Sleep-Disordered Breathing and Risk of Sudden Death in Multiple System Atrophy

Lisa Cutchen MD
Sleep Medicine Fellow
University of New Mexico Sleep Disorders Center
New Mexico Thoracic Society
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Objectives

1. Describe the three clinical syndromes known as multiple system atrophy.
2. Recognize the clinical features of multiple system atrophy.
3. Understand the management strategies for sleep-disordered breathing in patients with multiple system atrophy.
Case Study

54-year-old woman presents to her primary care physician and reports a disturbing noise that she makes during sleep with inspiration. Her husband reports that it began a year ago, but has become worse since then, now continuous throughout the night. The noise is described as a strange, high-pitched sound like the bray of a donkey. Her husband also describes episodes during sleep in which she has sudden violent movements which seem to be dream enactments. She has also had urinary frequency and urgency, although testing has not revealed a urinary tract infection. She recently fell on a walk with her husband which she attributed to clumsiness.
Multiple System Atrophy

- A fatal adult-onset neurodegenerative disorder characterized by autonomic failure, parkinsonism, cerebellar abnormalities, and corticospinal degeneration
- The pathological process in the brain affects the central autonomic, striatonigral, and olivopontocerebellar systems
Multiple System Atrophy

- Estimated annual incidence in population >50 years old is approximately 3 per 100,000
- Estimated annual prevalence is between 2 to 5 cases per 100,000
- Mean age of onset 54 years (range 31-78)
- Men = Women
Multiple System Atrophy

- There are three syndromes that are captured by the term Multiple System Atrophy
  - Striatonigral degeneration
  - Olivopontocerebellar atrophy
  - Shy-Drager Syndrome
Multiple System Atrophy

- There are three syndromes that are captured by the term Multiple System Atrophy
  - MSA-P
    - Striatonigral degeneration
  - MSA-C
    - Olivopontocerebellar atrophy
  - Shy-Drager syndrome
    - Shy-Drager syndrome
Multiple System Atrophy

- There are three syndromes that are captured by the term Multiple System Atrophy
  - MSA-P
    - predominant parkinsonism
  - MSA-C
    - predominant cerebellar ataxia
  - Shy-Drager syndrome
    - Predominant autonomic failure
MSA Clinical Features

- The neuropathologic changes probably begin several years before the disease becomes symptomatic.
- The onset of the disease is marked by the initial clinical manifestation of one of its characteristic features, motor or autonomic.
Multiple System Atrophy

- Clinical Features
  - Parkinsonism
    - Bradykinesia
    - Resting tremor
    - Rigidity
    - Postural instability
    - Gait changes
  - Cerebellar Ataxia
    - Gait ataxia
    - Ataxic dysarthria
    - Limb ataxia
    - Sustained gaze-evoked nystagmus
Multiple System Atrophy

- Clinical Features
  - Autonomic Dysfunction
    - Orthostatic hypotension
      - Light-headedness, altered vision, nausea, weakness, fatigue, and coat-hanger distribution pain only while standing
    - Bowel and bladder disturbances
      - Urinary urgency, frequency, and incontinence not due to a non-neurological cause
  - Sexual dysfunction
    - Erectile dysfunction
Multiple System Atrophy

- The initial motor symptom determines the morphological phenotype in an individual case
  - MSA-P
    - predominant parkinsonism
  - MSA-C
    - predominant cerebellar ataxia
  - Shy-Drager syndrome
    - Predominant autonomic failure
MSA Clinical Features

- MSA – P: The predominant motor feature is parkisonism
- MSA – C: The predominant motor feature is cerebellar ataxia
- MSA-P outnumbers MSA-C by between 2 and 4 to one in Europe and North America
- MSA-C more common in Japan
Multiple System Atrophy
Neuropsychiatric Features and Sleep Disturbance

- Depression 41%
- Psychotic symptoms 6%
  - Hallucinations 5.5%
- Delusions 2%
- Dementia 4.5%
- Psychotic symptoms MSA-P > MSA-C
- Insomnia 19%
- Excessive daytime sleepiness 17%
- Restless legs 10%

Multiple System Atrophy

- Sleep Symptoms in MSA
  - Obstructive sleep apnea, with upper airway obstruction mainly at the level of the larynx
  - Laryngeal stridor
  - Central hypoventilation
  - Reduced and fragmented sleep
  - Excessive daytime sleepiness
  - Periodic limb movements and restless legs syndrome
  - REM sleep behavior disorder
Neuropathology of Multiple System Atrophy (MSA)

