Laryngology Seminar: Multiple System Atrophy and the Laryngologic Manifestations

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70-year-old man

Neurologic disorders:
- Parkinsonism
- Autonomic dysfunction (urinary retention, orthostatic hypotension)

Respiratory symptoms:
- Nighttime stridor for several months
- Severe dyspnea and stridor for one day

Videolaryngoscopy:
- A 1- to 2-mm glottic airway with fixation during both inspiration and expiration
Differential Diagnosis of Bilateral Vocal Fold Adductor Paresis

- Neurologic
  - TIA
  - CNS neoplasms
  - Traumatic brain injury
  - Myasthenia gravis
  - Multiple sclerosis
  - Amyotrophic lateral sclerosis

- Malignancy
  - Bronchogenic cancer
  - Esophageal cancer
  - Thyroid cancer

- Endocrine
  - DM
  - Hypokalemia or hypocalcemia

- Medication
  - Vincristine Tx
  - I-131 Tx

- Other
  - Endotracheal intubation
  - NG tube syndrome
  - Radiation therapy
  - Cricoarytenoid joint fixation
Outlines

- Introduction of multiple system atrophy
- Bilateral vocal paresis
  - Clinical manifestation and laryngeal findings
  - Pathophysiology
  - Differential diagnosis
- Sleep-disordered breathing
- Treatment and prognosis
Multiple System Atrophy
Multiple System Atrophy (MAS)

- Parkinsonism
- Cerebellar dysfunction
- Autonomic dysfunction
  (Shy-Drager syndrome)
Multiple System Atrophy (MAS)

- Both sexes
- Middle age
- Progressing over intervals of 1-18 years
- Median survival: 9.3 years
Clinical Presentation

- Developing as one of the subdisorders
- A single syndrome typically predominates (typically parkinsonism).
- Patients may be treated for Parkinsonism for several years.
Symptoms

- Parkinsonism
  - Tremor, bradykinesia, rigidity, gait disturbance, and postural instability

- Autonomic dysfunction
  - Orthostatic hypotension, dysphagia, constipation, fecal incontinence, urinary retention, urinary incontinence, impotence, hypohidrosis, hyperhidrosis, and thermoregulation abnormality
Symptoms

- **Ataxia**
  - Gait ataxia and vocal ataxia

- **Bilateral vocal cord paralysis**
  - Sleep-related laryngeal stridor and respiratory distress

- **Cognitive dysfunction**
  - Reasoning deficit, learning deficit, memory deficit, and attention deficit
Pathologic Findings

- Glial cytoplasmic inclusions with degenerative changes in some or all of the following structures:
  - Substantia nigra
  - Putamen, caudate nucleus, globus pallidus
  - Pontine nuclei
  - Cerebellar Purkinje cells
  - Autonomic nuclei of the brainstem
  - Intermediolateral cell column and Onuf nucleus in the spinal cord
Diagnosis

- Consensus conference in Minneapolis, the American Autonomic Society and the American Academy of Neurology (1998)
<table>
<thead>
<tr>
<th>Clinical Domain</th>
<th>Feature (Characteristic of the Disease)</th>
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<tbody>
<tr>
<td>Autonomic and urinary dysfunction</td>
<td>* Orthostatic hypotension</td>
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<td>* Urinary incontinence or incomplete bladder emptying</td>
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<td>Parkinsonism</td>
<td>* Bradykinesia</td>
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<td></td>
<td>* Rigidity</td>
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<td>* Postural instability</td>
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<td></td>
<td>* Tremor - Postural, resting, or both</td>
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<td>Cerebellar dysfunction</td>
<td>* Gait ataxia</td>
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<td></td>
<td>* Ataxic dysarthria</td>
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<td></td>
<td>* Limb ataxia</td>
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<td></td>
<td>* Sustained gaze-evoked nystagmus</td>
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<td>Corticospinal tract dysfunction</td>
<td>* Extensor plantar response with hyperreflexia (pyramidal sign)</td>
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<td>Diagnostic Categories of MSA</td>
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<td>-----------------------------</td>
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<tr>
<td><strong>Possible MSA</strong></td>
<td></td>
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<tr>
<td>* One criterion</td>
<td></td>
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<tr>
<td>* Two features from separate domains</td>
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<tr>
<td><strong>Probable MSA</strong></td>
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<tr>
<td>* Criterion for autonomic failure/urinary dysfunction</td>
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<tr>
<td>* Poorly levodopa responsive parkinsonism or cerebellar dysfunction</td>
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<tr>
<td><strong>Definite MSA</strong></td>
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<tr>
<td>* Pathologically confirmed (A high density of glial cytoplasmic inclusions with degenerative changes in the nigrostriatal and olivopontocerebellar pathways)</td>
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## Exclusion Criteria for Diagnosis of MSA

