Parkinson’s disease and Atypical Parkinsonism: A Primer and Update

Shyamal H. Mehta MD, PhD
Associate Professor of Neurology,
Movement Disorders Division
Mayo Clinic, Arizona
FACULTY DISCLOSURE

• No Relevant financial relationships

  Scion, Supernus Pharma, Abbvie – consulting

• Off-label/investigational uses

  None
DIAGNOSIS AND DIFFERENTIAL: WHY IS IT IMPORTANT?

• Be able to recognize & differentiate from PD
• Accurately diagnose atypical parkinsonism
• Affects:
  • Work-up
  • Treatment choice
  • Discussion re prognosis
  • Research: enrollment and interpretation for all neurodegenerative disorders.
DAT SCAN

NORMAL

PARKINSON DISEASE
SSA CSF IN PD

• 1123 participants – 545 PD, 163 controls, 51 prodromal, 310 asymp carriers

• Sensitivity for Parkinson's disease overall was 87.7% and specificity for healthy controls was 96.3%

• 86% of prodromal participants - 44 of 51 people, including 16 of 18 with hyposmia and 28 of 33 with REM sleep behavior disorder.

Siderowf A et al. Lancet Neurol May 2023; 407-417
PARKINSONS DISEASE

Cardinal Features

• Bradykinesia
• Rigidity
• Rest Tremor
• Gait disturbance
• Postural Instability

Supportive Features

• Olfactory dysfunction
• RBD
• Constipation
• Depression, Apathy

Not common in PD

• Dementia and hallucinations do not precede motor signs/symptoms (think DLB)

• Dysautonomia (early) (think MSA)

• Gaze paresis (think PSP)

• Early falls (think PSP)
ABSOLUTE EXCLUSION CRITERIA FOR PD

• Cerebellar abnormalities
• Gaze Palsy
• Cortical Sensory Loss/
  • Ideomotor apraxia
• Lower limbs only >3yr
MEDICATIONS FOR PD (2023)

- Carbidopa/levodopa
  - IR, CR, Parcopa (orally disintegrating), Rytary (immediate + delay release), Inbrija (inhaled), Dhiyv (quarter-scored)

- Dopamine receptor agonist
  - Pramipexole
  - Ropinirole
  - Rotigotine
  - Apomorphine (dissolving strip)

- COMT inhibitor
  - Tolcapone
  - Entacapone
  - Opicapone

- MAO-B inhibitor
  - Selegiline
  - Rasagline
  - Safinimide

- NMDA receptor antagonist
  - Amantadine IR
  - Amantadine ER

- Adenosine 2A receptor antagonist
  - Istradefylline

Courtesy Dr. Bryan Klassen
# L-DOPA THERAPY TRIAL

## Response to L-dopa

- At high enough dose 94-100% of PD patients respond
- However, 20-30% PSP patients respond temporarily or partially
- MSA 60-70% patients may have a good response
- Parkinsonism improves in > 80% DLB patients with L-dopa
- SCA-2 dopa resp parkinsonism
- CBD usually does not respond

## L-dopa dyskinesias

- Majority PD patients with long term therapy
- Can occur in MSA usual facial, craniocervical dystonic dyskinesias
- Also reported in SCA-2, NIID, Kufor-Rakeb (PARK 9)
- Rare in PSP and CBD

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Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary

A Report of the AAN Guideline Subcommittee

Tamara Pringsheim, MD, Gregory S. Day, MD, MSc, Don B. Smith, MD, Alex Rae-Grant, MD, Nicole Licking, DO, Melissa J. Armstrong, MD, Rob M.A. de Bie, MD, PhD, Emmanuel Roze, MD, PhD, Janis M. Miyasaki, MD, Robert A. Hauser, MD, MBA, Alberto J. Espay, MD, Justin P. Martello, MD, Julie A. Gurwell, PhD, PA-C, Lori Billinghurst, MD, MSc, Kelly Sullivan, PhD, Michael S. Fitts, Nicholas Cothros, MD, PhD, Deborah A. Hall, MD, PhD, Miriam Rafferty, DPT, PhD, Lynn Hagerbrant, Tara Hastings, MA, Mary Dolan O'Brien, MLIS, Heather Silsbee, Gary Gronseth, MD, and Anthony E. Lang, MD, on behalf of the Guideline Subcommittee of the AAN

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Correspondence
American Academy of Neurology
guidelines@aan.com
SURGICAL TREATMENTS FOR PD

DBS

MRGFUS for PD Tremor

DUOPA Infusion Therapy

VIDEO DBS PD
PD AND ATYPICAL PARKINSONISM

Synucleinopathies

• Parkinson’s Disease
• Dementia w Lewy Bodies
• Multiple System Atrophy-P
• Multiple System Atrophy-C

Tauopathies

• Progressive Supranuclear Palsy
• Corticobasal Syndrome (CBD)
• Frontotemporal Dementia
• AD
• PPFG

