Banner Health

Parkinson's and Parkinsonism: What's the Difference?

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Objectives

1. Explain how neurologists determine the causes of parkinsonism
2. Discuss the most common “Parkinson’s Plus” syndromes
3. Review current and emerging treatments of atypical parkinsonism

What is “parkinsonism?”

- Motor Symptoms
  - Bradykinesia* with ”sequence effect” (decrement/arrests) plus at least one other feature:
  - Tremor (resting)
  - Rigidity (lead pipe)
  - Postural Instability (+ pull test)**

*must be present

** red flag for Parkinson’s Plus (atypical parkinsonian disorder) if severe in first 3 years

What are common symptoms of parkinsonism?

- Bradykinesia
  - Smaller handwriting, impaired fine motor skills, not swinging arm(s)/shuffling when you walk
- Tremor
- Rigidity, dystonia
  - Stiffness, unexplained muscle pain
- Postural Instability
  - Feeling off balance (dizzy), severe unprovoked falls

Parkinsonism: How do we decide the cause?

- Consider medication induced causes
  - Antipsychotics (Abilify/aripiprazole, Zyprexa/olanzapine, Risperdal/risperidone, Haldol/haloeridol)
  - Nausea drugs (Reglan/metoclopramide, Compazine/prochlorperazine, Phenergan/promethazine)
  - Mood stabilizers (Depakote/valproic acid, lithium
  - Heart medications (amiodarone)
- Consider toxic causes
  - Manganese (Welding fumes)

Parkinsonism: How do we decide the cause?

- Consider non motor symptoms
  - Longstanding problems with sense of smell
  - Chronic constipation
  - Recurrent dream enactment behavior
- Consider Family History
  - PD (LRRK2)
  - PD with early dementia (GBA)
  - ALS and/or parkinsonism (C9orf72)

Parkinsonism: When is PD likely

- Non motor symptoms
  - Anosmia, constipation, dream enactment
- Motor symptoms
  - Asymmetric or unilateral parkinsonism
  - Prominent rest tremor (absent in >30%)
  - Robust, sustained response to levodopa
- Absence of Red Flags

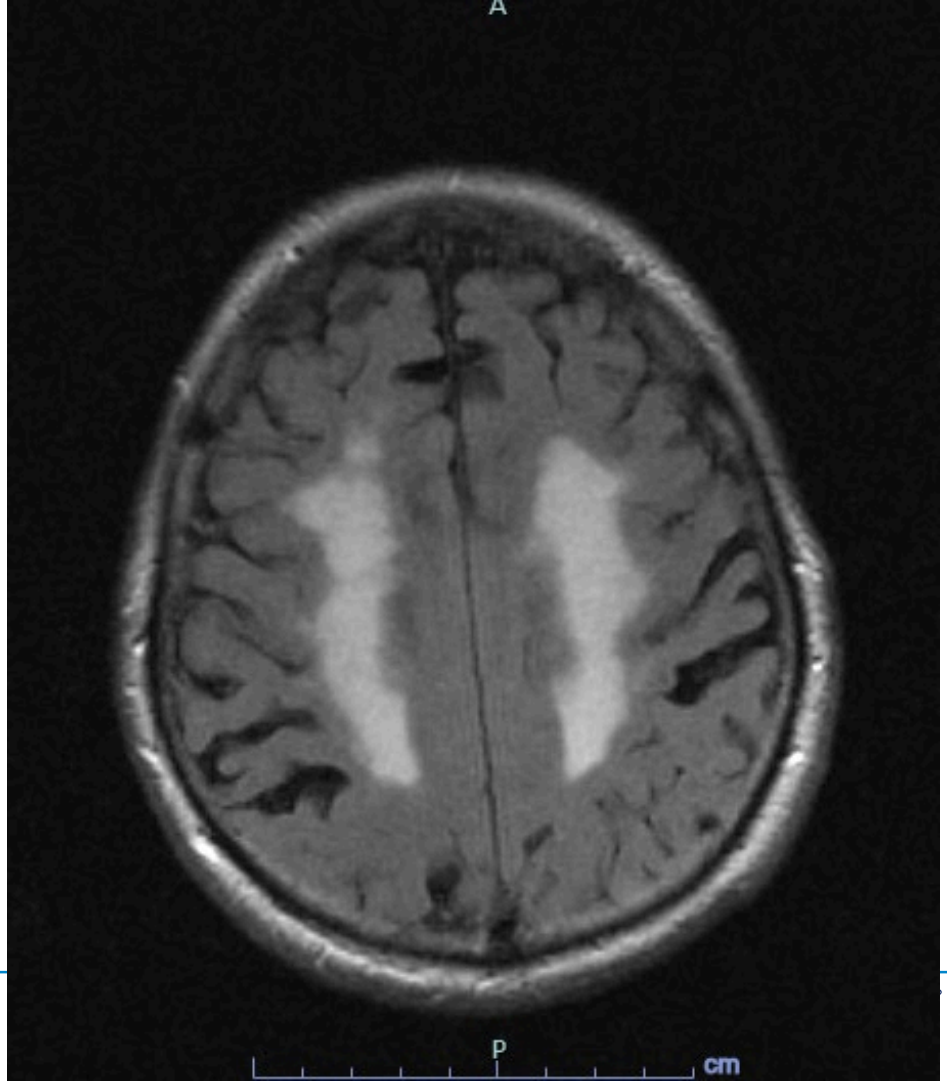
Parkinson Disease: Red Flags (Exclusions)

