TYPES OF DEMENTIA:
It’s not always Alzheimer’s disease

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Brain and Aging Conference 2025

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Goal and Talk Outline

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Identify various types of dementia and the differences between them

Outline

- Initial diagnosis of cognitive impairment and dementia
- Reminder of Alzheimer's disease, vascular dementia, Lewy body dementia
- Discuss atypical dementias:
  - Frontotemporal dementia
  - Atypical forms of AD
  - Progressive supranuclear palsy and corticobasal syndrome
  - CTE
  - LATE

Disclosures

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- Nothing relevant to disclose

Cognitive function

- Memory
  - Working/immediate
  - Short-term
  - Long-term
- Executive function
  - Planning
  - Multitasking, multistep tasking
  - Judgement, logic, making decisions
  - Calculations, money management
  - Abstraction
  - Praxis
- Psychological
  - Mood
  - Anxiety
  - Hallucinations, delusions
- Visuospatial
  - Finding objects
  - Depth perception
  - Getting dressed appropriately
  - Writing, reading
  - Navigation
  - Recognizing faces, objects
- Behavior
  - Personality
  - Social inhibition
  - Empathy, sympathy
  - Judgement
- Language
  - Appropriate word usage
  - Fluency
  - Grammar
  - Comprehension
  - Reading, writing

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What is dementia?

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- Process causing (usually) progressive cognitive dysfunction
- Greater than normal aging
- Interferes with daily social or occupational function
- *Non-reversible* process

- Mild Cognitive Impairment
  - *Subjective* complaints of cognitive difficulty
  - Abnormal cognitive function on testing (*objective findings*)
  - Daily function essentially preserved
  - Possible reversible

Is it dementia?

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- Medications
  - Benzos
  - Opioids
  - Hypnotics
  - Anticholinergics
  - Barbiturates
  - AEDs, muscle relaxers
  - Neuroleptics
- Other medical issues, deficiencies, toxicities
  - Vitamin deficiencies – B12, B1, folate
  - Endocrine dysfunction – thyroid
  - Chronic liver or kidney disease
  - Severe lung disease, CHF
  - Inflammatory/autoimmune disease
  - Infections
- Sleep disruption
  - OSA
  - Insomnia
- Depression, anxiety
- Other neurological causes
  - Longstanding MS
  - Epilepsy or seizures
  - TBI
  - Stroke
  - Tumors or other mass lesions
- Pain
- Hearing and/or vision loss

Workup for cognitive impairment

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- History
- Screen for OSA
- Screen for depression, anxiety
- Physical exam
- Cognitive screening
  - MMSE
  - MoCA
  - SLUMs
  - Mini-Cog, ACE-R, others

- Basic labs
  - CBC
  - Metabolic panel
  - TSH
  - B12, others if risk
  - Infections if risk – RPR, HIV

- Imaging
  - CT
  - MRI

Types of neurodegenerative (primary) dementia

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- Alzheimer's disease
- Parkinson's disease dementia and dementia with Lewy bodies
- Frontotemporal dementia
- Chronic traumatic encephalopathy (CTE)
- Progressive supranuclear palsy and corticobasal syndrome
- Limbic-predominant age-related TDP-43 encephalopathy (LATE)
- Others – Huntington's disease, prion disease (CJD)

- (Vascular dementia)

Why does it matter?

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- Many patients will come in with reported “memory” problems
  - A lot of these are not truly memory – executive dysfunction, language, attention
- Comorbidities vary
- Risks and genetics vary
- Diagnostic clarity for patients and families
- Treatments vary

Comparing dementias

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- Pathology
  - Amyloid-beta and 3R-tau
  - Alpha-synuclein
  - Tau species (4R)
  - TDP-43
- Demographics and symptoms
- Imaging and other diagnostic testing

