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TITLE: A 68-year-old female with probable multiple system atrophy

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SUMMARY

We present the case of a 68-year old woman with Multiple System Atrophy (MSA). Our patient first presented to the Emergency Department (ED) of a community hospital complaining of dizziness when standing from a supine or seated position. A detailed history uncovered helpful clues to her diagnosis; most importantly, she was being followed at another hospital for progressive cerebellar ataxia and a constellation of other neurologic symptoms that had been present for nearly ten years. That hospital's working diagnosis was possible MSA.

MSA is a rare and progressive neurodegenerative disease with an incompletely understood etiology, although it is believed to result from abnormal protein accumulation in the brain. Because definitive diagnosis can therefore only be made at autopsy, physicians must rely on specific clinical findings to make either a possible or probable diagnosis. Essential findings include autonomic dysfunction and either medication resistant parkinsonism or cerebellar ataxia. Although our patient had experienced cerebellar ataxia for a decade, autonomic dysfunction in the form of orthostatic hypotension was new at the time of presentation in the ED. We use this delay between the onset of the ataxia and autonomic dysfunction to illustrate the potential challenges in diagnosing MSA.

From the ED, our patient was admitted to a telemetry unit at the hospital with a goal of treating her orthostatic hypotension. Because there is no cure for MSA, management of the disease is directed at its symptoms. There are several recommended pharmacologic and non-pharmacologic therapies for the orthostatic symptoms experienced by our patient, but response to medication varies considerably. It took nearly seven weeks of adjusting various medication combinations and doses to reduce our patient's symptoms to a level where she could safely resume activities of daily living. Moreover, our patient's hospital stay was complicated by factors often associated with autonomic dysfunction; in particular, she was diagnosed with a urinary tract infection secondary to catheterization and physical deconditioning secondary to decreased ambulation. This extended hospital stay helps illustrate the potential challenges associated with managing the symptoms of MSA.
MSA is an incompletely understood neurologic disease that can be difficult to both
diagnose and treat. Symptoms are progressive and variable, but in general have a
significant impact on the day-to-day life of those affected. Effective management
requires a high degree of clinical suspicion for early diagnosis and pharmacologic
versatility for symptomatic treatment
ABSTRACT

Introduction
Multiple System Atrophy (MSA) is a rare, progressive neurodegenerative disease that encompasses elements of cerebellar abnormalities, parkinsonism and autonomic dysfunction. Autonomic dysfunction classically manifests as orthostatic hypotension and is present in all forms of MSA. While MSA can only be definitively diagnosed post-mortem, a probable diagnosis is obtained clinically. There is no cure for MSA and patients are managed symptomatically. Different symptoms vary greatly in their response to pharmacotherapy, which makes management a challenge.

Case Report
We present the case of a 68-year old woman with probable MSA. Our patient first presented to the ED of a community hospital complaining of dizziness when standing from a supine or seated position. On questioning it was learned that she was being followed at another hospital for possible MSA. Her orthostatic symptoms proved refractory to treatment with midodrine, so she was eventually started on fludrocortisone; this greatly reduced her symptoms. Early in her hospital stay, our patient also began experiencing urinary incontinence. This was effectively managed with catheterization; however, our patient’s hospital stay was prolonged due to a urinary tract infection and physical deconditioning.

Conclusion
Our case illustrates some of the many challenges associated with both diagnosing and managing MSA. We wish to reinforce the high-level of clinical suspicion required to diagnose MSA and the therapeutic resilience and pharmacologic versatility necessary to manage symptoms.