-Early, severe dementia
-Early severe postural instability/falls
-Early gait freezing
-Symmetric lower body parkinsonism
-Poor/waning levodopa response

- Early, severe dysautonomia
- Abnormal vertical gaze
- Stepwise progression
- Severe limb dystonia or apraxia

Red flags may warrant a brain scan

- MRI or CT brain
  - If abnormal, could help support diagnosis of
    - Vascular parkinsonism,
    - Normal pressure hydrocephalus
    - atypical parkinsonism (“Parkinson’s plus syndrome)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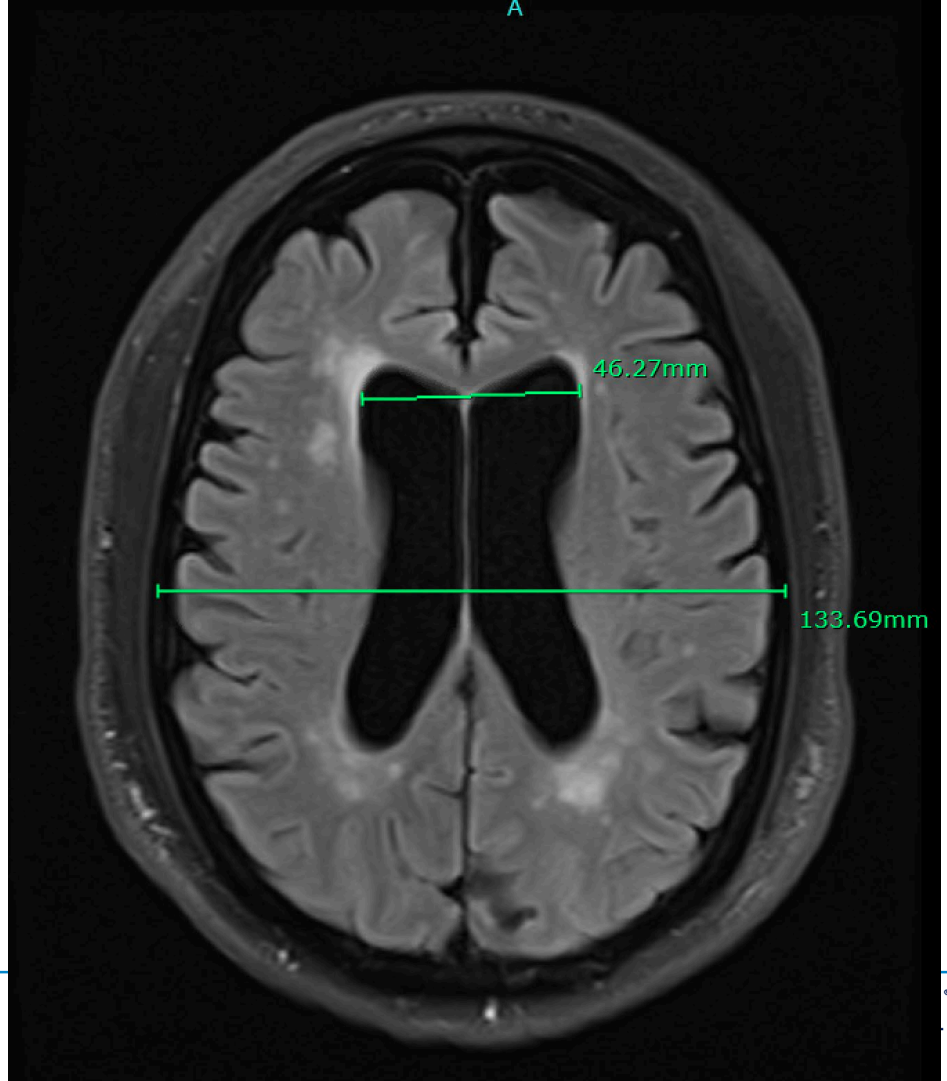
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Clinical tools for select cases

