Making a Diagnosis

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Disclosures

- Dr. Bower receives research funding from Abbvie Pharmaceuticals for a clinical trial on PSP

Case Study- Mr. T.

- Mr. T is a 66 year old man, married, retired high school principal with two adult children
- 2014-Family notes he's less engaged, doesn't smile
- Primary MD
  - Dx: Depression
  - Tx: Sertraline
  - Response: Not much
- 2015-Wife notes his gait is slow on their daily walk with the dog
- Mid-2015 Trouble buttoning collar/sleeve buttons
- Primary MD
  - "You need to see a neurologist."
Mr. T

- December 2015- Neurologist noted:
  - Masked face/little blinking
  - Right arm bradykinesia
  - Small shuffling steps
  - Stumbles on turns
  - No arm swing
- Dx: Parkinson disease
- Tx: Sinemet (carbidopa/levodopa) 25/100 pushed up to 2 tabs 3x/day
- Response: Maybe improvement in buttoning (?)

Mr. T.

- May 2017- speech slurred, fell in livingroom- needed stitches
  - Increases carbidopa/levodopa to 3 tabs 3x/day
  - Not much improvement
- September 2017- now falling once per week
- December 2017- sees Neurologist
  - "Maybe you don't have Parkinson's disease"
  - "I don't know what this is…"
  - Need to go to Mayo, or University of….
- April 2018- Visit to Mayo or University of….
What's the problem???

Dermatologists, Oncologists, Pulmonologists...

Neurologists
Parkinsonism

Syndrome with two of:
- Rest tremor
- Bradykinesia
- Rigidity
- Impaired postural reflexes
Tremor

- Rest
- Action
  - Postural
  - Kinetic
  - Intention

Bradykinesia Symptoms

- Facial expression/speech change
- Drooling
- Dexterity difficulties
- Small handwriting
- Difficulty with low chair/turning in bed
- Gait difficulties - "dizzy"

Bradykinesia Signs

- Face
- Gait
- Alternating motion rates
- Speech
Rigidity
- Feels "rigid"/non-descript pain
- Increased tone in a relaxed body part
- Appendicular vs. axial
- Contralateral distraction

Postural Instability
- Falls/"dizzy"
- Station
- Pull test

Parkinsonism
Syndrome with two of:
- Rest tremor
- Bradykinesia
- Rigidity
- Impaired postural reflexes
Parkinson's disease

- Parkinsonism
- Early falls
- Supranuclear downgaze palsy
- No or minimal levodopa response
- Other: axial rigidity, sitting en-bloc, spasticity, wide-based gait, reptilian stare, retrocollis, pseudobulbar affect, dysarthria, dysphagia, frontal dementia, behavioral changes

Progressive Supranuclear Palsy

- Parkinsonism
- Early falls
- Supranuclear downgaze palsy
- No or minimal levodopa response
- Other: axial rigidity, sitting en-bloc, spasticity, wide-based gait, reptilian stare, retrocollis, pseudobulbar affect, dysarthria, dysphagia, frontal dementia, behavioral changes
NINDS-SPSP Criteria for PSP

- Possible:
  - Gradually progressive with onset > 40 yrs.
  - Either:
    - Vertical supranuclear gaze palsy
    - Slowed vertical saccades and early falls
    - No other causative disease

- Probable: Same as above but both vertical palsy and early falls

- Definite: Requires pathologic confirmation

NINDS-SPSP Criteria for PSP

- Specificity is the ability of the test to correctly identify those without the disease
  - Specificity is 95-100%
  - i.e. If you FULFILL the criteria, you probably have it

- Sensitivity is the ability of a test to correctly identify those with the disease
  - Sensitivity median is 24% at first clinical visit
  - i.e. If you DON’T FULFILL the criteria, you still may have it

Mr. T.

- Exam:
  - Masked face
  - Soft, strained, strangled dysarthria
  - Symmetric bradykinesia
  - Rigidity at neck >> arms and legs
  - + Pull test
  - Slowed but full saccades
NINDS-SPSP Criteria for PSP

- Gradually progressive
- Age >40
- Either
  - 1. Vertical supranuclear palsy, or
  - 2. Slowed saccades and
    Falls within one year
June 2017-206 Autopsy-proven PSP cases from nine brain banks

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Four Core Clinical Features

- Oculomotor Dysfunction
- Postural Instability
- Akinesia
- Cognitive Dysfunction
Four Core Clinical Features