Note: DaTscan does not distinguish PD from MSA, PSP and CBD
<table>
<thead>
<tr>
<th>TABLE. DIFFERENTIATION OF ATYPICAL PARKINSONIAN SYNDROMES</th>
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<tbody>
<tr>
<td>Progressive supranuclear palsy</td>
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<td><strong>Red flags in the history</strong></td>
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<tr>
<td>- Early postural instability and falls especially going down</td>
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<td>- Difficulty looking down</td>
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<tr>
<td>- Early dysarthria and dysphagia</td>
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<tr>
<td>- Pseudobulbar affect</td>
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- Limb apraxia (eg, ideomotor, ideational)
- Alien limb syndrome
- Agraphia, astereognosis, 2-point discrimination lost
- Aphasia (typically nonfluent)
- Asymmetric parkinsonism (limb)
- Limb dystonia, contractures, myoclonus
- Neurogenic orthostatic vital signs (rise in HR/drop in SBP <0.5 bpm/mm Hg)
- Micturition and discolouration of skin
- High-pitch, strangled, “squeaky” voice
- Limb dysmetria on FN and HS testing, dysdiadochokinesis
- Ataxic dysarthria with scanning speech
- Hypo/hypermetric saccades
- Wide-based gait, anterocollis posture, camptocormia
- Bilateral Babinski signs with generalized hyperreflexia

- Vertical gaze palsy (downgaze >> upgaze)
- Horizontal ophthalmoparesis in later course
- Curvilinear vertical saccades
- Blinking to initiate vertical gaze
- Macrosaccadic intrusions with vertical pursuit, slow vertical saccades, reduced OKN, square wave jerks
- Intact VOR early; may be abnormal later
- Eyelid opening apraxia, blepharospasm
- Apraxia sign
- Early freezing of gait, retrocolic posture
- Axial more than limb rigidity
- Robotic, hypokinetic speech

- Sagittal MRI or CT: hummingbird sign
- Axial MRI or CT: morning glory sign
- Increased diffusivity values in the putamen, caudate nucleus, and globus pallidus
- SWI MRI: iron deposition pattern in basal ganglia (putamen, caudate, and globus pallidus)
- Resting state fMRI: disrupted dorsal midbrain—cortical/subcortical connections
- Oculography: slower peak horizontal and vertical saccade velocity and amplitude, lower gain of smooth pursuit eye movements
- FDG-PET: midbrain glucose metabolism decreased

- MRI: “Hot cross-bun” or “putaminal rim”
- MRI: Middle cerebellar peduncle atrophy

Abbreviations: bpm, beats per minute; FDG-PET, fluorodeoxyglucose positron emission tomography; FN, finger-to-nose; fMRI, functional MRI; HS, hemi-silence; HR, heart rate; OKN, optokinetic nystagmus; SPECT, single-photon emission computed tomography; SWI, subtraction-weighted imaging; SBP, systolic blood pressure; VOR, vestibulo-ocular reflex.
MULTIPLE SYSTEMS ATROPHY

• Neuropathology: α-synuclein +ve GCIs in oligodendrocytes, neurodegeneration of striato-nigral and/or olivopontocerebellar pathways. *No Lewy bodies!*

• Neuroimaging: “hot cross bun sign”, T2 hyperintense putaminal rim, atrophy of putamen, MCP, brainstem and/or cerebellum.

• Treatment: symptomatic
  - L-dopa (if parkinsonian); treat specific auto symptoms, PT/OT (falls, etc); ST (speech and swallow precautions); botulinum toxin (sialorrhea); CHEI’s (cognitive dysfunction); social service support
T2 hyperint cross - pontocerebellar fiber degeneration with a preserved corticospinal tract.
**PD VS MSA TESTS**

- Thermoregulatory Sweat Test
  - PD: distal, % anhidrosis low
  - MSA: regional, % anhidrosis greater, rapidly progressive.

- Cardiac $^{123}$I MIBG:
  - Assess cardiac sympathetic innervation
  - In MSA, cardiac $^{123}$I-MIBG uptake is preserved, but in PD it is reduced.
PROGRESSIVE SUPRANUCLEAR PALSY

• Average age: 65; unusual before 40
• Annual Incidence increases with age:
  - 2/100,000 in 6\(^{\text{th}}\) decade
  - 15/100,000 in 9\(^{\text{th}}\) decade
• Classic PSP (PSP-RS) 50% cases; PSP-P 2\(^{\text{nd}}\)
• Genetics: MAPT; H1 haplotype homozygosity ↑risk PSP and CBD
• H2 haplotype homozygosity makes PSP diagnosis less likely.
• MDS PSP diagnostic criteria in 2017: 8 variants & 4 domains
• Diag certainty: definite, probable, possible & suggestive.
PROGRESSIVE SUPRANUCLEAR PALSY

