Atypical Parkinsonism

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Learning Goals

1. Recognize criteria for Parkinsonism

2. Review differential diagnosis of Parkinsonism

3. Recognize clues suggestive of atypical Parkinsonism

4. Recognize: clinical features of atypical parkinsonian disorders, approach to management
1. Differential diagnosis of Parkinsonism

2. Atypical Parkinsonism: clues to diagnosis

3. Subtypes:
   - PSP
   - CBS/CBD
   - MSA
   - DLB
Parkinsonism Diagnostic Criteria

- Tremor at rest
- Bradykinesia
- Rigidity
- Loss of postural reflexes
- Flexed posture
- Freezing (motor blocks)

Definite: at least 2/3 of these features, 1 of them being 1 or 2

Probable: 1 or 2 alone is present

Possible: at least 2 of features 3 to 6 must be present

- Postural reflexes
Differential Diagnosis of Parkinsonism

- Secondary Parkinsonism
- Atypical Parkinsonism
- Heredo degenerative Parkinsonism
- Primary Parkinsonism
Differential Diagnosis of Parkinsonism

Primary idiopathic Parkinsonism

Secondary (symptomatic)
- **Vascular**
  - Multi-infarct, Binswanger
- **Trauma**
  - Dementia pugilistica
- **Other**
  - PTH abnormalities, hypothyroid, NPH
Differential Diagnosis of Parkinsonism

Secondary (symptomatic)

- **Infectious**
  - Post-encephalitic, AIDS, prions, SSPE
- **Immunologic/paraneoplastic**
- **Medications**
  - DA receptor blockers, reserpine, TBZ, Lithium, Flunarizine, Cinnarizine, Ectasy
- **Toxins**
  - MPTP, CO, Mn, Hg, Cyanide
Differential Diagnosis of Parkinsonism

Parkinson Plus Syndromes

- PSP
- MSA
- CBS
- DLB
- Parkinsonism-Dementia-ALS complex of Guam
- Primary pallidal degeneration
Heredodegenerative Parkinsonism (I)

- Huntington disease
- Wilson disease
- NBIA
  - Aceruloplasminemia
  - Neuroferritinopathy
- PKAN, PLAN, FAHN
Differential Diagnosis of Parkinsonism

Heredodegenerative Parkinsonism (II)

- SCA- 2,3,6,12,21
- Frontotemporal dementia
- X-linked dystonia parkinsonism
- Fahr’s disease
- Neuroacanthocytosis
Clues suggesting Atypical Parkinsonism - I

- Lack of adequate dopaminergic response in a patient with a parkinsonian syndrome

1. Marked symmetry of signs in early stages
2. Truncal more than appendicular symptoms
3. Early onset of dementia
4. Early onset of hallucinations
5. Early onset of postural instability
Clues suggesting Atypical Parkinsonism - II

6. Impaired vertical gaze
7. Square wave jerks
8. Apraxia of eyelid opening or closing

9. Prominent motor apraxia
10. Alien limb phenomenon
11. Pyramidal signs

12. Autonomic symptoms; postural hypotension, urinary incontinence, sexual dysfunction
Pathological Classification

Atypical Parkinsonism

Taupathies
PSP/CBS-CBD

Synucleiopathies
MSA/DLB
Progressive Supranuclear Palsy (PSP)
PSP Overview

• Disorder of Tau protein aggregation

• Sporadic; familial PSP reported

• More often in men, onset @ mean age of 63 years

• Classic picture: gait & balance impairment, gaze palsy, bradykinesia, spastic dysarthria & dysphagia
Cognitive & behavioral changes:

- Apathy, intellectual slowing, impairment of executive functions
- Apathy for disability + frontal impulsivity ("rocket sign")
- Frontal disinhibition: "applause sign", palilalia
- Asymmetric apraxia: arm levitation (overlap with CBD)
- Depression in > 50% of patients
PSP Clinical Features II