Alzheimer's disease

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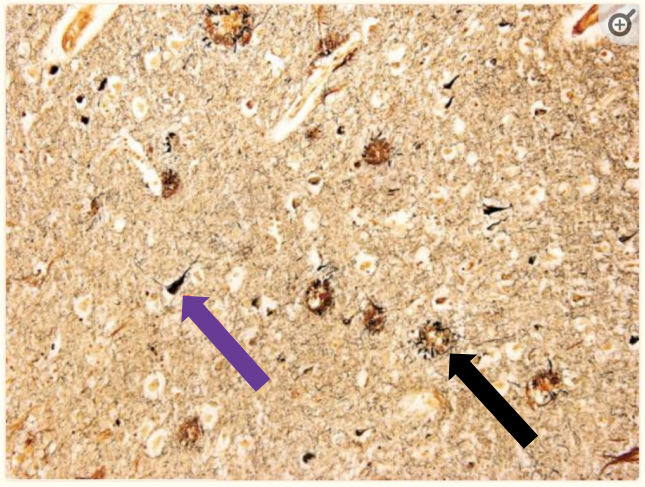
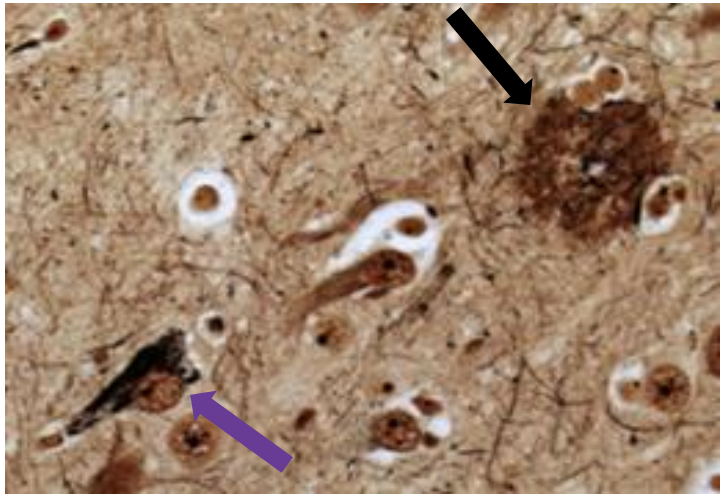
- Most common cause of dementia in the US and in the world
- Estimated prevalence of 6.5 million people over age 65 living with AD in the United States
  - 1/9 people over 65
  - 73% of these people are over age 75
- Due to accumulation of **amyloid-beta plaques** & **neurofibrillary tangles** of p-tau



Perl D. *Mt Sinai J Med* 2010; 77:32



Keene CD et al. *UptoDate* 2023

Alzheimer's disease

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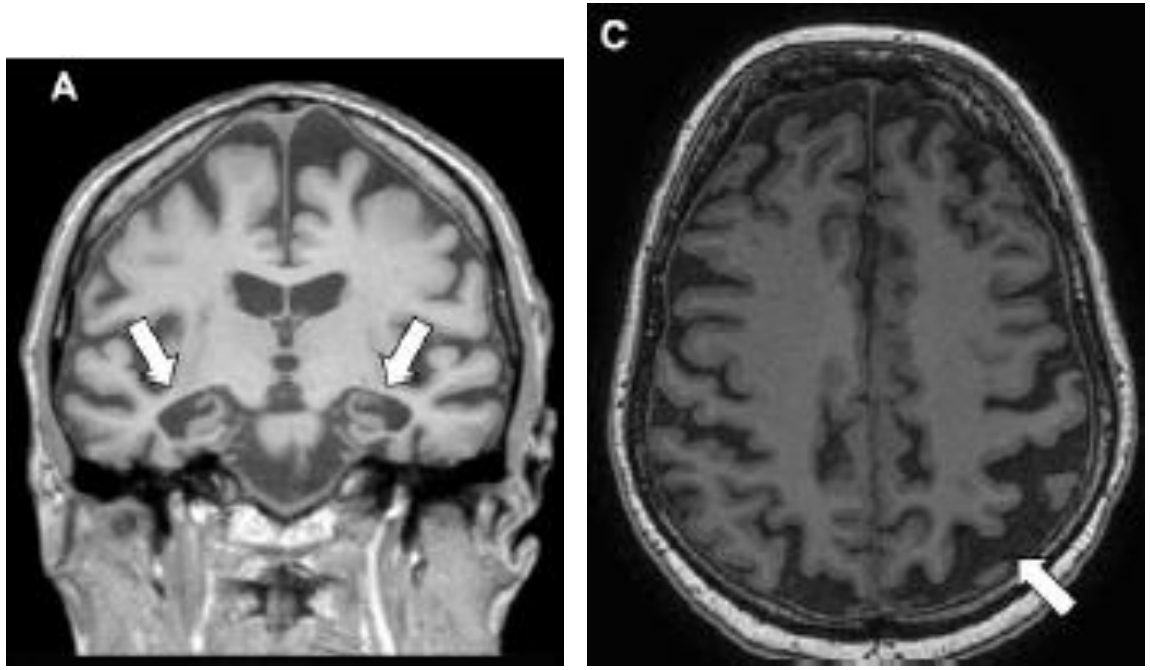
- Symptoms:
  - Short-term episodic memory loss
  - Executive dysfunction
  - Later: behavioral changes/agitation, delusions, worsening ADLs, wandering, single-word word-finding difficulties
- MRI/CT with atrophy especially mesial temporal and parietal