Keywords: Multiple System Atrophy, Shy-Drager Syndrome, Orthostatic hypotension, Autonomic dysfunction
INTRODUCTION

We present the case of a 68-year-old female who is being followed at the ataxia clinic of another institution for progressive cerebellar ataxia and a constellation of other neurologic findings that have progressed over the previous ten years. The working diagnosis at that institution is Multiple System Atrophy; however, until her presentation at the emergency department (ED), she had not experienced any symptomatic orthostatic hypotension. Current expert opinion posits that although definitive diagnosis of MSA requires the presence of protein accumulation around glial cells seen on autopsy, a probable diagnosis requires autonomic failure and poorly levodopa-responsive parkinsonism or cerebellar ataxia [1]. Highlighted in this case, then, is the potential challenge associated with diagnosing MSA. Although some elements of MSA such as motor symptoms are resistant to pharmacologic therapy, other elements may be managed medically [2]. Our patient’s presenting complaint was orthostatic hypotension, and studies have shown that certain medications do have a role in ameliorating this symptom [3]. However, our patient’s hospital stay was complicated by several factors related to MSA and thus also serves to illustrate some of the challenges associated with management of this disease.

CASE REPORT

A 68-year old African American female presented to the emergency department complaining of persistent dizziness over the previous three days. She stated this dizziness was most pronounced when she stood up and that due to a change in medication approximately two weeks prior, she had been drinking less than normal. On questioning, it was discovered that she was being followed at a large research institution for progressive cerebellar ataxia for the previous three years. The working diagnosis at that institution was Multiple System Atrophy, formerly known as Shy-Drager Syndrome.

In addition to her progressive cerebellar ataxia, her past medical history was significant for seizures, eye-movement abnormalities, wide-based gait, dysmetria, postural tremor, mild incontinence, and bilateral paresthesia of both upper and lower
extremities. These symptoms had been gradually worsening over the past ten years, however, were not evident on presentation in the ED. She was also being managed medically for hypothyroidism and diabetes. Her surgical history was significant for a left hemi-colectomy, secondary to colonic volvulus more than fifteen years ago. Her family history was non-contributory. She had no known allergies and had a 20-pack year history of smoking, but quit approximately 27-years prior. At the time of admission, she was living at home with her husband. Following a work-up in the emergency department, the patient was admitted to the telemetry floor for management of dehydration and orthostatic hypotension.

On the telemetry floor, she was started on 5mg midodrine PO TID, but after two days of poor response to the medication, her dose was increased to 10mg. On hospital day four, she was transferred to a sub-acute floor so that her medications could be optimized and she could begin physical and occupational therapy secondary to a chronically deconditioned state. Her hospital stay, however, was prolonged due to number of issues. First, her orthostatic hypotension proved resistant to pharmacotherapy. Despite thigh-high compression stockings, a high-salt diet and rising slowly from bed, our patient continued to experience symptomatic orthostatic hypotension even on 10mg midodrine PO TID. Second, she experienced rebound hypertension due to the midodrine. This was significant enough to require a reduction in the midodrine to 5mg TID, on day 11. Throughout this period, the patient also experienced urinary retention with post-void residuals occasionally in excess of 500mL. This prompted Foley catheterization, however on day 13, the patient was diagnosed with a multi-drug resistant catheter associated urinary tract infection (CAUTI). This spectrum of complications is common amongst patients with MSA [4]. On hospital day 24, the diagnosis of MSA was made and the decision to add fludrocortisone 0.1mg PO Qday to her treatment followed. Her orthostatic hypotension responded reasonably well to fludrocortisone and the patient’s rehabilitation continued on the sub-acute floor. On hospital day 35 the midodrine was discontinued. Her mean arterial pressure is presented over the course of her stay in Figure 1.
Despite a slow recovery, the patient’s presenting symptoms gradually improved; over the course of weeks, she regained the ability to ambulate independently and experienced minimal dizziness on standing. Her urinary retention remained, while the other pre-existing neurologic conditions did not surface clinically. However, it was decided that she could be managed on an outpatient basis in conjunction with a neurology follow-up. She was subsequently discharged on hospital day 45.