- Motor Parkinsonism:
  - Postural instability, falls

- PSP variant, “PSP-pure akinesia with gait freezing”

- Axial > appendicular rigidity & bradykinesia, retrocollis

- Tremor @ rest is not rare, 5-10%
PSP Video I
Gait & Spontaneous loss of balance (Video: Dr. Dewey)
• **Eye movement abnormalities:**

  • Slowing of vertical saccades, apraxia of gaze initiation, saccadic pursuit, poor convergence & square-wave jerks

  • Reduced blinking, blepharospasm – functional blindness

  • Levator inhibition
PSP Clinical Features IV

- Dysarthria, variable combination of spasticity, hypophonia & ataxia
- Dysphagia with risk of aspiration pneumonia
- Patients are uninhibited in stuffing the mouth
- Primary & secondary insomnia
- Day time hypersomnolence
- Urinary urgency & incontinence
PSP Video II
Spastic dysarthria and procerus sign (Video: Guy Sawle, MD)
PSP Video IV
Square Wave Jerks
PSP Video V
Doll’s Eye Overcoming Gaze Palsy

Copyright: Edwards, Quinn, Bhatia. Institute of Neurology, UCL, Queen Square, London, UK 2008
PSP Diagnosis

Diagnosis:
- Definitive diagnosis: histopathological confirmation
- NINDS-SPSP criteria
- PSP rating scale: disability measure
- MRI Brain
- PET scan/DAT scan
Differential diagnosis:
- CBD PD
- NPH Wilson disease
- Alzheimer disease
- Whipple disease
- Multi-infarct dementia
- Tumors Prion disease Syringomyelia
# NINDS-SPSP Diagnostic Criteria

## Table 1

National Institute of Neurological Disorders and Stroke—Society for Progressive Supranuclear Palsy criteria for the diagnosis of progressive supranuclear palsy (PSP; proposed by Litvan et al)

<table>
<thead>
<tr>
<th>&quot;Possible&quot; PSP</th>
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</thead>
<tbody>
<tr>
<td>All 3 of these:</td>
<td></td>
</tr>
<tr>
<td>Gradually progressive bradykinetic disorder</td>
<td></td>
</tr>
<tr>
<td>Onset at age 40 or later</td>
<td></td>
</tr>
<tr>
<td>No evidence for competing diagnostic possibilities. Plus either of these:</td>
<td></td>
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<tr>
<td>Vertical gaze palsy</td>
<td></td>
</tr>
<tr>
<td>Or</td>
<td></td>
</tr>
<tr>
<td>Slowing of vertical saccades and prominent postural instability with falls in the first year</td>
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</tr>
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<table>
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<th>&quot;Probable&quot; PSP</th>
<th></th>
</tr>
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<tbody>
<tr>
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Criteria that would exclude PSP from consideration:

- Recent encephalitis
- Alien limb syndrome, cortical sensory defects or temporoparietal atrophy
- Psychosis unrelated to dopaminergic treatment
- Important cerebellar signs
- Important unexplained dysautonomia
- Severe, asymmetric parkinsonian signs
- Relevant structural abnormality of basal ganglia on neuroimaging
- Whipple's disease on cerebrospinal fluid polymerase chain reaction, if indicated
Treatment

• Despite trials of hopeful neuroprotective agents, Rx remains symptomatic

• Levodopa: rigidity & bradykinesia

• Titrate to 1,000-1,200 mg/day

• No dyskinesia, response declines over following months

• Fall precautions and prevention
PSP Management II

- Botulinum toxin: “apraxia” of eyelid opening, retrocollis

- Prisms: help diplopia, Rx sleep disorders

- Rx dysphagia: PEG tube, Rx urinary urgency & incontinence, constipation

- Rx mood & cognitive issues: donepezil performed poorly/Rivastigmine
Corticobasal Syndrome (CBS/CBD)
CBD Overview

Overview:

- Rare progressive neurodegenerative disorder with distinct pathological features & multiple phenotypic presentations that occur in other conditions (AD, PSP, Pick’s)