Radiology 2023;308:e230173

Alzheimer's disease

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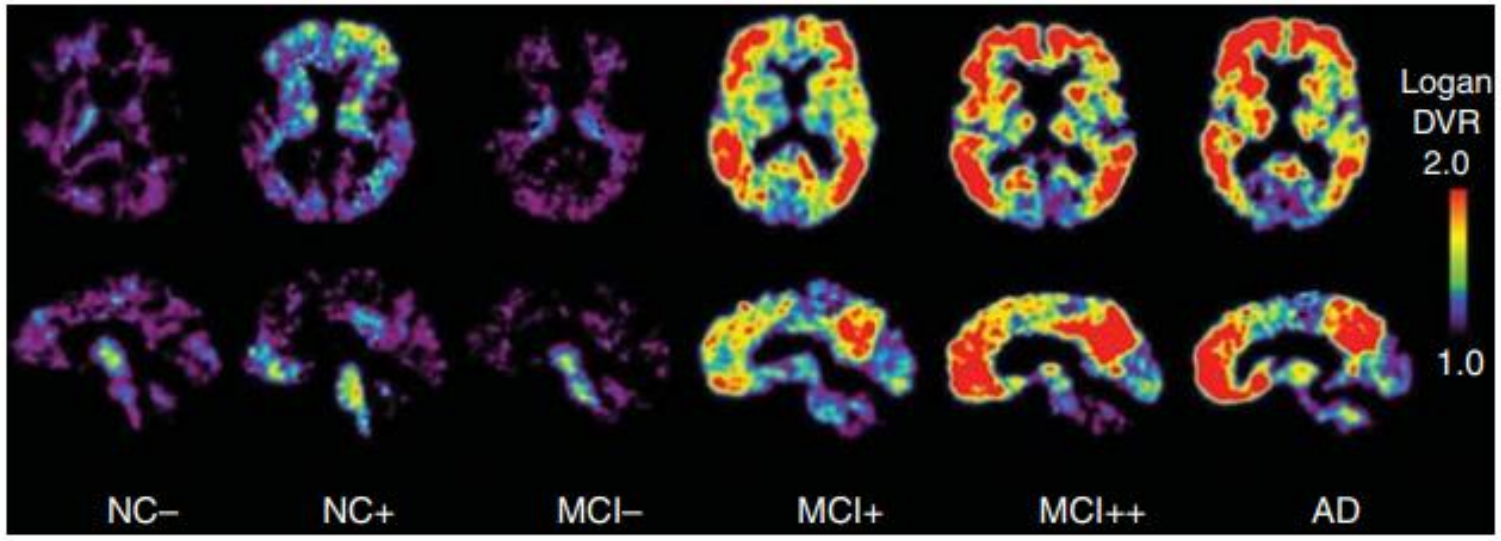
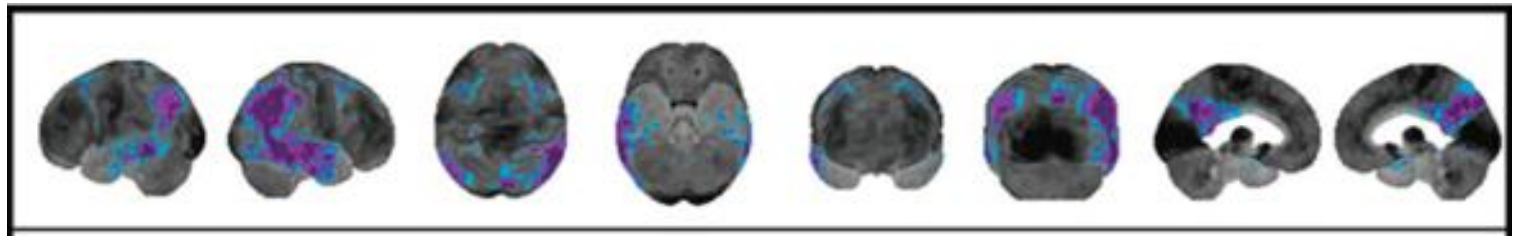
- CSF (and serum!) – levels of amyloid (Abeta40 and 42), total and p-tau
  - Ratios often used - P-tau/Abeta42 or Abeta42/40 ratios
- PET scan
  - Amyloid/tau shows accumulation of tracer



  - FDG-PET shows hypometabolism in parietal lobes



Brown et al. *Radiographics* 2014; 34:684

Vascular dementia

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- Cognitive impairment due to vascular brain injury
  - Ischemic stroke, hemorrhage, microvascular disease
- Second most common dementia type – 15-20% of diagnosed patients
- Two main types:
  - Slowly progressive over time due to microvascular disease – "Binswanger's disease"
  - Stepwise worsening of cognition due to new strokes over time – multi-infarct dementia

- Risk factors – cardiovascular
  - HTN
  - Hyperlipidemia
  - T2DM
  - Smoking
  - Atrial fibrillation
  - Coronary artery disease

Typical findings:

- Executive dysfunction
- Focal cognitive symptoms – language, praxis, visuospatial
- Non-cognitive focal findings