- DAT Scan (dopamine transporter SPECT)
  - Labels dopamine cells
  - If “normal”, could help support diagnosis of
    - Drug-induced
    - Essential tremor
    - Functional (aka Psychogenic)
- Syn One Skin Biopsy
  - If abnormal could support synucleinopathy

Atypical parkinsonism- the two main types

- Synucleinopathy
  - Lewy body diseases (Lewy bodies in neurons)
    - Parkinson disease
    - Dementia with Lewy bodies
  - Multiple system atrophy (MSA)
    - Glial cytoplasmic inclusions
- Tauopathy (aka 4 repeat tauopathies)
  - Progressive supranuclear palsy (PSP)
  - Corticobasal degeneration (CBD)

Dementia with Lewy Bodies: Diagnostic Criteria

- Central Features
  - Dementia in first year
    - Attention, executive, visuospatial impairment
    - Memory loss may occur later
- Core Features (2/4=prob, 1/4=possible)
  - Parkinsonism
  - Cognitive Fluctuations (esp of attention/alertness)
  - Recurrent Visual Hallucinations
  - Recurrent Dream enactment

McKeith et al. Diagnosis and Management of dementia with Lewy bodies: Fourth Consensus report of the DLB Consortium. Neurology, 2017. Jul 4; 89(1): 88-100

Dementia with Lewy Bodies: Diagnostic Criteria

- Biomarker Tests (1 biomarker plus 1 Core Feature= pDLB)
  - DaTScan (Dopamine transporter SPECT)
    - 78% sensitivity and 90% specificity for DLB vs other dementia
    - Some cases do NOT have abnormal DaTscan
  - Sleep study (for REM sleep without atonia)
  - MIBG Cardiac scintigraphy
    - In a multi center clinical cohort, sensitivity was 68.9% and the specificity was 89.1% to differentiate probable DLB from probable AD

McKeith et al. .Diagnosis and Management of dementia with Lewy bodies: Fourth Consensus report of the DLB Consortium. Neurology, 2017. Jul 4; 89(1): 88-100
Outeiro, T.F., Koss, D.J., Erskine, D. *et al.* Dementia with Lewy bodies: an update and outlook. *Mol Neurodegeneration* **14,** 5 (2019). https://doi.org/10.1186/s13024-019-0306-8
Yoshita et al. Diagnostic Accuracy of 123I-Meta-Iodobenzylguanidine Myocardial Scintigraphy in Dementia with Lewy Bodies: A Multicenter Study. 2015. PMC4368705

DLB can be challenging to diagnose

- ~75% of DLB patients also meet criteria for Alzheimer disease (based on the autopsy findings of amyloid plaques and tau tangles)[1]
- >85% of people with clinically diagnosed probable DLB actually have it[2]
- Only 32% of "pure" DLB and 12.1% of mixed AD/DLB in a national USA study were detected based on their symptoms during life[3]
- In the Arizona brain bank only 66% of 64 AD/DLB cases, were considered as DLB at any point; [4] In the Newcastle UK study of AD/DLB cases: only 23% were correctly diagnosed[5]

1. Malek-Ahmadi et al. Faster cognitive decline in dementia due to Alzheimer disease with clinically undiagnosed Lewy body disease. PLoS One 2019. PMC6592515

2. Rizzo et al. 2018. Accuracy of clinical diagnosis of dementia with Lewy bodies: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2018 Apr;89(4):358-36

