Multiple Systems Atrophy

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Demographics

- Prevalence of 2-4 per 100,000 population (may be underestimated)
- Median age of onset is 55 years (range 33-76)
- Men : women = 1.3 : 1
- Mean survival 6-9 years; half are disabled or wheelchair bound within 5 years of onset of motor symptoms
Former Names for MSA

- Shy-Drager syndrome (MSA-A)
- Striatonigral degeneration (MSA-P)
- Olivopontocerebellar atrophy “OPCA” (MSA-C)
MSA Subtypes

• Parkinsonian = MSA-P
  - Parkinson like features
    • Slowness
    • Muscle rigidity
    • Shuffling gait
    • But not resting tremor
  - Poorly or transiently responsive to levodopa and other Parkinson disease medications
MSA Subtypes

- Autonomic = MSA-A
  - Orthostatic hypotension
  - Reduced ability to sweat
  - Constipation
  - Bladder dysfunction
  - Erectile dysfunction
• Marked loss of ability to sweat over time compared to Parkinson’s disease

- **A**
  - 2002 TST result = 30%
  - 2005 TST result = 97%
  - 60-Year-Old Man With MSA
  - QSART, µg/cm²: 1.92, 1.59, 1.34

- **B**
  - 2004 TST result = 1%
  - 2008 TST result = 2%
  - 74-Year-Old Man With PD
  - QSART, µg/cm²: 0.75, 0.81, 0.56

- **C**
  - 2005 TST result = 0%
  - 69-Year-Old Woman With PD
  - With Autonomic Failure
  - QSART, µg/cm²: 0.28

- **D**
  - 2005 TST result = 28%
  - 78-Year-Old Man With PD
  - With Autonomic Failure
MSA Subtypes

- Cerebellar = MSA-C
  - Wide based gait
  - Intention tremor
  - Ataxia
  - Nystagmus
  - “Scanning Speech”
MSA Subtypes

- Most patients have a mixture of MSA-P, MSA-A, or MSC-C
Other MSA Symptoms

- Dysarthria
- Laryngeal stridor
- Anterocollis
- Sleep apnea or RBD
- Stimulus sensitive myoclonus
Symptoms of MSA

- Parkinsonism: stiffness, slowness, freezing
- Cerebellar features: balance, co-ordination
- Autonomic Features:
  - Bladder symptoms
  - Constipation
  - Blood pressure regulation
  - Snoring
  - Sleep apnoea
  - Erectile dysfunction
Not Compatible with MSA

- Asymmetric symptoms
- Resting tremor
- Early dementia
- Prominent ophthalmoplegia
  - Vertical gaze palsy
- Apraxia
- Cortical sensory loss
<table>
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<tr>
<th>Comparisons</th>
<th>PD</th>
<th>MSA</th>
<th>PSP</th>
<th>CBD</th>
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<td>Symmetry of deficits</td>
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<td>Axial rigidity</td>
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<td>Vertical gaze palsy</td>
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<td>Frontal behavior</td>
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<td>Dysautonomia</td>
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<td>L-dopa response early</td>
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<td>L-dopa response late</td>
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<td>Asymmetric cortical atrophy on MRI</td>
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Time Course of MSA Compared to Parkinson disease and PSP

Figure 1: Milestones of disease advancement and total disease course
The green rectangles indicate disease duration, commencing with the timepoint of first symptoms. The vertical lines denote time of clinical diagnosis of a parkinsonian or a cerebellar syndrome (Dx) and time of documentation of milestones of disease advancement. Reproduced from O’Sullivan and colleagues, with permission from Oxford University Press. C = cognitive disability. D = dysarthria or dysphagia. Dx = clinical diagnosis. F = frequent falls. MSA = multiple system atrophy. PD = Parkinson’s disease. PSP = progressive supranuclear palsy. R = residential care. U = urinary catheter. W = wheelchair dependent.
Treatment of Parkinsonian Symptoms

- Levodopa/carbidopa (Sinemet)
- Amantadine
- Physical Therapy
- Occupational Therapy
- Speech Therapy
Treatment of Low Blood Pressure

- Sodium
- Fluid intake
- Pressure stockings
- Midodrine
- Fludrocortisone

Matisse “Icarus”
Treatment of Genitourinary symptoms

- Oxybutinin or tolterodine for urinary frequency or incontinence
- Sildenafil for impotence
Treatment of Depression

- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants
- Counseling
Symptoms Resistant to Drug Treatment

- Ataxia
  - Physical Therapy helpful though
- Dementia (seen late in disease course)
  - Benefit of Alzheimer’s drugs uncertain
Pathology of MSA

Figure 2: Possible pathogenic pathways in MSA as seen in transgenic mouse models
Findings from transgenic mouse models with oligodendroglial α-synucleinopathy indicate three possible pathogenic pathways in MSA. GCI pathology could trigger microglial activation, which causes chronic oxidative stress and ultimately leads to neuronal cell death (1). Alternatively, GCI pathology could exacerbate susceptibility to exogenous oxidative stress and lead to neuronal cell death in striatonigral and olivopontocerebellar systems (2), or GCI pathology could lead to secondary axonal α-synuclein aggregation or oligodendroglial mitochondrial dysfunction, which eventually lead to neuronal cell death (3). Oligodendroglial α-synucleinopathy is shown with a sickle-shaped cytoplasmic inclusion composed of misfolded α-synuclein. In the dying neuron, condensed chromatia, disruption of the nuclear membrane, and cell shrinkage is seen.
3NP=3-nitropropionic acid. GCI=glial cytoplasmic inclusion. MSA=multiple system atrophy.
Fig. Summary of working model for oligodendroglia dysfunction in multiple system atrophy (MSA). (1) Normal oligodendroglia and myelin sheath; initial altered function of p25α and myelin basic protein (MBP). (2) Accumulation of p25α within oligodendroglia. (3) Reduction of MBP and deposition of degraded MBP in affected cell body. (4) Deposition of amorphous and fibrillar α-synuclein species within oligodendroglia, thereby forming glial cytoplasmic inclusions (GCIs). (5) Amorphous material (α-synuclein) of isolated GCIs. (6, 7) Schematic of core fibril comprising two subfibrils and a strand of interconnected 3 to 6nm fibrils. (8) Amorphous material deposited within neuropil. (9) Resultant glia degeneration and demyelination. (10) Resultant neurodegeneration.
Normal Dopamine Synapse

- dopamine
- dopamine receptor
Parkinson’s disease Synapse

- dopamine
- dopamine receptor
MSA Synapse

dopamine

dopamine receptor
MRI Findings in MSA

Watanabe H et al. Brain 2002;125:1070-1083
Hot Cross Buns
Hot Cross Bun Sign
Parkinson Disease PET Scan

Fig. 3a  FP-CIT dopamine SPECT

Fig. 3b  IBZM dopamine receptor SPECT
MSA PET Scan

Fig. 4a  FP-CIT dopamine SPECT
Fig. 4b  IBZM dopamine receptor SPECT
Summary

- MSA is a rare disease
- There are three basic subtypes that often overlap in one individual
  - MSA-A, MSA-P, and MSA-C
- The diagnosis is mostly based on history and physical findings
  - But brain imaging may be helpful
- Treatment is possible
  - But limited at this time