Drunk When You’re Not
A 67 year old male presents with feeling “off balance”

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Chief Complaint

• NOVEMBER 2015
  • Telephone call to primary care office.
    • 67 year old has been feeling “off balance” for “awhile” but starting to “feels worse.” When he walks, he “feels like he is drunk.”

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History of Present Illness

- NOVEMBER 2015
  - “Balance and coordination” issues since 2013 after right hip surgery
  - Plays tennis and “cannot swing well”
  - Multiple falls
  - Occasional slurred speech
  - Developed nighttime urinary incontinence (normal prostate exam in May 2015)
Past Medical History

- Past Medical History
  - Rheumatoid Arthritis
  - REM Sleep Disorder - since around 2011
  - Erectile Dysfunction: diagnosed in 2014
  - Obesity
  - Degenerative Joint Disease

- Past Surgical History
  - Right hip replacement in 2013 with difficult intubation
Past Medical History

- **Family History**
  - Cardiovascular Disease: Myocardial Infarctions (brother and mother), Type 2 Diabetes (brother)
  - No neurological, autoimmune family history

- **Social History**
  - Married with 3 adult children
  - Small business owner
  - 1-2 glasses of wine nightly, no smoking
Physical Exam

Vitals:
- General: NAD
- HEENT: mmm
- Cardiac: RRR, no murmurs
- Lungs: CTAB
- Abdomen: obese, NT, ND
- Extremities: without atrophy
- Neurologic:
  - CN 2-12 intact, but with mild dysarthria.
  - No word finding difficulties. No tremor with rest, action, or posture. Rocks to stand.
  - 5/5 upper and lower extremity strength
  - Negative Romberg.
  - Finger to nose, heel to shin with mild right>left dysmetria bilaterally. Gait: slightly wide base, decreased arm swing bilaterally, stooped posture

Medications: sildenafil, plaquenil
Investigations

- Labs
  - B 12, TSH, CPK all WNL
Investigations

- MRI 11/15
Investigations

• JANUARY 2016: NEUROLOGY CONSULT
  • Additional Clinical Information:
    • Decreased Blink Frequency
    • EMG: normal
    • Referral to Movement Disorders Clinic
Investigations

- DaT- SPECT scan
  - (Dopamine Transport Imaging with Single-Photon Emission Computed Tomography)
  - Radioligands attach to the dopamine transporter (DaT), a protein on the presynaptic membrane which serves as a portal for dopamine update.
  - Detects abnormal signal update in the striatum in patients with PD and other disease with nigrostriatal deficits
Investigations

"Comma"-shaped
Possible essential tremor

"Period"-shaped
Possible parkinsonian syndrome
DaT Scan - June 2016

- Abnormal size, shape and activity both basal ganglia.
- Prominent decreased activity both putamen.
- Moderate decreased activity both caudate nuclei
Differential Diagnosis

• Parkinson’s Disease
• Motor Neuron Disease
• Atypical Parkinson’s
• Multiple System Atrophy
• Lewy Body Dementia
Clinical Update

• MAY 2017
  • “Sudden leg weakness”
    • Unable to get out of bed
    • Orthostatic, with standing SBP 70
    • Now choking with meals
    • Started on fludrocortisone
Multiple System Atrophy

- Progressive fatal neurodegenerative disease characterized by
  - Progressive autonomic failure
  - Parkinsonian features
  - Cerebellar and Pyramidal Features

- Major diagnostic challenge with relevance in:
  - Cardiology
  - GI
  - ENT
  - Urology
  - Sleep Medicine
History

• 1969: combined three neurologic entities:
  • Olivopontocerebellar atrophy
  • Shy-Drager syndrome
  • Striatonigral degeneration
Diagnosis

• Definite MSA
  • Postmortem Diagnosis
    • Alpha synuclein positive glial cytoplasmic inclusions
    • Neurodegenerative changes in striatonigral or olivopontocerebellar region

• Probable
  • Sporadic, progressive disease in adults after 30 yr characterized by
    • autonomic failure, including urinary incontinence (with ED in men), or an orthostatic hypotension
    • plus either Parkinsonian or cerebellar features
Epidemiology

- Rare orphan disease
  - Incidence: 0.6 → 0.7: 100,000
  - Prevalence: 3.4 → 4.9: 100,000

- 2 forms
  - MSA-P: Parkinsonian features, more common in North America and Europe
  - MSA-C: cerebellar features, more common in Japan

- Disease Onset: usually sixth decade with both sexes affected equally

- Survival: 6-10 years
Causes

- **Unknown**
- **Sporadic**
  - Some families genetics
    - Loss of function mutation *COQ2* in some Japanese and sporadic cases
    - Loss of copy number of *SHC2* in monozygotic twins and Japanese patients with sporadic MSA
    - Mutations, duplications, and triplications of *SNCA* may cause Parkinson’s disease with features similar to MSA
Neuropathological Features

• Variable degrees of
  • olivopontocerebellar atrophy \(\rightarrow\) cerebellar syndrome
  • striatonigral degeneration \(\rightarrow\) poorly levodopa responsive parkinsonism
  • Degeneration of brain stem and medullary autonomic nuclei \(\rightarrow\) multidomain autonomic failure