3.Nelson et al. Low sensitivity of clinical diagnoses of dementia with Lewy bodies. J Neurol. 2010 March; 257(3): 359–366. doi:10.1007/s00415-009-5324-y

4. Faster Cognitive Decline in Dementia due to Alzheimer disease with Cimically Undiagnosed Lewy Body Disease. Beach et al. bioRxiv. Posted 1-3/2019. **doi:** https://doi.org/10.1101/510453

5.Thomas *et al.* Improving the identification of dementia with Lewy bodies in the context of an Alzheimer's-type dementia. *Alz Res Therapy* **10,** 27 (2018)

Diagnosis of DLB is important

- Treatment
  - Lower doses of carbidopa/levodopa, zonisamide can be helpful
  - Amantadine, trihexyphenidyl generally not tolerated
  - Rivastigmine, donepezil can be very helpful for non motor symptoms
- Antipsychotics may cause profound worsening
- Patients are more prone to orthostatic hypotension
- Prognosis is worse than PD

1. Molloy et al.The role of levodopa in the management of dementia with Lewy bodies. 2005. PMC1739807
2.Murata et al. Effect of zonisamide on parkinsonism in patients with dementia with Lewy bodies: A phase 3 randomized clinical trial. Park Rel Disord. July 2020.

Emerging Therapies for DLB

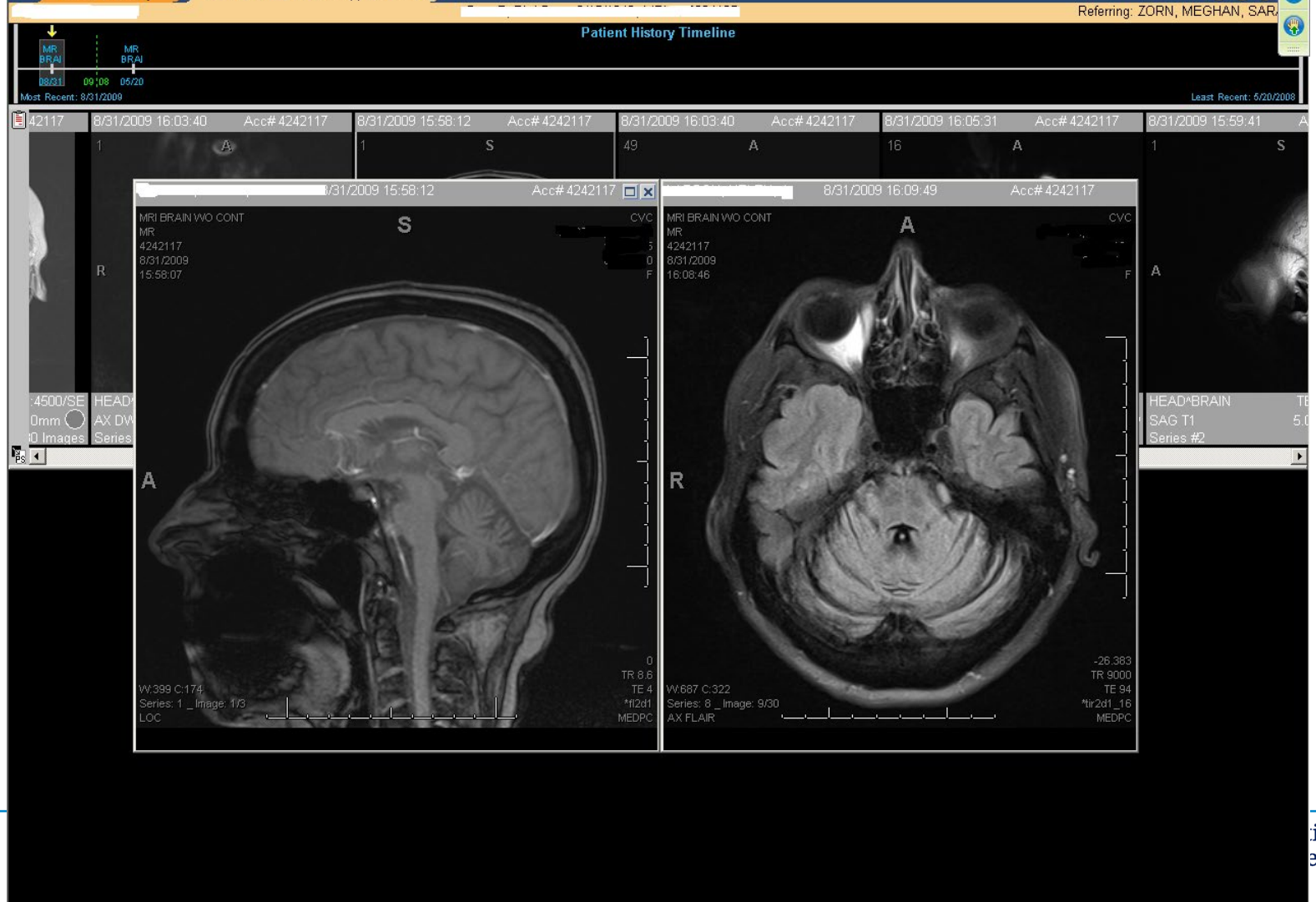
- Neflapimod
  - A P28 alpha kinase inhibitor (may help preserve circulatory system of the neurons)
- CT1812
  - A small molecule antagonist of the sigma 2 receptor (may block toxic forms of synuclein and beta amyoloid from binding to neurons)