- Oculomotor Dysfunction
  - Vertical supranuclear palsy O1
  - Slow saccades O2
  - Square wave jerks or eyelid opening apraxia O3
- Postural Instability
  - Falls within 3 years P1
  - +Pull test within 3 years P2
  - >2 steps backward on pull test within 3 years P3

Four Core Clinical Features

- Akinesia
  - Gait freezing within 3 years A1
  - Akineti-rigid, axial and L-dopa resistant A2
  - Parkinsonism with tremor and/or asymmetric and/or levodopa responsive A3
- Cognitive Dysfunction
  - Speech/language disorder C1
  - Frontal cognitive/behavioral presentation C2
  - Corticobasal syndrome C3

Supportive Features

- Clinical Clues
  - Levodopa resistance CC1
  - Hypokinetik spastic dysarthria CC2
  - Dysphagia CC3
  - Photophobia CC4
- Imaging findings
  - Midbrain atrophy/hypometabolism IF1
  - Postsynaptic striatal dopaminergic degeneraia IF2
Diagnostic Criteria

Progressive Supranuclear Palsy

- PSP- Richardson's syndrome
- PSP- Progressive gait freezing
- PSP- Predominant parkinsonism
- PSP- Predominant frontal presentation
- PSP- Predominant oculomotor dysfunction
- PSP- Predominant speech/language disorder
- PSP- Predominant corticobasal syndrome
- PSP- Predominant postural instability
Mr. T.

- Oculomotor Dysfunction
- Slow saccades = O2
- Postural Instability
  - Falls within 3 years = P1

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Diagnostic Criteria

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Mrs. P.
- Mrs. P. is a 74 year old right-handed woman, farmer, mother of four children
- Thanksgiving 2015- Noticed some difficulty whisking whipped cream for the pies
- March 2016- R forearm cramping
  - Prescribed muscle relaxants
- October 2016 increased R arm pain and slowing of gait
- Thanksgiving 2016- Noticed small jerks of arm while cooking. Very difficult to whisk whipped cream
Mrs. P.
- June wedding of granddaughter - Family noted significant slowing of gait, fixed posture of R arm, jerky tremor R arm
- Neurologist:
  - R arm>leg rigidity
  - R fingers and hands - moderately severe slowing of finger taps and hand movements (bradykinesia)
  - R arm dystonic posturing
  - Ideomotor apraxia when asked to pretend brushing hair

Parkinsonism
Syndrome with two of:
- Rest tremor
- Bradykinesia
- Rigidity
- Impaired postural reflexes

Parkinsonism
Corticobasal Syndrome

- Asymmetry
- Limb rigidity
- Limb apraxia
- Myoclonus
- Dystonia
- Alien limb

Nomenclature

- Corticobasal Syndrome
  - CLINICAL diagnosis with clinical symptoms and signs
- Corticobasal Degeneration
  - PATHOLOGIC diagnosis

- SHOULD be one and the same, but...

Corticobasal Syndrome Vs. Degeneration

- Clinical ➔ Pathological
  - 36 Cases with CBS diagnosed in life
  - Only 20 had CBD on autopsy (56% diagnostic accuracy)
  - Others had PSP, AD, CJD, FTLD, Pick’s

- Pathological ➔ Clinical
  - 29 cases of CBD in a Brain Bank
  - Only 12 had been diagnosed with CBS (41% had been given correct dx)
  - Others had PSP, AD, PPA, FTD, PCA, etc.
Corticobasal Syndrome

- Limb rigidity or akinesia
- Limb dystonia
- Limb myoclonus
- Limb or orobuccal apraxia
- Cortical sensory deficit
- Alien limb

Armstrong et al. Neurology, 2013

Corticobasal Syndrome

- Probable
  - Asymmetric presentation of 2 of
    - Limb rigidity or akinesia
    - Limb dystonia
    - Limb myoclonus
  - 2 of:
    - Orobuccal or limb apraxia
    - Cortical sensory deficit
    - Alien limb
- Possible
  - Similar to above but could be symmetric and one of each in the two groups

Mrs. P

- Asymmetry
- Limb rigidity or akinesia
- Limb dystonia
- Limb myoclonus
- Limb or orobuccal apraxia
- Cortical sensory deficit
- Alien limb
- DX= Possible CBS
Corticobasal Syndrome

- Only 12/29 cases with CBD (from autopsy) had been diagnosed correctly in life
- Many others had been given diagnoses of different dementia types