Vascular dementia

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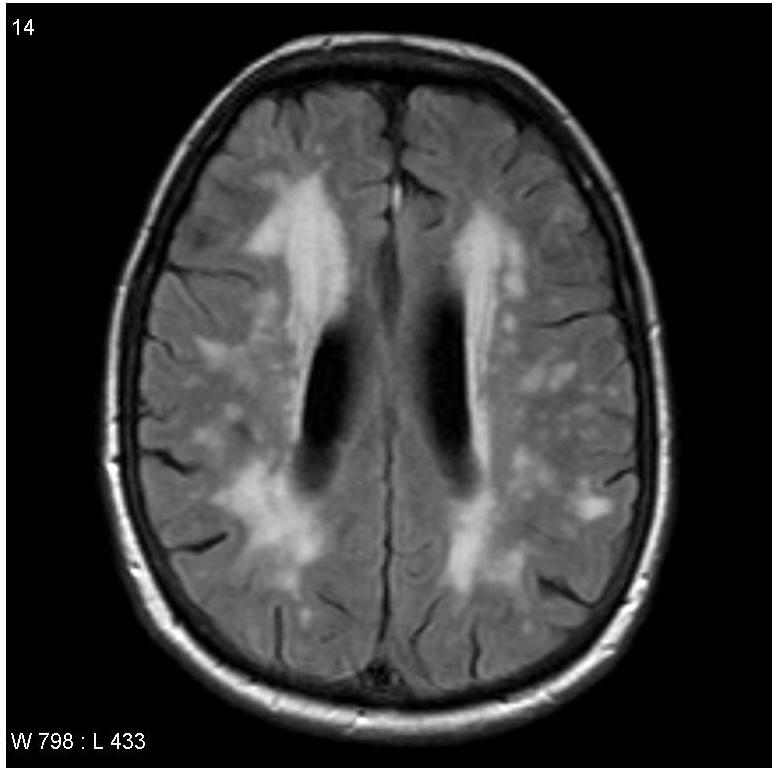
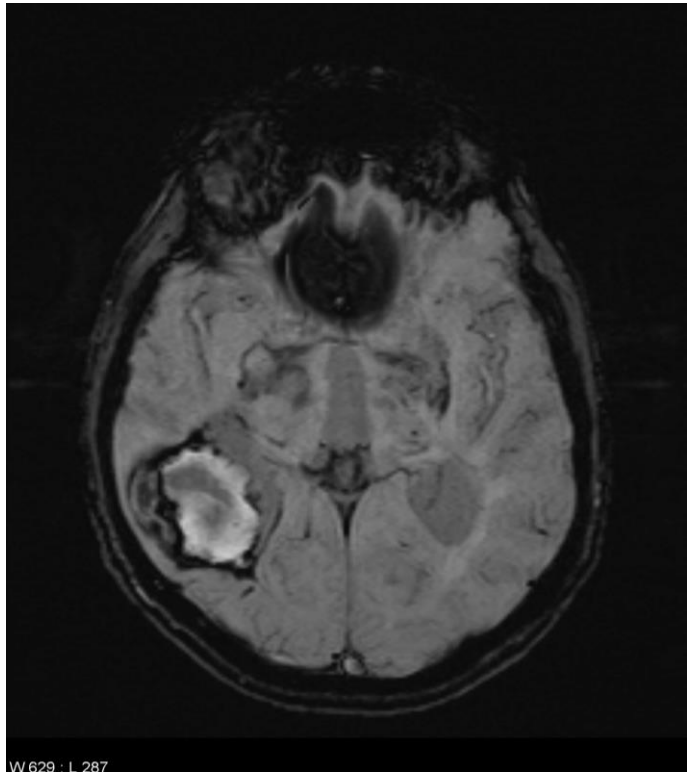
Microvascular disease



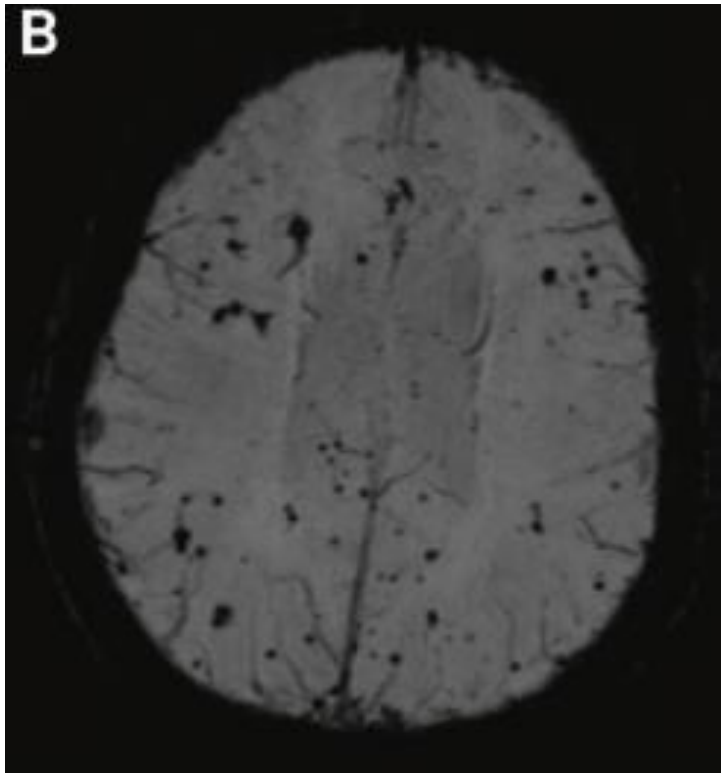
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 10674