https://clinicaltrials.gov/study/NCT05869669
https://pubmed.ncbi.nlm.nih.gov/36130946/
https://clinicaltrials.gov/study/NCT05225415
https://pubmed.ncbi.nlm.nih.gov/33559354/

Multiple System Atrophy (MSA)- clinically *established*

- Autonomic dysfunction- at least one of:
  - Unexplained voiding difficulties with post-void urinary residual volume ≥100 mL
  - Unexplained urinary urge incontinence
  - Neurogenic OH (≥20/10 mmHg bp drop) within 3 minutes of standing or head-up tilt test
- **And** Poorly levodopa-responsive parkinsonism **or** Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)
- **And** Motor/nonmotor supporting features- at least two of:
  - Within 3 years of motor onset: Rapid progression, Moderate to severe postural instability, Severe speech impairment, Severe dysphagia
  - Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia
  - Unexplained Babinski sign or Postural deformities or Jerky myoclonic postural/kinetic tremor
  - Cold discolored hands and feet, ED (before age 60), or PBA (Pathologic laughter/crying)
- **And** MRI features (at least one)-
  - Atrophy/increased diffusivity of putamen, MCP, pons, or cerebellum
  - “Hot cross bun” sign

Wenning, G.K., et al (2022), The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Mov Disord. https://doi.org/10.1002/mds.29005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Multiple System Atrophy (MSA)- clinically *probable*

- Autonomic dysfunction- at least one of:
  - Unexplained voiding difficulties with post-void urinary residual volume ≥100 mL
  - Unexplained urinary urge incontinence
  - Neurogenic OH (≥20/10 mmHg bp drop) within 3 minutes of standing or head-up tilt test
- **And** Poorly levodopa-responsive parkinsonism **or** Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)
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Wenning, G.K., et al (2022), The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Mov Disord. https://doi.org/10.1002/mds.29005

Emerging Therapies in MSA

- Selective norepinephrine reuptake inhibitor ampreloxitine
  - Small phase 2 trial (34 participants w NOH): increased norepiphrine levels and improved orthostatic symptoms and seated/standing blood pressure with little change in supine bp
  - Phase 3 trial initiated Jan 2023 in MSA patients
- Gene Therapies
  - Glial Cell Line Derived Neurotrophic Factor delivered to the putamen by adeno-associated virus type 2