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Findings</th>
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<tbody>
<tr>
<td>History taking</td>
<td>- Symptomatic onset at &lt;30 years</td>
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<td>- Family history of similar disorder</td>
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<td>- Systemic diseases or other identifiable causes for features</td>
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<td>- Hallucinations unrelated to medication</td>
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<td>Physical examination</td>
<td>- Prominent slowing of vertical saccades or vertical supranuclear gaze palsy</td>
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<td>- Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction</td>
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<tr>
<td>Laboratory study</td>
<td>- Metabolic, molecular genetic, and imaging evidence of alternative cause of features</td>
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</table>
Laboratory Investigations

In clinically well-established cases rather than in the early stages

- Autonomic function tests
- Sphincter electromyography
- Neuroimaging
  - Excluding other conditions
  - Normal in up to 20% of cases
  - Abnormalities of striatum, cerebellum, and brainstem
Prognosis

- Poor response to levodopa therapy
- Rapid progression
- Relatively fast disability
  - 30% decrease of activities of daily living in 1 year
  - 40% of patients in a wheelchair within 5 years (wheel chair sign)
- Poor prognosis
Bilateral Vocal Fold Paresis
Clinical Features

- **Stridor**
  - A very loud and high pitched sound at inspiration
  - Fundamental frequency:
    - MSA-related stridor: 260-330 Hz
    - Soft palate snoring: 170 Hz

- **Insidious course:** nocturnal --> daytime as well
- **Within 4 years of the onset of the disease**
- **Accompanied with hoarseness and dysphagia**
Primary Presenting Symptom of MAS

- Unexplained central respiratory failure, stridor, or refractory central sleep apnea
- Uncertain frequency with which MSA presents primarily as a respiratory disorder
- Early clues:
  - Autonomic symptoms
  - Dream enactment behavior
Vocal Fold Findings

- Slight restriction of the abductor function
- Ataxic movement of the vocal cords
  - Irregular tremor of the arytenoids
  - Periodic or persistent involuntary movements
- Adductor paralysis as well (daytime stridor)
Paradoxical Vocal Cord Motion

- “Steroid-resistant asthma”
- Adduction of the vocal cords at inspiration
- PVCM-related stridor
  - During inspiration
  - Originating from larynx
Stridor in MSA

- Passive?
  - Abductor paralysis
  - Bernoulli effect

- Active?
  - Inspiratory activation of the adductor
The Mechanism of Paradoxical Vocal Cord Motion in MSA

- Respiratory center damage theory
- Laryngeal closure reflex theory
Respiratory Center Damage Theory

- Loss of cells in the **nucleus ambiguus**
- Abnormalities of **inhibitory transmitters and receptors** in the brain stem
  - ↓ Glycine transporter mRNA
  - ↓ GABA$_A$/BZD receptor binding ability
- Depletion of NK1R neurons in the **rostral ventrolateral medulla** (essential for respiratory rhythm)
Histopathologic Features

- Atrophy of the posterior cricoarytenoid muscle (PCA); normal in size of the laryngeal adductors
- Lipofuscin deposition and necrosis of the sarcoplasmic reticulum in the PCA
- Loss of cells in the nucleus ambiguus and loss of axons in the recurrent laryngeal nerves
Laryngeal Closure Reflex Theory

- Glottis narrowing
- Inspiratory effort
- Reflexive adductor activation
- Powerful negative pressure in the trachea
Laryngeal Closure Reflex

- Laryngeal irritation:
  - Infections of the upper respiratory tract, GERD, inhaled irritant exposures and strong odors, PND, and thyroid surgery
- Psychogenic factors: lowering the threshold levels
EMG Study