- Classic presentation is CBS: asymmetric parkinsonism, rigidity, myoclonus, dystonia, ideomotor apraxia, alien limb
CBD Clinical Features I

- Age of onset: 5th-7th decade
- ? Predominance in women

Higher cortical features:

- Apraxia: upper extremities, orofacial region

- Ideomotor apraxia (not knowing how to do it) vs ideational apraxia (not knowing what to do)
CBD Clinical Features II

Higher cortical features:

• Language disturbance: mild impairment to severe progressive non-fluent aphasia or even complete mutism

• Alien limb phenomena: involuntary & purposeful hand movements with feeling of foreignness of the limb, failure to recognize ownership of the limb in absence of visual cues
CBD Clinical Features III

- Cortical somatosensory loss; agraphesthesia, extinction & astereognosis

- Visual neglect/agnosia, optic ataxia

- Cognitive impairment: executive dysfunction with behavioral changes
CBD Clinical Features IV

• Neuropsychiatric disturbances are common; apathy, irritability, depression

• Prominent memory impairment

Motor features:

• Parkinsonism: asymmetric onset of parkinsonism with absent of transient L-Dopa responsiveness
• Leg apraxia: falls

• Dystonia: mostly upper limb or hemi-dystonia

• Myoclonus: upper limbs, face, superimposed with limb dystonia. Usually focal, on action or stimulus-sensitive
CBD Clinical Features VI

- Dysarthria/dysphagia
- UMN signs, hyperreflexia, positive babinski’s sign
- Increased horizontal latency of reflexive visually guided saccades
- EOG recordings may help distinguish patients with CBS from PSP
CBD Video I
Clinical Features
CBD Video II
Alien Limb Phenomenon
CBD Video III
Reflex Myoclonus (Video: Guy Sawle, MD)
CBD Video IV
Starfish Hand (Video: Guy Sawle, MD)
CBD Diagnosis

Diagnosis:

• Definitive diagnosis: histopath
• New diagnostic criteria

• MRI Brain: posterior lateral & medial frontal cortical atrophy, lack of brain stem atrophy (PSP)
• Recent 3 dimensional MRI-based volumetric study

PSP/CBS
CBD Differential Diagnosis

- Diagnosis
  - SPECT: limited value
  - Evoked potentials: abnormal SEP asymmetry
  - Neuropsychological testing:
  - No specific biomarkers

Differential diagnosis:
- PD       AD       PSP       FTLD
- Other neuro-degenerative d/o    Strokes
- Tumors      Rapidly progressive dementias
<table>
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<tr>
<th>CBD Diagnostic Criteria</th>
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</table>

**Table 2** Diagnostic criteria for corticobasal degeneration

<table>
<thead>
<tr>
<th></th>
<th>Clinical research criteria for probable sporadic CBD (cr-CBD)</th>
<th>Clinical criteria for possible CBD (p-CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Insidious onset and gradual progression</td>
<td>Insidious onset and gradual progression</td>
</tr>
<tr>
<td><strong>Minimum duration, y</strong></td>
<td>1 year symptoms</td>
<td>1 year symptoms</td>
</tr>
<tr>
<td><strong>Age at onset, y</strong></td>
<td>≥50</td>
<td>No minimum</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>Exclusion</td>
<td>Permitted</td>
</tr>
<tr>
<td><strong>Permitted phenotypes</strong></td>
<td>Probable CBS or FBS or NAV plus at least one CBS feature (a–f)</td>
<td>Possible CBS or FBS or NAV or PSPS plus at least one CBS feature (b–f)</td>
</tr>
<tr>
<td><strong>Genetic mutation affecting tau (e.g., MAPT)</strong></td>
<td>Exclusion</td>
<td>Permitted</td>
</tr>
</tbody>
</table>

Abbreviations: CBD, corticobasal degeneration; CBS, corticobasal syndrome; FBS, frontal behavioral-spatial syndrome; NAV, nonfluent/agrammatic variant of primary progressive aphasia; PSPS, progressive supranuclear palsy syndrome.