- MSA is one of the alpha-Synucleinopathies
  - alpha-Synuclein
- Microscopically, glial cytoplasmic inclusions of aggregates of misfolded alpha-Synuclein
- Macroscopically, cerebellar atrophy or pronounced pallor of the substantia nigra
- The underlying neuropathology contributes to the sleep disorders associated with MSA

Alpha-Synucleinopathies

- Multiple System Atrophy
- Parkinson Disease
- Lewy Body Dementia
Respiratory Manifestations of Multiple System Atrophy

- MSA affects the brainstem areas involved in respiratory rhythmogenesis, chemosensitivity, and control of laryngeal function
- Brainstem areas controlling ventilation
  - Dorsolateral pons
  - Nucleus of the solitary tract
  - Ventrolateral medulla

Respiratory Manifestations of Multiple System Atrophy

- Brainstem areas controlling ventilation
  - Dorsolateral pons
  - Nucleus of the solitary tract
  - Ventrolateral medulla
- The neurons in these areas are involved in
  - Respiratory rhythm
  - Respiratory reflexes
  - Control of cranial neurons that drive the muscles of the upper respiratory airway
  - Control of spinal neurons that drive the muscles of the respiratory pump

Respiratory Manifestations of Multiple System Atrophy

- In addition, there are neurons near the ventral medulla that are responsive to CO$_2$/pH, hypoxia, or both
- Drive automatic respiration, especially during sleep

Respiratory Manifestations of Multiple System Atrophy

- \(\alpha\)-Synuclein depositions cause neurodegeneration in multiple areas:
  - Substantia nigra
  - Cerebellum
  - **Pontine and medullary nuclei**
  - Spinal cord

Respiratory Manifestations of Multiple System Atrophy

- Respiratory Rhythm
  - Generated in the pre-Botzinger complex

- Respiratory Chemosensitivity
  - Carotid bodies (mainly oxygen sensitive)
  - Rostral ventrolateral medulla (hypoxia-activated)
  - The main chemosensitive role of the brainstem depends on neurons sensitive to pH (CO$_2$/H$^+$)

Respiratory Manifestations of Multiple System Atrophy

- Laryngeal muscles are innervated by vagal motoneurons located in the nucleus ambiguus
- Posterior cricoarytenoid muscle activated during inspiration causes laryngeal abduction
- Thyroarytenoid muscle activated during expiration causes laryngeal adduction

Laryngeal Dysfunction
Laryngeal Stridor in MSA

- Paralysis of abductor vocal cord muscles
- Sustained tonic activity of adductor vocal cord muscles
- Laryngoscopic evaluation during wakefulness may not show laryngeal narrowing in these patients
- Selective denervation atrophy of the posterior cricoarytenoid muscle possible
- Impaired laryngeal function alone may not account for the high incidence of sudden death in MSA patients

Sleep and MSA

- Leading cause of death in MSA
  - Bronchopneumonia (48%)
    - Bulbar palsy predisposes patients to aspiration pneumonia
  - Sudden death (21%)
    - Laryngeal obstruction
    - Central hypoventilation with a blunted CO$_2$ response curve resulting in hypercapnic respiratory failure
    - Cardiac arrhythmia related to dysautonomia

Predictors of Survival in MSA

- Retrospective research study published 2015
- All cases of MSA evaluated at Mayo Clinic, Rochester, between January 1998 and December 2012
- Individuals excluded if there was secondary cause of parkinsonism or ataxia or if clinical or laboratory features suggested alternative diagnosis to MSA
- 685 patients identified
  - 594 probable MSA
  - 91 possible MSA

Predictors of Survival in MSA

- Patient Demographics
  - 685 total
  - 330 (48%) female vs. 355 (52%) male
  - MSA-P 430 patients (63%)
    - MSA-P: 203 (47%) female vs. 227 (52%) male
  - MSA-C 255 patients (37%)
    - MSA-C: 127 (50%) female vs. 128 (50%) male
  - Mean age of onset 61 years (range 34-86 years)
    - MSA-C earlier at 58.4 years vs. MSA-P at 62.3 years
  - Median time from onset of symptoms to initial evaluation at Mayo was 3.07 years
  - Median time from onset of symptoms to death was 7.51 years
  - Median time from diagnosis to death was 3.33 years