- Thyroarytenoid muscle
- Posterior cricoarytenoid muscle

- No evidence of spontaneous activity from degeneration (i.e., fibrillation potentials, complex repetitive discharges, positive sharp waves)
- A rapidly recruiting, prolonged EMG tonic activity alternating with short periods of electric silence
No Conflict of the Two Theories

- MSA-related central changes ➔ lower the threshold level for the paradoxical adductor activation

- Other factors activating the adductor:
  - Restricted dilatation of the glottis
  - Inhibitory transmitter abnormalities
  - Hypoxia
  - Hypercapnia
Vocal Fold Adductor Paresis in Parkinson’s disease

- Not exacerbated during sleep
- No abnormalities of the posterior cricoarytenoid muscle
- Associated with severe dysphagia
Sleep-Disordered Breathing
Sleep-Disordered Breathing

- Nocturnal stridor: associated with sudden death during sleep
- Sleep disturbances:
  - Broken sleep
  - Restless leg syndrome
  - Talking and vigorous movements associated with dreaming
Polysomnography

- Reduced total sleep time
- Nocturnal stridor (all sleep stages and all body positions)
- Obstructive sleep apnea (Glottis)
- Periodic leg movements
- REM sleep behavior disorder
EMG Study

At sleep:
- PCA: gradual decreased activity (fade-out phenomenon)
- TA: apparent inspiratory phasic activity
Treatment and Prognosis
Treatment for Laryngeal Stridor

- CPAP (continuous positive airway pressure)
- Tracheostomy
- Laryngeal surgery
CPAP

- The first choice of treatment
- Cannot abolish the stridor
  - Vocal cords fixed at midline
  - Daytime stridor
- Biphasic positive airway pressure (BiPAP)
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<tr>
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<th>Baseline</th>
<th>CPAP</th>
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<tbody>
<tr>
<td>Episodes of apnoea per h</td>
<td>21.3 (5.6)</td>
<td>2.4 (0.5)*</td>
</tr>
<tr>
<td>CT85 (%)</td>
<td>22 (7.6)</td>
<td>0†</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>238.3 (64.4)</td>
<td>247.6 (37)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>54 (15.8)</td>
<td>53.6 (8.3)</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>44 (10.1)</td>
<td>76 (13)</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>158.3 (70.4)</td>
<td>125 (55.3)</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>7.6 (5.7)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>29.8 (4.8)</td>
<td>44 (13.9)</td>
</tr>
<tr>
<td>Stages 3 and 4 (%)</td>
<td>43.9 (11.1)</td>
<td>35 (21.4)</td>
</tr>
<tr>
<td>REM (%)</td>
<td>18.5 (13.8)</td>
<td>5.4 (9.4)</td>
</tr>
<tr>
<td>Leg movements per h</td>
<td>50 (46.8)</td>
<td>51 (45.9)</td>
</tr>
</tbody>
</table>

Values are mean (SD). *p=0.03, †p=0.02 by paired t-test. CT85=percentage of oxygen saturation below 85% during sleep, sleep efficiency=total sleep time per total time in bed, WASO=wake time after sleep onset. REM=rapid eye movement sleep.

**Polysomnographic studies at baseline and after 1 month of CPAP in three patients with multiple system atrophy and stridor**
Tracheostomy

- Advanced stage with restricted adduction of the vocal cords during wakefulness and daytime stridor
- Cuffed cannula for prevention of aspiration
- Tubal feeding
- Lowering the quality of life
Laryngeal Surgery

- Vocal cord laterofixation
- Arytenoidectomy
- Partial cordectomy
- Botulinum toxin injection into the adductors
- Aspiration and severe hoarseness
- Not recommended at advanced stage
References

References


7. Laryngeal electromyography with separated surface electrodes in patients with multiple system atrophy presenting with vocal cord paralysis. Isozaki E. et al., J Neurol 1994; 241: 551-556


9. Daytime hypoxemia, sleep-disordered breathing, and laryngopharyngeal findings in multiple system atrophy. Shimohata T. et al., Arch Neurol 2007; 64:856-861