*Exclusion criteria for both clinical research criteria for probable sporadic CBD and possible CBD: (1) Evidence of Lewy body disease—classic 4-Hz Parkinson disease resting tremor, excellent and sustained levodopa responsiveness, or hallucinations; (2) evidence of multiple system atrophy—dysautonomia or prominent cerebellar signs; (3) evidence of amytrophic lateral sclerosis—presence of both upper and lower motor neuron signs; (4) semantic- or logopenic-variant primary progressive aphasia; (5) structural lesion suggestive of a focal cause; (6) granulin mutation or reduced plasma progranulin levels, TDP-43 mutations, FUS mutations; (7) evidence of Alzheimer disease (excluding some cases of CBD with coexisting amyloid pathology)—cerebrospinal fluid profile strongly suggestive of AD such as low CSF Aβ42/tau ratio or positive [11C]Pittsburgh compound B positron emission tomography (amyloid imaging), or genetic mutation suggesting AD (e.g., presenilin, amyloid precursor protein).

*Two or more relatives.

See Table 1 for details about phenotypes.
CBD Management

Treatment:

• Trial of L-Dopa is reasonable, at least a month with 1000-1200 mg

• Myoclonus: valproic acid, clonazepam, levatiracetam

• Dystonia: botulinum toxin

• PT/OT/ST
Multiple System Atrophy (MSA)
MSA Overview

- Rare, adult onset neurodegenerative disorder characterized by autonomic dysfunction and variable combination of Parkinsonism & cerebellar ataxia

- Age at onset: 53-65 years

- Other clinical findings include REM-BD, sleep apnea, stridor, hyperreflexia
MSA Clinical Features I

Signs & Symptoms:

- Autonomic dysfunction is a key feature necessary for diagnosis

- Erectile dysfunction in men, urinary dysfunction with urgency

- Orthostatic hypotension; syncopal episodes, postural lightheadedness, pain in neck & shoulders called, “coat hanger pain”
MSA Clinical Features II

• Postural hypotension, supine hypertension, anhydrosis with thermoregulatory disturbance, constipation, poor lacrimation & salivation

• Parkinsonism in 90% of cases

• 76% of patients with MSA-C have parkinsonism, 54% with MSA-P have cerebellar symptoms

• Tremor in 80% of MSA patients, > common in MSA-P
MSA Clinical Features III

• Postural tremor, resting tremor

• Polyminimyoclonus, continuous generalized myoclonus of tiny amplitude resembling an irregular tremor

• Jerky myoclonic action tremor

• Cerebellar dysfunction: intention tremor, gait & appendicular ataxia, dysarthria, sustained gaze-evoked nystagmus, hypometric saccades
• REM-BD in 70% of MSA patients

• Central & obstructive sleep apnea - sudden death

• Laryngeal dystonia – stridor

• Pyramidal signs: hyperreflexia, babinski’s
• Dystonia; facial dystonia, L-Dopa-induced complication

• Postural abnormalities, anterocollis, camptocormia & Pisa syndrome
MSA Clinical Features VI

- Square wave jerks, slowing of saccades, INO & reduced vertical gaze

- Extremities may be cold & violaceous, "cold hands & cold feet" signs
MSA Clinical Features VII

- Contractures of hands or feet
- Emotional lability
- Impaired frontal lobe function; verbal retrieval difficulties, impairment in controlling attention & learning new verbal information in MSA-C
- Hyposmia is very mild or absent in MSA
MSA Video I
Clinical Features
• Definitive diagnosis: histopathological confirmation

• Clinical criteria for diagnosis
• MSA-P: T2 MRI: putaminal atrophy, lateral rim hyperintensity

• MSA-C: atrophy of the medulla, MCP, pons, inferior olives, cerebellum, “hot cross buns” sign
### Table 1 Clinical criteria for the diagnosis of multiple system atrophy (MSA)