• Oligodendroglialopathy
  • Histology: Proteinaceous oligodendroglial cytoplasmic inclusions (Papp-Lantos bodies)
  • Misfolded alpha-synuclein, normally found in neuronal axons and synapses
Clinical Presentation

• Prodromal premotor phase
  • Sexual dysfunction
  • Urinary urge incontinence
  • Orthostatic Hypotension
  • Inspiratory Stridor
  • Rapid Eye Movement Sleep Behavior Disorder
REM Sleep Behavior Disorder (RBD)

- Abnormal behaviors during REM sleep
  - Vocalizations and complex motor ranging from aggressive to pleasurable.
  - Dream enactment behavior
  - Polysomnography- loss of skeletal muscle atonia during REM sleep
- 50% with spontaneous RBD develop parkinsonism
  - 1817 “An Essay on Shaking Palsy”: Case VI demonstrated a violent parasomnia
- 81-90% develop a neurodegenerative disorder
- Most reveal alpha synuclein abnormalities post mortem
Clinical Presentation

• Motor Features
  • Multiple System Atrophy- Parkinsonism (MSA-P)
    • Slowness of movements, rigidity, fall tendency
    • Lack of “pill rolling” tremor
    • Irregular postural and action tremor with superimposed jerks (50%)
    • Degeneration of striatum → poor response to levodopa though transient response can be seen in 40% of patients
Clinical Presentation

• Motor Features
  • Multiple System Atrophy - Cerebellar
    • Cerebellar ataxia
      • Wide based gait, uncoordinated limb movements, action tremor, downbeat nystagmus
      • Lack of spasticity
      • Can see hyperreflexia in 30-50% of cases
      • Abnormal posturing: bent spine and antecollis
      • Dysphonia, dysarthria, dysphagia
      • Recurrent falls
Clinical Presentation

• Nonmotor Features
  • Autonomic dysfunction hallmark of disease
  • Erectile Dysfunction
  • Urinary Dysfunction
    • Often misdiagnosed as BPH in men or perineal laxity in women
  • Orthostatic Hypotension
    • Syncope, dizziness, weakness, nausea, pain in neck and shoulder region
Clinical Presentation

- **Nonmotor Features**
  - Respiratory disturbances
    - Inspiratory stridor in 50% of patients especially in advanced disease
    - This can occur with sleep apnea together
    - Risk factor for sudden death
  - Autonomic Failure
    - Constipation, Thermoregulatory Problems
Clinical Presentation

• Nonmotor Features
  • Dementia and hallucinations are not a part of the disease
  • Frontal lobe dysfunction can occur- emotional incontinence, behavioral changes
  • Depression, anxiety, and suicidal ideation are more common
Figure 2. Multidisciplinary Presentation of MSA.
Radiographic Signs

- MRI
  - MSA-P:
    - atrophy of putamen, middle cerebellar peduncle, pons or cerebellum
    - “putaminal rim sign” - hyperintense signal of the dorsolateral border of putamen plus putaminal hypointensity in T2 weighted sequences
  - MSA-C
    - Atrophy of putamen, middle cerebellar peduncle, or pons
    - “Hot cross bun sign” (Cruciform hyperintensity in the pons) in T2 weighted sequences
- Putaminal rim sign and hot cross bun signs are specific but not sensitive
Transverse T2-weighted MR image of the brain of a patient with multiple system atrophy (MSA) of the cerebellar-predominant subtype (MSA-c) shows the hot cross bun sign as a cruciform hyperintensity in an atrophied pons (arrow). Cerebellum and middle cerebellar peduncles (arrowheads) are also atrophied, with increased signal intensity.
Disease Progression

- Worsening of symptoms over 10 year period
  - 50%: walking aids within 3 years
  - 60%: wheelchair by 5 years
  - 6-8 years: bedridden

- Causes of death:
  - Pneumonia, Sepsis secondary to UTI, Sudden Death due to bilateral vocal cord paralysis or disruption of brainstem cardiorespiratory drive
  - Poor prognostic indicators: older age, parkinsonian phenotype, and early development of severe autonomic failure
Disease Progression

Figure 3. Natural History of MSA.
The premotor phase of MSA can last for months to years. Year 0 denotes the time of onset of motor symptoms. A diagnosis of definite
Treatments

- Symptomatic therapy with low evidence
- Motor Features
  - Slow increase in levodopa- 40% responsive at first
Treatments

• Nonmotor Features
  • Neurogenic bladder: screen regularly for UTIs
  • Urge incontinence: antimuscarinic agents, with caution
  • Sildenafil for ED; intracavernous injections of prostaglandins may be an alternative
  • Orthostatic hypotension
    • Fludrocortisone or midodrine
    • Behavioral changes
  • Inspiratory Stridor or Sleep Apnea
    • CPAP or botox injection in vocal cord adductors
    • Glycopyrrolate or botox of salivary glands for drooling, impaired swallowing
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References


