Respiratory Insufficiency as the Primary Presenting Symptom of Multiple-System Atrophy

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Background: Respiratory stridor, sleep-disordered breathing, and respiratory insufficiency are part of the clinical spectrum of multiple-system atrophy (MSA). We have encountered cases where these were presenting symptoms, with the diagnosis of MSA being initially unrecognized.

Objective: To describe cases in which breathing difficulties were the initial and primary manifestation of MSA.

Design: Database review from January 1, 1996, through October 31, 2005.

Setting: Mayo Clinic, Rochester, Minn.

Patients: All patients diagnosed as having MSA, cross-referenced for apnea, hypopnea, or hypoventilation. On review, we included only cases in which respiratory dysfunction was the primary initial clinical event in MSA, excluding equivocal cases.

Interventions: None.

Main Outcome Measures: Characteristics and clinical course of patients.

Results: Six cases were identified in which substantial respiratory insufficiency occurred as an early, presenting symptom of MSA. Three patients had been examined emergently for acute respiratory distress before the ultimate diagnosis of MSA; the other 3 patients were diagnosed as having obstructive sleep apnea unresponsive to therapy, with bilateral vocal cord paralysis found on ear, nose, and throat examination. Stridor was noted early in the course in all. All patients required tracheostomy, and all eventually developed features consistent with probable MSA.

Conclusions: Multiple-system atrophy may occasionally present as primary respiratory failure or dysfunction, with initially mild motor and autonomic symptoms. Otherwise unexplained central respiratory failure, bilateral vocal cord paralysis, stridor, or refractory central sleep apnea should prompt consideration of MSA.
examined these patients as well, either in-house or at an outside hospital. Two of the cases are described in detail in the next section to illustrate the presentations. The presentation of the remaining 4 cases is summarized in Table 1; these cases evolved into probable MSA, as documented in Table 2. All 6 cases ultimately had substantial dysautonomia by history that was confirmed on autonomic testing.5

Respiratory insufficiency was a presenting symptom in all 6 cases, and 3 (patients 1, 2, and 5) had previously been emergently examined because of acute respiratory distress before neurologic evaluations. Patients 2, 3, and 4 all had visualized bilateral vocal paralysis, although stridor was noted in all 6 patients. Patient 1 had definite central respiratory failure, whereas patients 3, 4, and 5 were noted to have central apneas during sleep with tracheostomy in place. All patients required tracheostomy, although patient 6 refused. In 3 patients, bilateral vocal cord paralysis may have initially been diagnosed as obstructive sleep apnea unresponsive to conventional therapy, although, alternatively, they may have had simple obstructive sleep apnea for a number of years and then subsequently developed upper airway resistance secondary to vocal cord paralysis. The respiratory problems overshadowed the neurologic complaints in all of these cases, and the ultimate diagnosis of MSA was unsuspected or at least not definite at presentation. Important early clues to the diagnosis were autonomic symptoms, which were eventually present in all 6 patients, and dream enactment behavior, which was present in 3 cases. Dream enactment behavior suggests underlying α-synuclein neuropathology and is well described in MSA.6