DISCUSSION

This case serves to underscore the potential challenges of diagnosis and management of a patient with MSA. MSA is a rare condition, with an incidence rate in the United States of approximately 3 per 100,000 individuals over the age of 50 [5]. MSA encompasses several progressive neurodegenerative disorders, including Shy-Drager Syndrome, striatonigral degeneration, and olivopontocerebellar atrophy [6]. In striatonigral degeneration (termed, MSA-P) parkinsonian symptoms predominate, while in olivopontocerebellar atrophy (termed, MSA-C) cerebellar ataxia predominates. The predominate feature in Shy-Drager Syndrome is autonomic dysfunction and it is expressed to varying degrees in both MSA-P and MSA-C. These three conditions share a common, although incompletely understood etiology of alpha-synuclein accumulation in glial cells [7]. Consequently, the manifestations of MSA in a single patient may incorporate elements from all three subtypes. For instance, our patient presented to the ED with orthostatic hypotension, a finding classically associated with Shy-Drager; however, her initial clinical manifestation and the symptom which initiated specialist care was ataxia, the classic finding in MSA-C.

Due to the neurodegenerative etiology of MSA, the disease can only be definitively diagnosed on autopsy. However, an expert panel convened in 2007 and produced a second consensus statement on the diagnosis of MSA that concluded probable MSA required a sporadic, progressive adult-onset disorder including rigorously defined autonomic failure and poorly levodopa-responsive parkinsonism or cerebellar ataxia [8]. The same panel published tables for aiding in the diagnosis of probable MSA (Table 1) and possible MSA (Table 2), as well as additional features supporting
possible MSA-P and MSA-C specifically (Table 3) [9]. Our patient’s clinical presentation in the ED supported a diagnosis of probable MSA-C. Studies have shown that Computerized Tomography (CT) is of limited value in the diagnosis of MSA; in fact, when the diagnosis of MSA can be made clinically, as was the case in our patient, the role of CT imaging is best suited to rule out intracranial pathologies, such as tumors [10]. For this reason, CT imaging was ordered for our patient. It demonstrated mild generalized atrophy and patchy, non-specific periventricular white matter hypoattenuation. These are presented as Figures 1 and 2. Due to the non-specific nature of the CT and clinical diagnosis of MSA-C, we determined that no further cranial imaging was warranted.

While diagnosis of MSA is a challenge, so too is the disease’s management. No effective disease-modifying or neuroprotective treatment is currently available for MSA [11]. Indeed, treatment is directed at individual symptoms and responses vary greatly. For instance, the motor symptoms associated with MSA-C and the bradykinesia and rigidity associated with MSA-P are both typically resistant to pharmacologic treatment [12]. Although there are clinical trials in phases II and III currently underway, current management of these symptoms focus on physical and occupational therapy. Modern technology may be adapted to facilitate some activities of daily living. For instance, to address our patient’s dysgraphia secondary to ataxia, we took advantage of her smartphone’s voice-to-text features to make lists and encouraged her to practice typing, which she was still able to do reasonably well. Unfortunately, MSA is still progressive and even these solutions will eventually prove inadequate without medical intervention.