Predictors of Survival in MSA

- No difference in survival between motor subtypes
- There was symptom overlap of parkinsonism and ataxia, although parkinsonism was more likely to occur in MSA-C than was ataxia to occur in MSA-P.
- No difference in survival between MSA-P and MSA-C
  - Either from time of symptom onset or time of diagnosis
- Sleep symptoms of dream enactment and stridor were similar between MSA-P and MSA-C
  - Of 304 patients with reported dream enactment behavior, it preceded onset of motor and autonomic symptoms in 34%

Predictors of Survival in MSA

- Factors Not Associated with Survival
  - MSA subtype (adjusted for age of onset)
  - Classification as probable vs. possible MSA
  - Gender

Predictors of Survival in MSA

- Factors associated with shortened survival included
  - Later age at onset
  - Early autonomic symptoms
  - The presence of bladder symptoms
  - Early need for urinary catheterization
  - Early falls (considered a motor symptom)
  - Stridor
  - Severity of autonomic dysfunction

Predictors of Survival in MSA

- Six variables were maintained in the final model as independent predictors of shortened survival
  - The strongest predictor was falls occurring within 3 years of symptom onset
- Four of the other five independent predictors related to autonomic symptoms or degree of autonomic impairment
- Stridor was not maintained as an independent predictor, possibly due to significant associations between stridor and several other predictors

Predictors of Survival in MSA

- Did recognition of stridor during evaluation for MSA prompt treatment that may have affected survival?
- In earlier studies, stridor was shown to be a good prognostic indicator of survival.

Predictors of Survival in MSA

Table 3 Multivariate analysis of survival factors in MSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>From symptom onset</th>
<th>Hazard ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls within 3 years</td>
<td></td>
<td>2.33</td>
<td>1.92</td>
<td>2.83</td>
<td>&lt;0.0001</td>
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<td>Bladder symptoms</td>
<td></td>
<td>1.96</td>
<td>1.61</td>
<td>2.38</td>
<td>&lt;0.0001</td>
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<td>Urinary catheterization within 3 years</td>
<td></td>
<td>1.67</td>
<td>1.19</td>
<td>2.35</td>
<td>0.003</td>
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<tr>
<td>Early orthostatic intolerance (^a)</td>
<td></td>
<td>1.29</td>
<td>1.06</td>
<td>1.58</td>
<td>0.011</td>
</tr>
<tr>
<td>CASS total</td>
<td></td>
<td>1.07</td>
<td>1.02</td>
<td>1.11</td>
<td>0.002</td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td>1.02</td>
<td>1.01</td>
<td>1.03</td>
<td>0.001</td>
</tr>
</tbody>
</table>

\(^a\)Within 1 year of onset.

Predictors of Survival in MSA

- Retrospective research study published in 2014
- 49 autopsy-confirmed cases at the Mayo Clinic, Rochester
- 16 women, 33 men
- Mean age of onset 56.1 years
- Symptoms at onset
  - 50% autonomic
  - 30% parkinsonism
  - 20% cerebellar

Predictors of Survival in MSA

- Prognostic indicators for shorter survival were
  - Older age at onset (hazard ratio 1.04, $P = 0.03$)
  - Early requirement of bladder catheterization (hazard ratio 7.9, $P = 0.004$)
    - 7 vs. 9.8 years
  - Early generalized (CASS $\geq 6$) autonomic failure (hazard ratio 2.8, $P = 0.047$)
    - 7.3 vs. 13.7 years
Composite Autonomic Severity Score (CASS)

- A validated instrument for laboratory quantitation of autonomic failure derived from the Autonomic Reflex Screen and Thermoregulatory Sweat Testing.
  - 1 to 3, mild and limited
  - 4 to 6, moderate
  - 7 to 10, severe and generalized
Composite Autonomic Severity Score (CASS)

- Autonomic Reflex Screen
  - The Quantitative Sudomotor Axon Reflex Test at proximal and distant standard sites to assess sympathetic postganglionic sudomotor axon function
  - Heart rate responses to deep breathing and the Valsalva maneuver to assess cardiovagal function
  - Beat-to-beat blood pressure responses to the Valsalva maneuver and head-up tilt to assess sympathetic adrenergic function
Composite Autonomic Severity Score (CASS)