Table 1. Initial Findings in Cases 3 Through 6

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Presenting Pulmonary Problems</th>
<th>Additional History at Presentation</th>
<th>Pulmonary/Sleep Evaluation Findings</th>
<th>Neurologic Examination Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/M/70</td>
<td>OSA, CPAP failed; daytime hypersomnolence</td>
<td>Dysphonia, dysarthria, sialorrhea</td>
<td>RBD, bilateral vocal cord paralysis</td>
<td>Bilateral brisk UE reflexes, mildly ataxic gait, nystagmus</td>
</tr>
<tr>
<td>4/F/66</td>
<td>Dyspnea on exertion; daytime hypersomnolence</td>
<td>Constipation, urinary retention, dysphonia</td>
<td>OSA, stridor, bilateral vocal cord paralysis</td>
<td>Normal</td>
</tr>
<tr>
<td>5/M/60</td>
<td>Dyspnea on exertion; acute SOB at night</td>
<td>Impotence, subjective unsteadiness</td>
<td>Laryngospasm, stridor, RBD</td>
<td>Ataxic gait, bilateral brisk UE reflexes, right Babinski sign</td>
</tr>
<tr>
<td>6/M/46</td>
<td>OSA, CPAP failed</td>
<td>Erectile dysfunction, enuresis, diarrhea/constipation, subjective unsteadiness, orthostatic hypotension</td>
<td>RBD, high-pressure CPAP requirement</td>
<td>Pancerebellar ataxia, nystagmus, bilateral terminal UE tremor</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; RBD, rapid eye movement sleep behavior disorder; SOB, shortness of breath; UE, upper extremity.

Table 2. Follow-up and Confirmation of MSA in Cases 3 Through 6

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Subsequent Evaluations</th>
<th>Additional Findings</th>
<th>MSA Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/M/70</td>
<td>Hypersomnolence despite tracheostomy, right distal UE weakness, bilateral rigid LE, orthostatic hypotension</td>
<td>Central hypoventilation on PSG</td>
<td>Dysautonomia, ataxia, corticospinal tract signs, extrapyramidal signs</td>
</tr>
<tr>
<td>4/F/66</td>
<td>Dry mouth and eyes, respiratory improvement with tracheostomy, orthostatic hypotension, ataxic gait</td>
<td>Central hypoventilation on PSG, abnormal autonomic reflex screen, bilateral LE incoordination, elevated calcium-channel antibodies with normal results of cancer workup and EMG</td>
<td>Dysautonomia, ataxia</td>
</tr>
<tr>
<td>5/M/60</td>
<td>Urinary retention, diplopia, worsening gait, pancerebellar ataxia, constipation, heat intolerance, urinary urgency with incontinence</td>
<td>Central hypoventilation on PSG, pancerebellar ataxia, bilateral Babinski signs, TST suggestive of MSA, bilateral LE rigidity, bilateral LE myoclonus</td>
<td>Dysautonomia, ataxia, corticospinal tract signs, extrapyramidal signs</td>
</tr>
<tr>
<td>6/M/46</td>
<td>Presyncope</td>
<td>Stridor on PSG, bilateral vocal cord paralysis, abnormal autonomic reflex screen and TST consistent with MSA</td>
<td>Dysautonomia, ataxia, extrapyramidal signs</td>
</tr>
</tbody>
</table>

Abbreviations: EMG, electromyography; LE, lower extremity; MSA, multiple-system atrophy; PSG, polysomnogram; TST, thermoregulatory sweat test; UE, upper extremity.
toms and signs were present early but were mild. Ultimately these declared themselves, with 2 cases evolving to a parkinsonian phenotype and 4 cases to a spino-cerebellar phenotype.7

REPORT OF CASES

CASE 1

While on vacation, a 54-year-old woman awoke one morning and told her husband she was tired. An hour or so later, he found her unconscious in bed, but with a pulse. In the emergency department she was cyanotic and hyperventilating, requiring intubation. During the hospitalization, carbon dioxide retention delayed extubation and prompted evaluation of neuromuscular causes; results of a workup were negative. After extensive and unrevealing cardiopulmonary studies, the patient was transferred for rehabilitation; 1 month after admission, she was discharged home without a definite diagnosis. Because of the unexplained loss of consciousness, the workup had included an electroencephalogram, which was normal, and a tilt table test, which showed an abnormal result, with the blood pressure dropping from 156/66 mm Hg supine to 117/64 mm Hg after 8 minutes of 70° tilt and 64/44 mm Hg after 20 minutes of tilt. Because the loss of consciousness had occurred when the patient was supine in bed, it was unclear how these findings related to the episode. Previously, she had had no cardiopulmonary problems except for a several-month history of sleep apnea, treated with continuous positive airway pressure.

