In the early stages of disease, differentiation between MSA and Parkinson's can be difficult.²⁰ Patients suffering from MSA often show sleeping disorders like snoring, apnea, REM sleep behavioral disorders which are less common in Parkinson's. There is mild loss of cognitive inability but frank dementia-like Parkinson's is uncommon. The average time from the beginning of symptoms to the first fall is much longer in Parkinson's.²¹ The response to levodopa is very characteristic, as it is very effective in Parkinson's but in MSA there will initially be a response, however, there is no long-term benefit.²² These slight differences are often used by clinicians to differentiate Parkinson's from MSA.

In literature there are not many cases documenting multiple system atrophy and most cases use clinical imaging as their main diagnostic tool but this should not be the case. Clinical imaging should be supportive but not ultimately necessary to make a probable diagnosis of MSA. In this current case, the diagnosis of the patient's disease was not made apparent, as was previously diagnosed as having Parkinson's. His subsequent follow-ups, therefore, were only for Parkinson's as no one questioned the diagnosis even though the patient had experienced long-term urinary incontinence with multiple episodes of bacterial infection. His standing and prone blood pressures were 35/33 mmHg, which was never checked before his hospital visit. The previous finds suggested autonomic dysfunction, but was never caught by his prior physicians. The patient had a positive Romberg test, and was also unstable with his finger nose test, which meant he had some cerebellar signs. The MRI also showed mild cerebellar, and pontine atrophy which supported the diagnosis of MSA. The patient has suffered from this disorder for many years without knowing the diagnosis.

CONCLUSION

Multiple system atrophy is a diagnosis based on clinical suspicion and physicians should follow the guidelines written. Any patient with recurrent falls, orthostatic hypotension or autonomic bladder presents MSA should be included in the differential diagnosis to differentiate between MSA and Parkinson's the first step should be a levodopa trial to see its effectiveness and due to the high rate of complications associated with MSA an early diagnosis would allow patients to get treatment which would improve quality of life.

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