• Neuropathology: Neuronal & glial 4R Tau inclusions

• Neuroimaging:
  - abnormal DaTscan (does not distinguish)
  - FDG-PET: hypometabolism frontal/midbrain

• Treatment: Symptomatic
  - L-dopa (if parkinsonian); PT/OT (falls, etc); ST (speech and swallow precautions); botulinum toxin (sialorrhea); CHEI’s (cognitive dysfunction); social service support
On T1 Ratio of midsagittal midbrain to pontine base distances of less than 0.5 is highly sensitive and specific for PSP-RS but not other PSP variants.
DEMENTIA WITH LEWY BODIES

• Neuropathology: \(\alpha\)-synuclein deposition, Lewy bodies.

• Neuroimaging: Abnormal DaTscan; reduced parieto-occipital uptake on FDG-PET.

• Clinical: Parkinsonism, dementia either concurrent or in proximity, hallucinations, delusions, fluctuations, dysautonomia, RBD, sensitivity to neuroleptics

• Treatment: L-dopa (if parkinsonian); PT/OT/ST (falls, dysarthria, dysphagia); clonazepam, melatonin (RBD); botulinum toxin (sialorrhea); CHEI’s (cognitive dysfunction); treat dysautonomia; social service support
CORTICOBASAL SYNDROME

- Annual Incidence < 1/100,000; <5% in MDS Clinics
- Genetics: MAPT H1/H1 haplotype homozygosity
- CBD pathology only 50% cases
- PSP and AD 20-25% each, TDP-43, Pick’s disease, LBD
CORTICOBASAL SYNDROME (CBS)

• Neuropathology: 4R tau inclusions in neurons, glia.

• Neuroimaging: Frontoparietal atrophy and hypometabolism on PET

• Clinical: asymmetric parkinsonism, dystonia, apraxia, alien limb, cortical sensory deficit.

• Treatment: L-dopa (if parkinsonian); PT/OT/ST (falls, dysarthria, dysphagia); botulinum toxin (sialorrhea, dystonia); CHEI’s (cognitive dysfunction); social service support
VIDEOS

MSA

PSP

Videos used with patient permission
Verdiperstat (M-STAR)
- MPO inhibitor
- 600 mg bid vs placebo
- Failed Phase III

Alterity (ATH434)
- Phase II
- Reduce α-syn
- Modulates iron
ANTI-TAU MONOCLONAL AB IN PSP

• Tilavonemab (failed study): A 1-year, Phase 2 trial involving 378 subjects with PSP (Höglinger et al., 2021)
• Target engagement by tilavonemab was shown through lower free tau levels in CSF and higher levels in plasma, compared with placebo.
• Gosuranemab (failed study): 486 patients; unbound N-terminal tau levels in CSF decreasing by 98% and increasing by 11% with placebo (Dam et al., 2021).

*Lowering soluble tau does not produce clinical benefits*
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<thead>
<tr>
<th>Drug/Phase</th>
<th>Mechanism</th>
<th>Dosing</th>
<th>Status</th>
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<tbody>
<tr>
<td>Sodium Selenate</td>
<td>Enhances dephosphorylation of tau by protein phosphatase 2</td>
<td>Oral</td>
<td>Recruiting</td>
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<td>Australian govt (2)</td>
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<tr>
<td>Fasudil (2a)</td>
<td>Rho kinase inhibitor</td>
<td>Oral</td>
<td>End 11/2023</td>
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<tr>
<td>TPN-101 (2a)</td>
<td>Reduces tau production</td>
<td>Oral</td>
<td>End 7/2023</td>
</tr>
<tr>
<td>NIO-752 (1)</td>
<td>Anti-sense oligonucleotide; reduces tau production</td>
<td>Infusion into lumbar space</td>
<td>4 inj over 3 mth Completion 5/2024</td>
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<tr>
<td>Novartis</td>
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<tr>
<td>AZP2006 (1)</td>
<td>Reduces phosphor-tau by enhancing progranulin</td>
<td>Oral solution</td>
<td>France; small study</td>
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<tr>
<td>AlzProtect (1)</td>
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<tr>
<td>RT001 (di-deuter linoleic acid ester)</td>
<td>Reduce lipid perox; enhance mitochondria</td>
<td>Oral</td>
<td>Non-contr. Slow prog 2 years</td>
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</tbody>
</table>
CONCLUSIONS

• Important to distinguish atyp park from PD

• Overlap between clinical features – diagnosis difficult

• Research Studies

**MSA**
- Early dysautonomia,
- +/- Parkinsonism, ataxia,

**PSP**
- Early gait problems, falls
- Gaze palsy

**CBD**
- Apraxia, alien limb phenomenon
- Asymmetric, dystonia,

**DLB**
- Dementia, hallucinations at least 1 year prior to parkinsonism