The patient was referred to our institution approximately 3 months later, with mild dyspnea on exertion as her only residual pulmonary complaint. Further studies showed findings consistent with chronic obstructive pulmonary disease with moderate airflow obstruction on pulmonary function testing, which reversed with a bronchodilator; she had a 35 pack-year history of smoking. Results of oximetry were normal at rest but declined with exercise. Autonomic testing was done because of the abnormal tilt table test results, and this showed moderate dysautonomia.5 The conclusion was that there was no good evidence of a neuromuscular cause for her pulmonary episode, but there was still no definite explanation.

The patient was contemporaneously examined in the Neurology Clinic with complaints of mild imbalance during the previous 18 months, fatigue, and, more recently, a tendency to drag one leg. A complete neurologic examination showed only limited abnormalities: mild difficulty rising from sitting; mild gait unsteadiness with asymmetrically reduced arm swing plus left leg movements that were slightly slow and stiff; and alternate motion rate in the left leg. A complete neurologic examination showed only limited abnormalities: mild difficulty rising from sitting; mild gait unsteadiness with asymmetrically reduced arm swing plus left leg movements that were slightly slow and stiff; and alternate motion rate in the left leg. A complete neurologic examination showed only limited abnormalities: mild difficulty rising from sitting; mild gait unsteadiness with asymmetrically reduced arm swing plus left leg movements that were slightly slow and stiff; and alternate motion rate in the left leg.

The patient’s history was uneventful until 5 months later, when she had an episode similar to the first one: her husband recognized an ashen appearance one morning after a night’s sleep and noted her to be stuporous. In her local emergency department, she was intubated because of hyperventilation, with a PCO₂ of 134 mm Hg. She could not be weaned from the ventilator during the hospitalization, with elevated PCO₂ values (50-70 mm Hg), ultimately requiring tracheostomy. She was discharged with a diagnosis of central hyperventilation.

She was reexamined at our institution several months later, and the pulmonologist ultimately concluded that she had hypercapnic respiratory failure secondary to neurologic disease. The neurologic history at that time documented that stridor had been heard by her husband before tracheostomy, and she had paroxysms of blood pressure swings. The neurologic examination again showed findings of mild parkinsonism, but now with a left Babinski sign. An MR image of the brain was remarkable for posterior putamen hypointensity, consistent with MSA,8 and a thermoregulatory sweat test demonstrated widespread anhidrosis.9 The autonomic reflex screen showed moderately severe dysautonomia. Given the constellation of findings—parkinsonism (partially levodopa responsive), corticospinal tract sign, dysautonomia, putamen hypointensity on MR imaging, plus stridor and central hyperventilation—she was diagnosed as having MSA.

CASE 2

A 65-year-old man presented to our institution with exertional dyspnea. It had begun abruptly 3 years previously with an episode of acute unprovoked dyspnea, which had improved within minutes but never completely resolved; it was partially responsive to inhalers. Recent exacerbations were treated with multiple nebulized inhalers plus a course of oral corticosteroids. He had smoked 20 pack-years but had quit 20 years before this episode. On presentation, he reported the need to rest after walking 3 to 4 blocks because of dyspnea. Other complaints included mild dysphagia, weak hands, and a new tremor of the right hand. Examinations by the internist and neurologist showed wheezing with forced expiration on lung auscultation, a mild postural-action tremor of the hands, and sensorimotor findings of carpal tunnel syndrome, confirmed by electromyography.