- Thermoregulatory Sweat Testing (TST)
  - Assesses the integrity of central and peripheral sudomotor pathways involved in the thermoregulatory response to changes in environmental temperature by providing quantitative evaluation of the proportion of anterior body surface that does not sweat. A TST of 40% or greater indicates moderate to severe anhidrosis and a TST of 100% indicates complete anhidrosis.
Predictors of Survival in MSA

- The medullary serotonergic neurons modulate the micturition reflex and are central respiratory chemosensors that participate in the regulation of arousal, respiratory rhythmogenesis, and ventilatory response to hypoxemia and hypercarbia. They are also involved in sympathetically mediated thermoregulation.

Treatment of Stridor and Laryngeal Dysfunction

- Direct laryngoscopy during sleep without pharmacologic sedation
  - documented inspiratory adduction of the vocal cords
  - with downward displacement of the larynx
- Application of CPAP resulted in
  - improvement in stridor,
  - distension of the hypopharynx,
  - abduction of the vocal cords, and
  - reduction of the downward displacement of the larynx

Treatment of Stridor and Laryngeal Dysfunction

- Retrospective review of 38 patients seen at the Mayo Clinic, Rochester, from 1975 to 2010 who had MSA and had received otolaryngologic examination
- Mean age at diagnosis 68.0 years +/- 8.2 years
- Median age at diagnosis 67.3 years (range 45.7-86.4)
- Median age at symptom onset 63.7 years (range 37.7-84.8)
- Median age at diagnosis of true vocal fold impairment 66.2 years (range 45.7-84.6)

Treatment of Stridor and Laryngeal Dysfunction

- Median duration of vocal or respiratory symptoms (stridor, dysphonia, respiratory difficulty) prior to diagnosis of MSA was 12 months (range 1-60 months)
- Median duration of MSA symptoms prior to diagnosis of MSA was 36 months (range 3-180 months)
- Stridor was present in 25 (68%) of the patients

Treatment of Stridor and Laryngeal Dysfunction

- True vocal fold paralysis in 15 (39.5%) patients
- True vocal fold paresis in 21 (55.3%) patients
- True vocal fold mixed paresis/paralysis in 2 (5.3%) patients
  - Included with the paralysis group for analysis
- Median survival after diagnosis with vocal fold motion impairment was 51.6 months
- Survival of those with stridor was not significantly different from those without stridor
  - 24.9 months vs. 61.7 months, $P = 0.6735$

Treatment of Stridor and Laryngeal Dysfunction

- Decreased survival rate in patients with shorter duration of voice symptoms (stridor, dysphonia, respiratory difficulty) before the diagnosis of VFMI ($P = 0.0113$).
- Decreased survival rate in patients with shorter duration of any MSA-related symptom before MSA diagnosis ($P = 0.0002$).
- These associations likely related to symptom severity or disease velocity.
Treatment of Stridor and Laryngeal Dysfunction

- There was not a significant relationship between stridor and survival.
- There was decreased survival associated with unilateral or bilateral vocal cord paralysis on laryngoscopy ($P = 0.0384$).
  - Vocal fold motion impairment rather than stridor carries the implication of poor prognosis.
Treatment of Stridor and Laryngeal Dysfunction

- CPAP is effective therapy for eliminating stridor during sleep.
- Median survival time not significantly different between subjects without stridor and those with stridor treated with only CPAP.
- However, if the patient develops **daytime** stridor, and it is not treated with tracheostomy, then mean life expectancy is 0.8 years.


Treatment of Stridor and Laryngeal Dysfunction

- Besides CPAP and tracheostomy, there is surgery of the larynx—a sampling:
  - laryngofissure
  - cord lateralization
  - Cymetra injection
  - bilateral type I thyroplasty
  - carbon dioxide laser left transverse cordotomy
  - partial arytenoidectomy and vocal fold lateralization

- This study too small to detect impact on survival of these airway interventions
Nocturnal Sudden Death in MSA

- Seems to be caused by a mechanism other than upper airway obstruction
- Even if treated with CPAP or tracheostomy, there is still risk of sudden death
- Tracheostomy has been known to make central sleep apnea worse
  - Likely involves dysfunction of the respiratory regulation center
Recommended Reading