Even without a cure, and despite resistance to pharmacotherapy, some symptoms are amenable to medical therapy. The characteristic orthostatic hypotension common to both MSA-P and MSA-C is a result of autonomic dysfunction and unlike the motor symptoms, may respond to pharmacotherapy [13]. Current guidelines for the treatment of orthostatic hypotension in MSA recommend the corticosteroid volume expander fludrocortisone (brand name Florinef®, manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08540 USA) and the α1-receptor agonist midodrine. The U.S. Food and Drug Administration also recently approved the
synthetic amino acid precursor Droxidopa (Lundbeck Inc. 6 Parkway North, Deerfield, IL 60015) for treatment of these symptoms [14]. This orally administered medication is converted to norepinephrine in the body. The enzyme aromatic amino acid decarboxylase is responsible for this conversion and is so ubiquitous that systemic norepinephrine levels increase even in the absence of failing postganglionic sympathetic neurons [15]. We use the case of our patient’s presenting complaint and the subsequent challenges achieving adequate orthostatic blood pressure control to illustrate MSA’s variable response to pharmacotherapy. Despite IV rehydration in the emergency department, our patient continued to suffer from orthostatic hypotension. Once on the telemetry floor, 5mg midodrine PO TID was started. Midodrine represents a first-line pharmacologic therapy in the treatment of orthostatic hypotension [16]. Our patient’s average supine to standing orthostatic drop in systolic blood pressure was 58mmHg and her drop in diastolic blood pressure was 25mmHg during this period and she remained symptomatic. Given these findings, the decision was made to increase the midodrine dose from 5mg to the maximum recommend 10mg TID. Although she initially responded with significant rebound hypertension (169/94mmHg one day after increasing the midodrine dose, illustrated in Figure 3), over the following 23 days, the average recorded orthostatic systolic blood pressure drop was 34mmHg and the average diastolic blood pressure drop is 16mmHg. This was achieved by titrating the dose of midodrine down from 10mg to 5mg again and eventually up to 7.5mg. The patient’s symptoms improved, but she still complained of occasional dizziness. After the diagnosis of MSA was made, the patient was started on fludrocortisone 0.1mg PO Qday. Fludrocortisone is another first line therapy used in the treatment of orthostatic hypotension, particularly in cases associated with MSA [17]. In our patient, the average orthostatic systolic and diastolic blood pressure drops were smaller on fludrocortisone: 19mmHg and 5mmHg, respectively. These values are presented in Table 4. Of note, our patient also reported ‘much less dizziness’ after starting fludrocortisone and tolerated increasing amounts of physiotherapy. Given our patient’s positive response to Fludrocortisone and the much higher cost of
Droxidopa, the recently FDA approved medication was not considered necessary in our patient’s medical management. Notwithstanding the challenges of obtaining effective pharmacotherapy to treat orthostatic hypotension in MSA, non-drug therapies have also been shown to improve symptoms. These therapies include abdominal binders, compression stockings, increased salt intake, and taking care to rise slowly from a horizontal or seated position [18]. The latter three therapies were implemented throughout our patient’s hospitalization.

CONCLUSION

MSA is a rare and progressive neurodegenerative disorder that encompasses elements of three subtypes: MSA-P with parkinsonian symptoms predominating, MSA-C with cerebellar symptoms predominating and Shy-Drager, which classically presents with autonomic dysfunction and is present in varying degrees in both MSA-P and MSA-C. There is no cure for MSA and at present, it can only be diagnosed definitively at autopsy. Instead, a probable diagnosis is typically made clinically. Current medical management of the disease is aimed at improving symptoms; although some symptoms, such as the motor symptoms of MSA-C and MSA-P, are generally resistant to medical therapy.

Although our patient presented to the ED with a working diagnosis of MSA from another institution, her case illustrates the challenges of making a diagnosis of MSA, as well as managing the associated orthostatic hypotension. It also highlighted some of the potential complications of prolonged MSA-associated hospitalization, including physical deconditioning and CAUTIs. We therefore wish to reiterate that a high-level of clinical suspicion is required to diagnose MSA and that therapeutic resilience along with pharmacologic versatility are key to symptomatic management.

CONFLICT OF INTEREST

The authors declare no conflict of interest.
AUTHOR'S CONTRIBUTIONS

Kidnie RT
Group 1- Conception and design, acquisition of data, analysis and interpretation of data,
Group 2- Drafting the article, critical revision of the article and
Group 3- Final approval of the version to be published.

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Group 2- Critical revision of the article, and
Group 3- Final approval of the version to be published

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Group 1- Conception and design,
Group 2- Critical revision of the article, and
Group 3- Final approval of the version to be published

Nicklas RD
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Group 2- Critical revision of the article, and
Group 3- Final approval of the version to be published

Rangarajan R
Group 1- Conception and design, acquisition of data,
Group 2- Critical revision of the article, and
Group 3- Final approval of the version to be published

Wenning GK
Group 1- Conception and design,
Group 2- Critical revision of the article,
Group 3- Final approval of the version to be published
REFERENCES


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<th>No.</th>
<th>Reference</th>
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</table>
Table 1: Criteria for the diagnosis of probable MSA as established by the Second consensus statement on the diagnosis of multiple system atrophy, 2008. MSA = Multiple System Atrophy.