He returned to our institution 5 months later because his wife complained that she had been kept awake by extremely “noisy breathing.” Also, when driving recently through the mountains at elevated altitudes, he had become severely dyspneic. Arterial blood gas values included a PO₂ of 61 mm Hg and a PCO₂ of 52 mm Hg; with exercise the PO₂ dropped to 48 mm Hg, with no change in the PCO₂. Results of pulmonary function tests suggested airflow obstruction, with a 42% reduction in maximal inspiratory pressure but a normal maximal expiratory pressure. Stridor was documented during polysomnography, and bilateral vocal cord paralysis was noted by the otolaryngologist and treated with tracheostomy. Neurologic consultation at this time elicited a new complaint of impotence of many years’ duration, and the examination was remarkable only for the previously noted mild postural-action hand tremor, in addition to thenar weakness and atrophy explained by the known carpal tunnel syndrome. An MR image of the brain and results of spinal fluid examination were normal.
Neurologic reevaluation 19 months after the patient’s initial presentation documented new findings, including antecollis (after a whiplash injury in a car accident) and mild parkinsonism with stooped posture, reduced arm swing, and shortened stride, in addition to the postural-action hand tremor without a rest component. He also had hand weakness consistent with bilateral ulnar and median neuropathies, confirmed by electromyography. Neurologic reassessment 6 months later documented the foregoing findings plus bilateral Chaddock signs, but still with normal brain MR imaging.

By 4 years after the initial presentation, additional symptoms surfaced, including urinary hesitancy, fecal incontinence, increasing parkinsonism (partially levodopa responsive), and bilateral Babinski signs. The results of an autonomic reflex screen were moderately abnormal. At that time, arterial blood gas values were consistent with central hypoventilation (Po2, 48 mm Hg; PCO2, 53 mm Hg). The neurologic diagnosis was MSA, given the combination of parkinsonism, antecollis, corticospinal tract signs, dysautonomia, stridor, and central hyperventilation. Five and a half years after initial presentation, one morning his wife found him dead in his easy chair; no autopsy was performed.

This case series suggests that irregularities in respiration may occasionally arise early in MSA and may be clues to diagnosis. Assessment of respiratory function, when both awake and asleep, may be diagnostically helpful in patients with atypical parkinsonism, ataxia, or dysautonomia.

The life expectancy of patients with MSA is typically 8 to 10 years from symptom onset.112 The causes of mortality in MSA have not been clearly delineated; however, many patients die during the night, presumably because of respiratory insufficiency.11 It is known that stridor in the setting of MSA is associated with poor prognosis, but it is unclear whether death results from the vocal cord paralysis per se, central hypoventilation, or both. Case 1 illustrates the mortality risk tied to central hypoventilation; the patient likely would have died during 1 of her 2 episodes if they had not been recognized by her husband. Whether this was the cause for the death of patient 2, whose wife found him dead in his chair, is open to speculation.

Patients with MSA have been studied for ventilatory drive, demonstrating minimal to no chemosensitivity to hypoxia12; thus, they may be at a significantly higher risk of becoming hypoxic without the unconscious ability to compensate. In addition, patients with MSA often have disturbances of respiratory rhythm during sleep.3,13 These facts may explain why patients with MSA may die of respiratory insufficiency despite tracheostomy.11 Clearly, some of our patients had central hyperventilation in addition to stridor, which likely would not have been discovered had they not undergone repeat sleep evaluations.

The neuropathologic findings of MSA are prominent in brainstem regions, where the respiratory centers are located. The region presumed responsible for respiratory chemosensitivity, the ventral medullary arcuate nucleus, degenerates in MSA.14 In addition, the pre-Botzinger complex of the medulla, thought responsible for respiratory rhythmogenesis, is similarly markedly affected.15

It should be emphasized that these were selected cases, and we have no data regarding the frequency with which MSA presents primarily as a respiratory disorder. Certainly, however, otherwise unexplained central respiratory failure, bilateral vocal cord paralysis, stridor, or refractory central sleep apnea should provoke consideration of MSA. In addition, when MSA is routinely diagnosed, attention should be directed to respiration, since it appears that this may be the cause of death in most patients. It has become standard practice to offer tracheostomy to patients with stridor and MSA, yet more aggressive measures such as ventilator support during the sleeping hours may be necessary for treatment of central hypoventilation.11

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