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Clinical criteria</th>
</tr>
</thead>
</table>
| **Probable**          | Sporadic, progressive disorder with age at onset ≥30; Autonomic failure:  
  • Urinary incontinence (with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic with either  
  poorly levodopa-responsive parkinsonism (MSA-P)  
  • Bradykinesia with rigidity, tremor, or postural instability  
  or a cerebellar syndrome (MSA-C)  
  • Gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction |
| **Possible**           | Sporadic, progressive disorder with age at onset ≥30 with either parkinsonism or a cerebellar syndrome and at least one feature suggesting autonomic dysfunction  
  • Otherwise unexplained urinary urgency, frequency or incomplete bladder emptying,  
  erectile dysfunction in males, or significant orthostatic blood pressure decline not meeting requirements for probable MSA  
  and at least 1 additional feature:  
  MSA-P or MSA-C:  
  • Babinski sign or hyperreflexia  
  • Stridor  
  MSA-P:  
  • Rapidly progressive parkinsonism  
  • Poor response to levodopa  
  • Postural instability within 3 y of motor onset  
  • Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction  
  • Dysphagia within 5 y of motor onset  
  • Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum  
  • Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum  
  MSA-C:  
  • Parkinsonism (bradykinesia and rigidity)  
  • Atrophy on MRI of putamen, middle cerebellar peduncle, or pons  
  • Hypometabolism on FDG-PET in putamen  
  • Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET |

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography.

MSA Diagnosis III

- Autonomic testing: abnormalities early in the course of the disease compared to PD; OH, QSART, NE levels, CASS score, urine residual volume > 100 ml increases likelihood of MSA

- EMG: external anal sphincter (Onuf’s nucleus) denervation

- MIBG uptake preserved in MSA as pre-ganglionic neurons are affected
Treatment:

- No clinical trials proving efficacy of any Rx for MSA

- Only 30% respond to L-Dopa, short-lived benefit. Dosing limited by s/e, hypotension, nausea, hallucinations

- Limb & neck dystonia: botulinum toxin, can also be tried for stridor (elective tracheostomy)
MSA Management II

- Rx of OH: midodrine, fludrocortisone, droxidopa, pyridostigmine

- ED: sildenafil, exacerbate hypotension

- REM-BD: clonazepam, melatonin, Rx OSA – sudden death

- PT, OT, ST, exercise
Dementia with Lewy Bodies (DLB)
• 2\textsuperscript{nd} most common cause of dementia, prevalence: 3-26\% in > 65 years

• Slightly > male predominance

• Time course of 1 year from cognitive changes to motor onset

• Manifests clinically with fluctuating alertness, visual hallucinations and parkinsonism with features of both cortical and subcortical dementia
DLB Clinical Features I

- Fluctuating attention early

- Well formed visual hallucinations

- Paranoid delusions, anxiety, depression, apathy

- Working memory impairment

- Bilaterally symmetrical parkinsonism; limb rigidity & bradykinesia, symmetric postural tremor
• Falls: autonomic, cognitive & motor causes

• Autonomic features: constipation, OH, sialorrhea

• REM-BD, precedes cognitive & motor features by years

• Neuroleptic sensitivity even with atypical antipsychotics
DLB Diagnosis

- Definitive: histopath confirmation
- Diagnostic criteria for DLB
  - MRI – generalized cortical atrophy
  - FDG-PET/DAT scan
- No definite biomarkers
- Reversible causes: lab work up
DLB Differential Diagnosis

- AD, PDD
- FTD
- Other PD plus syndromes
- Lacunar syndromes
- Hydrocephalus
# DLB Diagnostic Criteria