Intracerebral hemorrhage



Case courtesy of Charlie Chia-Tsong Hsu, Radiopaedia.org, rID: 19872

Microhemorrhages



Suppiah et al. *Diagnostics (Basel)* 2019; 9:65

Dementia with Lewy bodies and Parkinson's disease dementia

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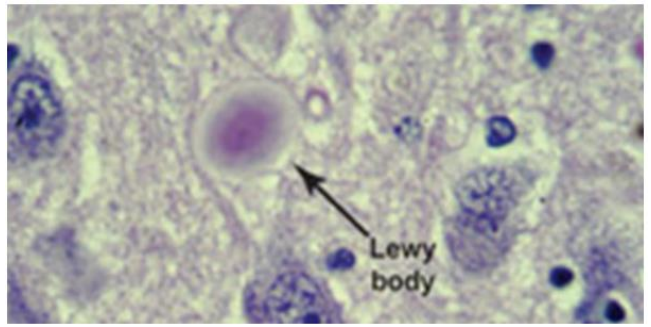
- Due to accumulation of α-synuclein – Lewy bodies = Lewy body dementia (LBD)
- Exist on a spectrum relating to timing of symptoms



https://www.alz.org

Parkinson's disease

Dementia with Lewy bodies

Motor symptoms only

Dementia only

Lewy body dementia

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- Cognitive impairment/dementia
  - Executive dysfunction
  - Trouble with attention
  - Bradyphrenia and slowed processing
  - Visuospatial difficulties
- Visual hallucinations
- Prominent fluctuations in cognition – esp in DLB
- REM behavior disorder

- Parkinsonism – bradykinesia, resting tremor, postural instability, rigidity

Lewy body dementia

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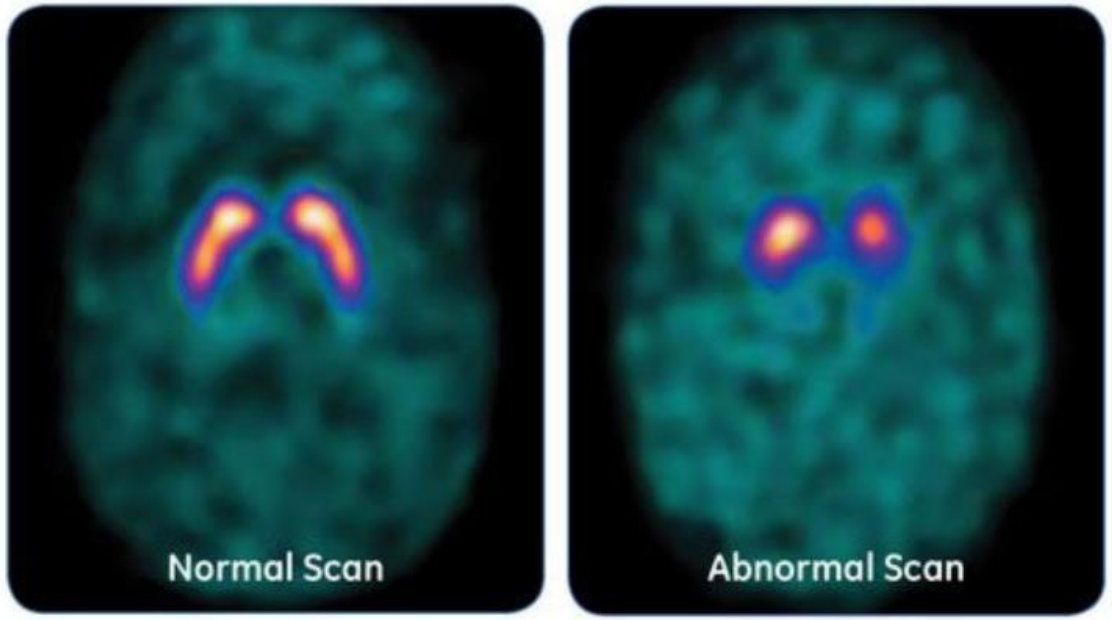
- History and physical exam critical
- No biomarker scans… yet
- DaT scan positive especially if parkinsonism present
  - Not specific to dementia
  - Usually not needed

- Synuclein skin test
  - May help distinguish from AD
  - Not clearly specific to disease
  - Not covered by insurance?