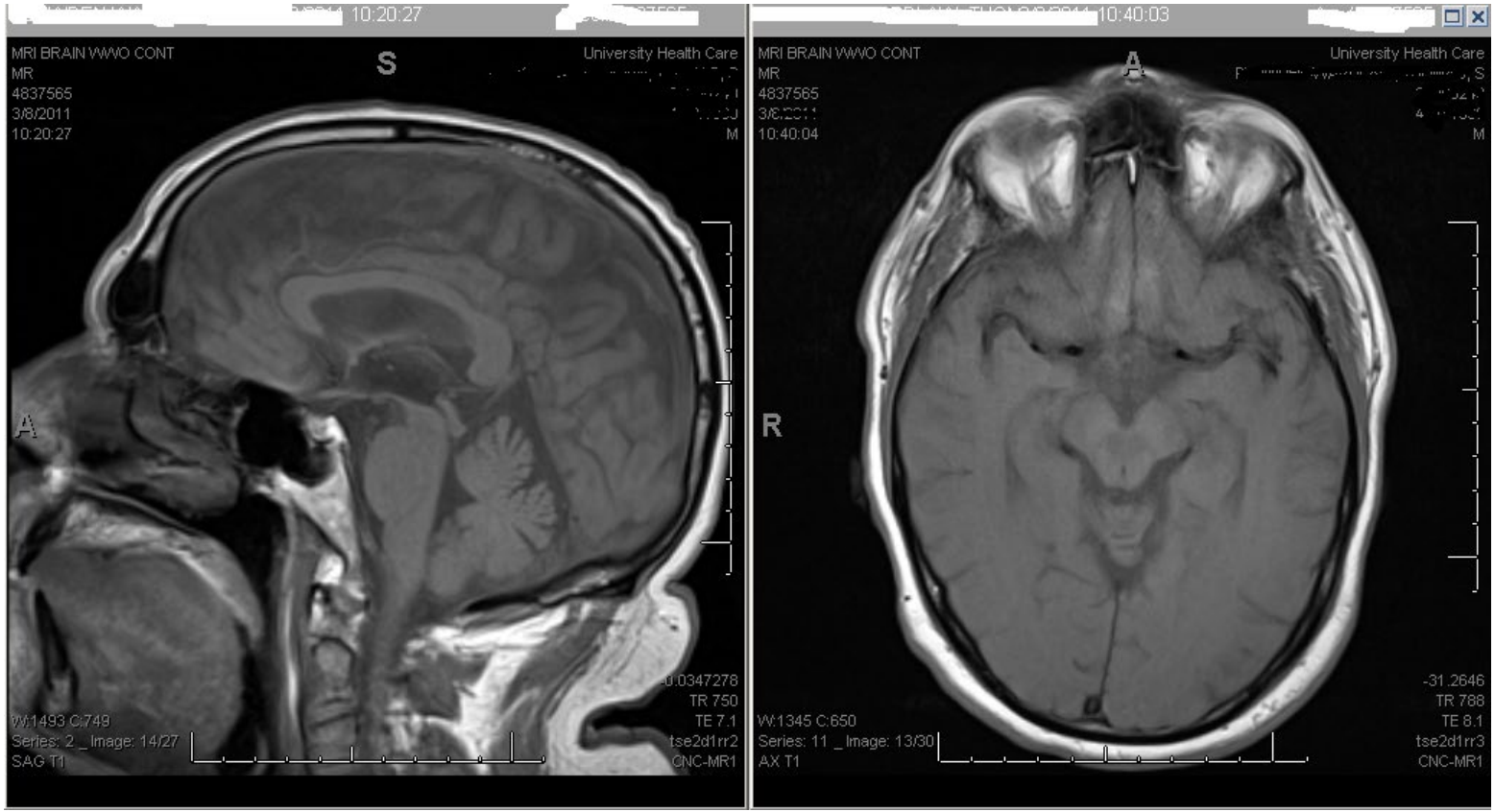
Kaufmann et al. Safety and efficacy of ampreloxetine in symptomatic neurogenic orthostatic hypotension: a phase 2 trial. Clin Auton Res. 2021 Dec;31(6):699-711. doi: 10.1007/s10286-021-00827-0. Epub 2021 Oct 17.

https://clinicaltrials.gov/ct2/show/NCT04680065

Other Causes of Parkinsonism: Progressive Supranuclear Palsy (PSP)

- Early severe postural instability/falls
- Slowed vertical saccades or Vertical gaze palsy w intact oculocephalic response
- Atypical parkinsonism
- Frontotemporal type dementia
- Primary pathology: 4 repeat tau

Hoglinger et al. Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria. 2017. DOI: 10.1002/mds.26987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Exclusion criteria against PSP

1. Predominant, otherwise unexplained impairment of episodic memory-suggestive of AD
2. Predominant, otherwise unexplained orthostatic hypotension -suggestive of MSA or LBD
3. Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness-suggestive of DLB
4. Predominant, otherwise unexplained upper and lower motor neuron signs-suggestive of motor neuron disease
5. Sudden onset or step-wise or rapid progression of symptoms- suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
6. History of encephalitis
7. Prominent appendicular ataxia
8. Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction,severe spasticity, or lower motor neuron syndrome
9. Genetic causes of FTD (other than microtuble associated protein tau mutuations)