<table>
<thead>
<tr>
<th>Criteria for the diagnosis of probable MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A sporadic, progressive, adult (&gt;30 y) ~ onset disease characterized by</td>
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<tr>
<td>• 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 minutes of standing by at least 30 mmHg systolic or 15 mmHg diastolic and</td>
</tr>
<tr>
<td>• Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or</td>
</tr>
<tr>
<td>• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)</td>
</tr>
</tbody>
</table>
Table 2: Criteria for the diagnosis of possible MSA as established by the Second consensus statement on the diagnosis of multiple system atrophy, 2008. MSA = Multiple System Atrophy

<table>
<thead>
<tr>
<th>Criteria for the diagnosis of possible MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A sporadic, progressive, adult (&gt;30 y) ~ onset disease characterized by</strong></td>
</tr>
<tr>
<td>• Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or</td>
</tr>
<tr>
<td>• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and</td>
</tr>
<tr>
<td>• 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 probably MSA) and</td>
</tr>
<tr>
<td>• At least one of the additional features shown in Table</td>
</tr>
</tbody>
</table>
Table 3: Additional features of possible MSA as established by the Second consensus statement on the diagnosis of multiple system atrophy, 2008, MSA = Multiple System Atrophy; MSA-P = MSA with predominant parkinsonism; MSA-C = MSA with predominant cerebellar ataxia; FDG = [18F]fluorodeoxyglucose

<table>
<thead>
<tr>
<th>Additional features of possible MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Possible MSA-P or MSA-C</strong></td>
</tr>
<tr>
<td>- Babinski sign with hyperreflexia</td>
</tr>
<tr>
<td>- Stridor</td>
</tr>
<tr>
<td><strong>Possible MSA-P</strong></td>
</tr>
<tr>
<td>- Rapidly progressive parkinsonism</td>
</tr>
<tr>
<td>- Poor response to levodopa</td>
</tr>
<tr>
<td>- Postural instability within 3 y of motor onset</td>
</tr>
<tr>
<td>- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction</td>
</tr>
<tr>
<td>- Dysphagia within 5 y of motor onset</td>
</tr>
<tr>
<td>- Atrophy of MRI of putamen, middle cerebellar peduncle, pons or cerebellum</td>
</tr>
<tr>
<td>- Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum</td>
</tr>
<tr>
<td><strong>Possible MSA-C</strong></td>
</tr>
<tr>
<td>- Parkinsonism (bradykinesia and rigidity)</td>
</tr>
<tr>
<td>- Atrophy on MRI of putamen, middle cerebellar peduncle, or pons</td>
</tr>
<tr>
<td>- Hypometabolism on FDG-PET in putamen</td>
</tr>
<tr>
<td>- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET</td>
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Table 4: Average orthostatic systolic and diastolic decreases in blood pressure during our patient’s hospital stay and in response to various pharmacologic therapies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Systolic BP Orthostatic Decrease in mmHg (Supine to Standing)</th>
<th>Diastolic BP Orthostatic Decrease in mmHg (Supine to Standing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial midodrine dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-2</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>Titrating midodrine dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3-26</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>0.1mg fludrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 27-45</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>
FIGURE LEGEND

Figure 1: Transverse cranial Computerized Tomography (CT) of our patient on admission to the ED demonstrated mild generalized atrophy and patchy, non-specific periventricular white matter hypoattenuation.

Figure 2: Coronal cranial Computerized Tomography (CT) of our patient on admission to the ED demonstrated mild generalized atrophy and patchy, non-specific periventricular white matter hypoattenuation.

Figure 3: Our patient's orthostatic Mean Arterial Pressure (MAP) plotted over the course of her hospital stay. Drugs and doses are listed when they were begun. The dramatic rise in supine MAP between admission and day 3 likely represents rebound hypertension from starting the midodrine. She was started on fludrocortisone on day 26 and remained symptomatic until approximately day 40.
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