www.apdaparkinson.org

Lewy body dementia

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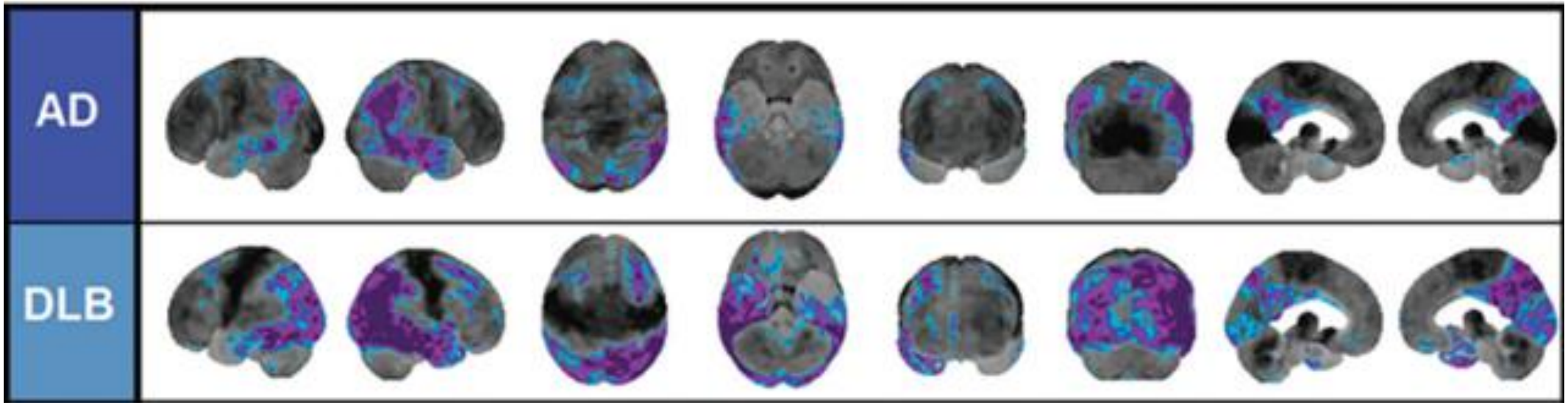
- MRI/CT with more diffuse atrophy in DLB, may be normal in PD
  - Sparing of medial temporal lobes
- FDG-PET – posterior hypometabolism



Brown et al. *Radiographics* 2014; 34:684

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Atypical dementia

Frontotemporal dementia

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- Most common cause of *early onset dementia* – before age 65
- Multiple causative processes, leading to frontal and/or temporal lobe predominant degeneration
  - "tauopathies" – p-tau but different isoform than that in AD
  - TDP-43
  - "FET" – FUS, EWSR1, TAF15
- At least 20% (may be up to 40%) may be genetic, dominantly inherited
  - Mostly from *MAPT* (tau), *GRN* (progranulin), and *C9orf72* genes – at least 50% of familial FTD from these three genes

Frontotemporal dementia

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- Three main subtypes
  - Behavioral variant frontotemporal dementia (bvFTD)
  - Semantic primary progressive aphasia (svFTD)
  - Nonfluent agrammatic primary progressive aphasia (nfvFTD)

Frontotemporal dementia

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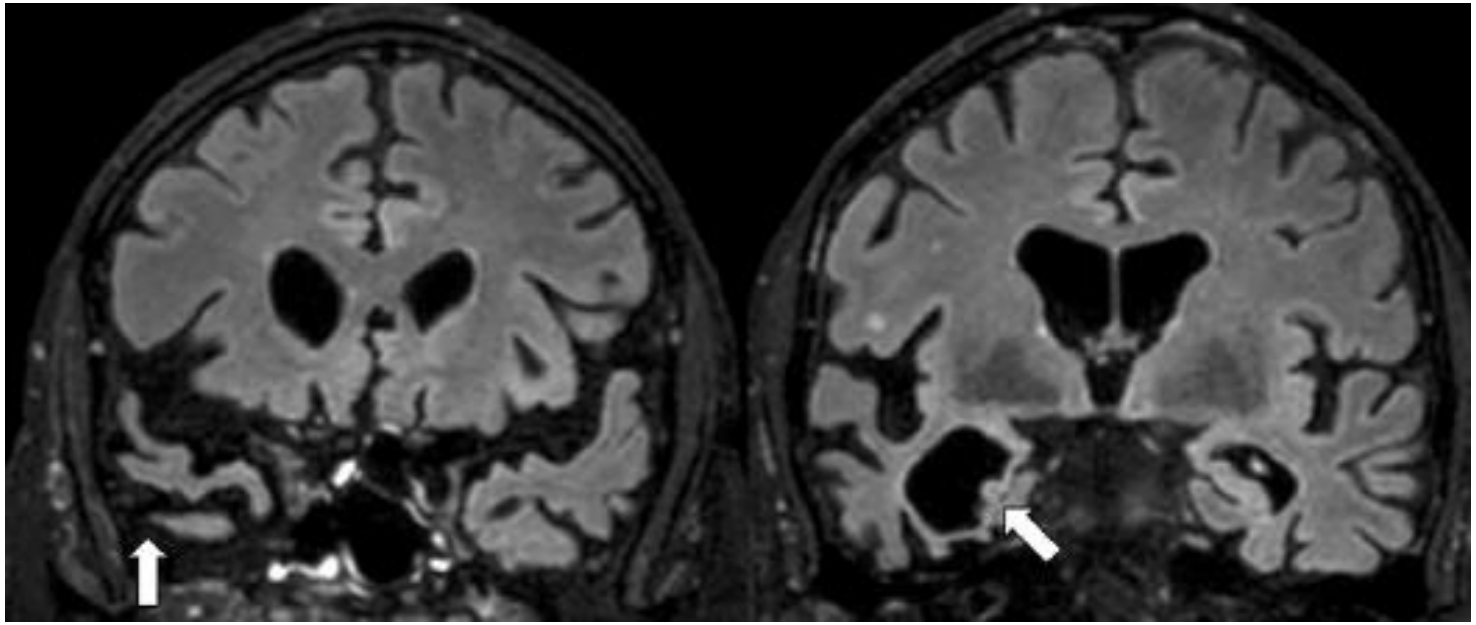
- CT/MRI – significant frontal and/or temporal atrophy