Hoglinger et al. Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria. 2017. DOI: 10.1002/mds.26987

PSP Sub-types

- PSP-RS (Richardson syndrome)
- PSP-P (Parkinsonian variant)
- PSP-PI (Postural instability predominant)
- PSP-F (frontotemporal dementia)
- PSP-PGF (Progressive Gait Freezing)
- PSP-CBS (Corticobasal syndrome)
- PSP-SL (speech language predominant)

Hoglinger et al. Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria. 2017. DOI: 10.1002/mds.26987

Treating Involuntary Emotional Expression in PSP and MSA

- Cerebellar/brainstem pathology may explain higher prevalence of PBA
  - Frequently misdiagnosed as depression
  - Dextromethorphan 20mg/quinidine 10mg-FDA approved for PBA
    - Most trials focused on MS, ALS, TBI, dementia, stroke
    - One open label trial included 11 PD and 7 atypical parkinsonian patients
      - Similar benefits and side effects (dizziness, HA, somnolence, fatigue, dry mouth)

Hakimi M, Maurer CW. Pseudobulbar Affect in Parkinsonian Disorders: A Review. J Mov Disord. 2019 Jan;12(1):14-21. doi: 10.14802/jmd.18051. Epub 2019 Jan 30. PMID: 30732430; PMCID: PMC6369372.

Emerging Therapies for PSP

- Anti-tau antibodies
  - Negative results were previously announced for anti tau antibodies BIIB092 and ABBV-8E12
  - UCB0107 (Bepranemab) - was in a long term open label safety/tolerability extension study for PSP since 2020.

ClinicalTrials.gov NCT04658199

Emerging Therapies for PSP

- AMX0035
  - Sodium phenylbutyrate and taurursodiol
  - Clinical trial may launch late 2023
- NIO752
  - Antisense oligonucleotide (intrathecal)
  - Interferes with translation of tau mRNA

https://investors.amylyx.com/static-files/4a2e66ce-8516-488c-9745-29164875869f

https://clinicaltrials.gov/study/NCT04539041

Corticobasal Syndrome- Asymmetric Presentation:

- 2/3:
  - Limb rigidity or akinesia
  - Limb dystonia
  - Limb myoclonus
- 2/3:
  - Orobuccal or limb apraxia
  - Cortical sensory deficit
  - Alien limb phenomena

23% of CBS patients have autopsy diagnosis of Corticobasal Degeneration (>50% CBD or PSP)

Remainder have AD, DLB, FTD, prion disease

Ling et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain 2010.https://doi.org/10.1093/brain/awq123

Armstrong MJ, Litvan I, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013 Jan 29;80(5):496-503.

Atypical Parkinsonian Syndromes- What to Expect?

- DLB- median time to death
  - within 5.3 y of symptom onset, 3.5 y of diagnosis
- MSA
  - 50% need walking aid in 3y, 60% require w/c in 5 y
  - Median survival 6-9 years
- PSP
  - Median disease duration 9 y
- CBD
  - Median survival 8 years

Armstrong et al. Cause of Death and End-of-Life Experiences in Individuals with Dementia with Lewy Bodies. J Am Geriatr Soc. 2019 Jan;67(1):67-73. doi: 10.1111/jgs.15608. Epub 2018 Oct 6. PMID: 30291740.

Multiple System Atrophy. Fanciulli and Wenning NEJM, 372: 249-253, 2015.

Golbe et al. Prevalence and natural history of PSP. Neurology. 1988 Jul 38(7) 1031-4.

Wenning G et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination J Neurol Neurosurg Psychiatry. 1998 Feb;64(2):184-9. doi: 10.1136/jnnp.64.2.184.

Key Points

- Diagnosing the specific cause of parkinsonism requires detailed history and exam
- Accurate diagnosis guides symptom management and prognosis
- Volunteering in Clinical Trials is essential to discovering better treatments for atypical parkinsonism

Recommended Resources

Lewy Body Dementia Association

http://www.lbda.org/

CurePSP

https://www.psp.org/

MSA Coalition

https://www.multiplesystematrophy.org/

To Find Active Clinical Trials

http://ClinicalTrials.gov