Corticobasal Syndrome

- Fronto behavioral-spatial syndrome
  - TWO of
    - Executive dysfunction
    - Behavioral or personality changes
    - Visuospatial deficits
Corticobasal Syndrome

- Nonfluent/agrammatic variant of primary progressive aphasia-
  - Effortful agrammatical speech plus ONE of
    - Impaired grammar/sentence comprehension with good single word comprehension
    - Apraxia of speech (groping)

Corticobasal Syndrome

- Progressive supranuclear palsy syndrome
  - Three of:
    - Limb rigidity or akinesia
    - Postural instability or falls
    - Urinary incontinence
    - Behavioral changes
    - Slowed vertical saccades or supranuclear vertical gaze palsy

Corticobasal Syndrome

- Probable CBS
- Possible CBS
- Fronto behavioral–spatial syndrome
- Nonfluent/agrammatic variant of primary progressive aphasia
- Progressive supranuclear palsy syndrome
Dr. G.

- Dr. G is a 57 year old female psychologist
- 2012 (age 51)- Urinary urgency with occasional incontinence
- 2013- increasing incontinence
  - Dx= Neurogenic Bladder
- 2015 Masked face, small handwriting, slowed shuffling gait
- 2016- Neurologist
  - Patient reported two unexplained falls
  - Bed partner reports she acts out dreams
  - Slowed AMRs- R > L
  - Rigid tone R>L arms, R leg, neck
  - Shuffling gait
  - Dx= Parkinson disease

Dr. G.

- Carbidopa/Levodopa 25/100 2.5 pills 3x/day
  - Some improvement in shuffling and dexterity
- Mid 2017- Increased falls, increasing lightheadedness with standing, worsening gait
- Late 2017- Falls twice/month
- January 2018- Fainted on standing
- March 2018 Neurologist
  - "You don't have Parkinson disease. You have Multiple System Atrophy."
Multiple System Atrophy

- Poorly (modestly) levodopa responsive parkinsonism
- Dysautonomia
  - Orthostatic hypotension
  - Erectile dysfunction
  - Anhidrosis
  - Constipation
- Urinary Dysfunction
  - Brainstem atrophy
  - Detrusor (bladder muscle) denervation
  - Sphincter denervation

Multiple System Atrophy

- MSA-P (Previous slide)
- MSA-C
  - Cerebellar ataxia and dysautonomia, urinary dysfunction
Parkinsonism

- PSP
- CBS
- Parkinson's disease
- MSA

REM Sleep Behavior Disorder

Yes
- Parkinson's disease
- Multiple System Atrophy

No
- Progressive Supranuclear Palsy
- Corticobasal Degeneration

Multiple System Atrophy

- Probable MSA- Sporadic, progressive Adult (>30 yrs)
- Autonomic Failure
  - Urinary incontinence with ED in males, or
  - Orthostatic drop in BP within 3 minutes of 30/15
- Poorly L-dopa responsive parkinsonism (MSA-p) OR cerebellar ataxia (MSA-C)
Multiple System Atrophy
- Possible MSA
  - Parkinsonism OR cerebellar ataxia
  - Autonomic dysfunction - One of
    - Unexplained urinary issues
    - Unexplained ED
    - OH less severe than described for Probable
  - AT least one of other unusual features
    - Spasticity
    - Stridor
    - Early falls
    - Early dysphagia
    - MRI/PET findings
    - Parkinsonism and cerebellar ataxia

Dr. G.
- Sporadic, progressive
- Urinary incontinence
- Orthostatic drop of 30/15
- Poorly L-dopa responsive, or
- Cerebellar ataxia
- DX= Probable MSA-P

Multiple System Atrophy
Multiple System Atrophy

![Image of brain MRI]

Multiple System Atrophy

Autonomic Testing

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<th>TST</th>
<th>GSART (μl/min)</th>
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<tr>
<td>99% anhidrosis</td>
<td>1.48</td>
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<tr>
<td>66% anhidrosis</td>
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<table>
<thead>
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<th>TST</th>
<th>1/19/96</th>
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<tr>
<td>0% anhidrosis</td>
<td>1/19/96</td>
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**Parkinsonism**

- Prevalence in USA
  - PD 840,000
  - PSP 20,000
  - MSA 15,000
  - CBS 2500

**Conclusions- Making a Diagnosis**

**Conclusions**

- Most (but not all) patients with PSP, CBS or MSA have parkinsonism
- Frequently confused with Parkinson's disease in the beginning
- Have many overlapping features
- Clinical diagnostic accuracy is not perfect