<table>
<thead>
<tr>
<th><strong>Table 1</strong> Diagnostic criteria for dementia with Lewy bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central characteristic</strong></td>
</tr>
<tr>
<td><strong>Dementia with impairments in daily functioning</strong></td>
</tr>
<tr>
<td>(may have intact memory function at onset)</td>
</tr>
<tr>
<td><strong>Core characteristics</strong></td>
</tr>
<tr>
<td>Fluctuation cognition/attention and alertness</td>
</tr>
<tr>
<td>Visual hallucinations</td>
</tr>
<tr>
<td>Parkinsonism</td>
</tr>
<tr>
<td><strong>Suggestive characteristics</strong></td>
</tr>
<tr>
<td>REM sleep behavior disorder</td>
</tr>
<tr>
<td>Neuroleptic sensitivity</td>
</tr>
<tr>
<td>Reduced dopaminergic activity in the basal ganglia demonstrated by SPECT or PET imaging</td>
</tr>
<tr>
<td><strong>Probable DLB</strong></td>
</tr>
<tr>
<td>Central characteristic and</td>
</tr>
<tr>
<td>At least 2 core characteristics or 1 core and 1 suggestive characteristic</td>
</tr>
<tr>
<td><strong>Possible DLB</strong></td>
</tr>
<tr>
<td>Central characteristic and</td>
</tr>
<tr>
<td>1 core characteristic or 1 or more suggestive characteristic</td>
</tr>
<tr>
<td><strong>Supporting characteristics</strong></td>
</tr>
<tr>
<td>Repeated falls or syncope, transient impairments in consciousness, autonomic dysfunction (i.e., in the form of orthostatic hypotension or urinary incontinence), hallucinations in nonvisual modalities, systematic delusions, depression, intact medial temporal lobe on anatomic imaging, reduced (particularly occipital lobe) metabolism on metabolic imaging (SPECT or PET), pathologic MIBG-SPECT scan of the myocardium, EEG showing slow activity with intermittent temporal sharp waves</td>
</tr>
</tbody>
</table>

**Abbreviations:** DLB, dementia with Lewy bodies; EEG, electroencephalogram; MIBG, [I-123] myocardial scintigraphy; PET, positron emission tomography; REM, rapid eye movement; SPECT, single photon emission computed tomography.

**Source:** Adapted from McKeith et al\textsuperscript{15}. 
Treatment:

• Cholinesterase inhibitors; help with cognitive, behavioral impairments & hallucinations

• Avoid neuroleptics; quetiapine, clozaril can be helpful for psychosis

• Parkinsonism: DA agents, L-Dopa, agonists less well tolerated
DLB Management II

- SSRI – anxiety & depression
- REM-BD: clonazepam
- Management of OH
- Fall prevention
Atypical Parkinsonism – Summary I

- Atypical parkinsonian syndromes: atypical features & lack of levodopa responsiveness
- Significant impact on cost of care & quality of life
- Currently, no effective Rx that alter the natural history of disease or affect survival
- Current therapies only focus on symptomatic management
Atypical Parkinsonism – Summary II

- Complex diagnosis, low prevalence, lack of longitudinal follow up; clinical trials have been limited by poor funding, small size, lack of biomarkers

- Recent breakthroughs in genetics, molecular biology & neuroimaging

- Efforts to develop targeted therapeutic agents with disease-modifying properties have slowly begun
Atypical Parkinsonism - References

- Principles and practice of Movement Disorders; Fahn, Jankovic & Hallett
- Corticobasal degeneration; Grijalvo-Perez et al, Semin Neurol, 2014
- Progressive Supranuclear Palsy; LI Golbe, Semin Neurol, 2014
- Multiple System Atrophy; T Peeraully, Semin Neurol, 2014
- Dementia with Lewy Bodies; Mayo et al, Semin Neurol, 2014
- Clinical trials: past, current and future for atypical parkinsonian syndromes; Tsai et al, Semin of Neurol, 2014
- Utility of neuroimaging in the diff dx of parkinsonian syndromes; Holtbernd et al, Semin of Neurol, 2014
KEEP CALM

THANKS FOR LISTENING

ANY QUESTIONS?