Radiology 2023;308:e230173

Frontotemporal dementia

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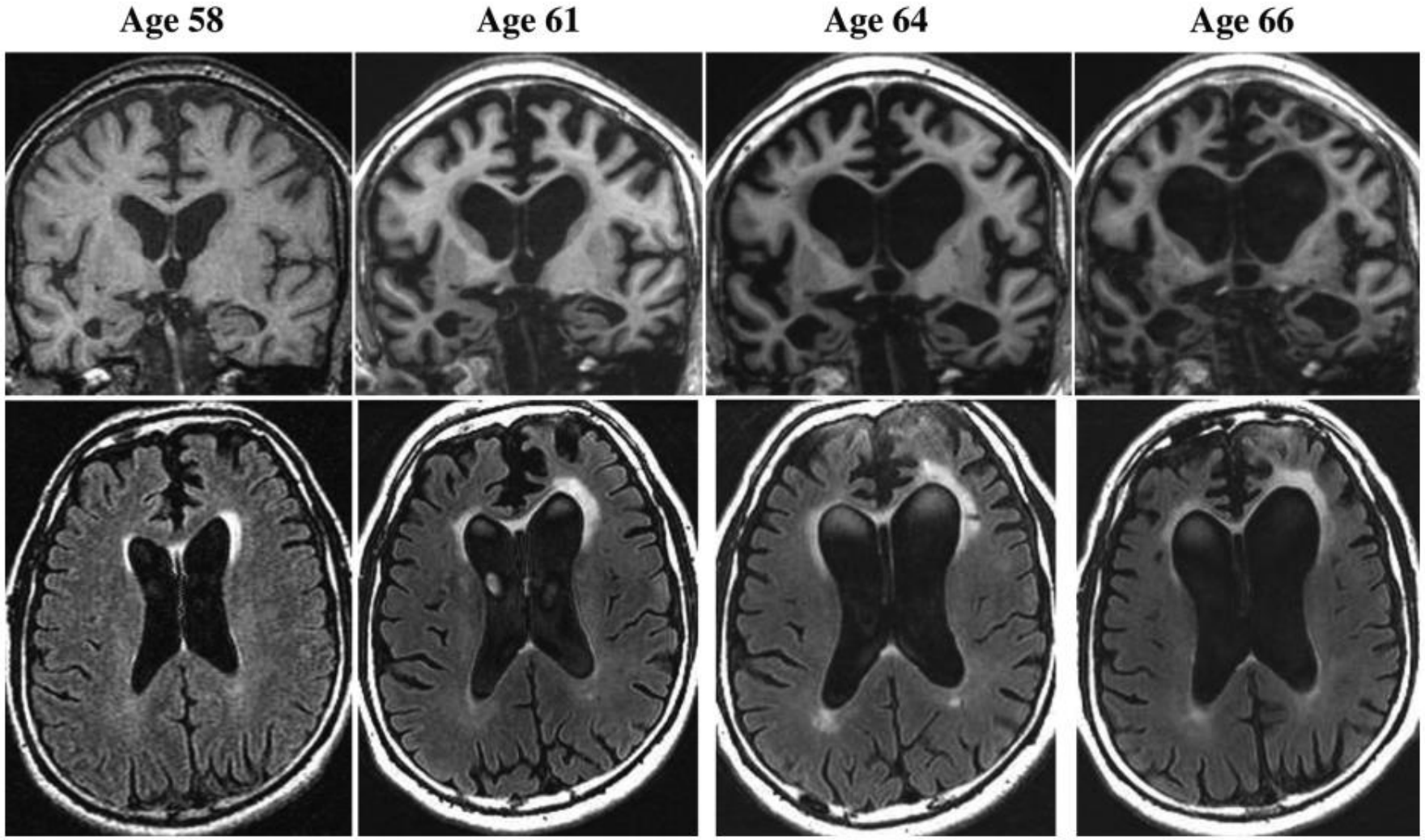

From Boeve B. *Continuum* 2022; 28:702

Frontotemporal dementia

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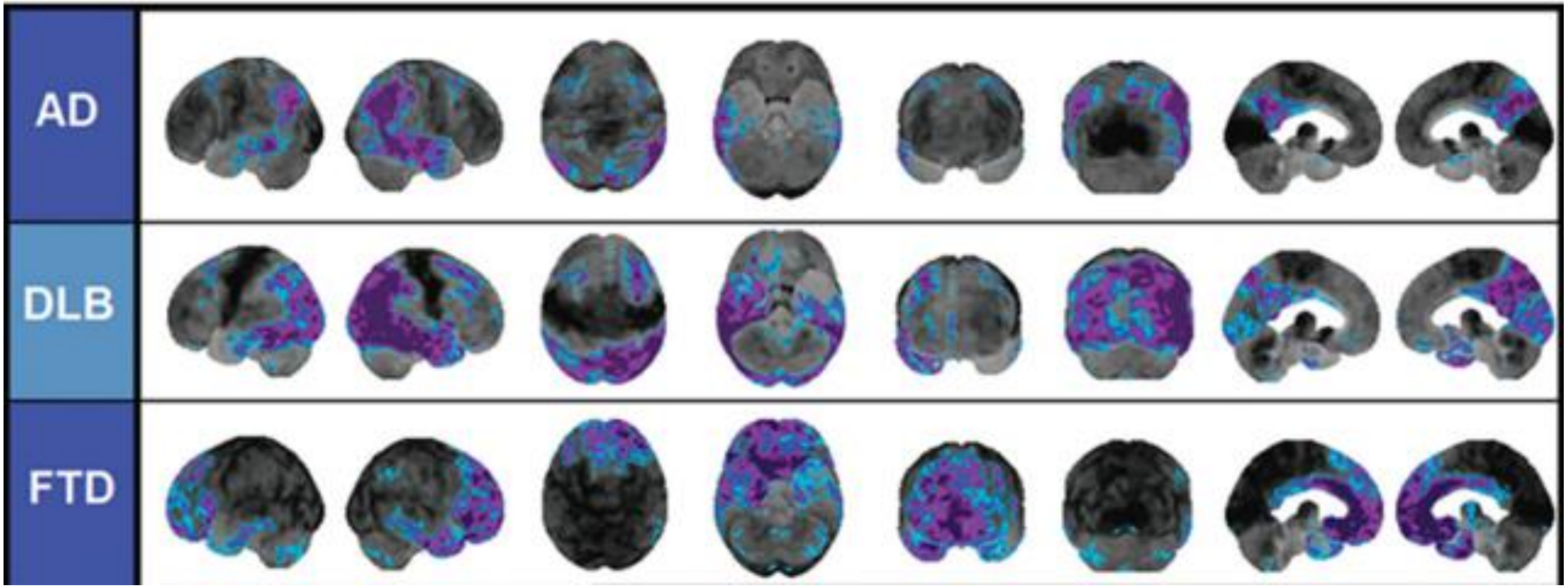

- Best use of FDG-PET is to distinguish AD from FTD in unclear cases
- Covered by Medicare for this purpose

Brown et al. *Radiographics* 2014; 34:684

Frontotemporal dementia

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- No biomarker PET scans – tau-PET not useful, no ligands from other proteins
- No serum studies
  - May be able to eventually distinguish AD from FTD if amyloid or p-tau markers are found
- No CSF markers
  - Similar to serum, may be useful to distinguish AD biomarkers in patients with unclear diagnosis
- Neuropsychological testing may miss symptoms
  - Attention/concentration, executive function, language can also be affected in other neurodegenerative diseases and non-neurodegenerative diseases

Behavioral Variant FTD (bvFTD)

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- Progressive deterioration of behavior or social cognition

- Findings
  - Early behavioral disinhibition
  - Early apathy or inertia
  - Early loss of sympathy or empathy
  - Early perseverative, stereotyped, or compulsive/ritualistic behavior
  - Hyperorality and dietary changes

- Neuropsychological profile with executive dysfunction with relative sparing of memory and visuospatial functions

bvFTD

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- What it is NOT:
  - New psychosis – hallucinations or delusions
  - ADHD
  - Depression and/or anxiety
  - Memory loss
  - Spatial orientation problems

Primary progressive aphasia

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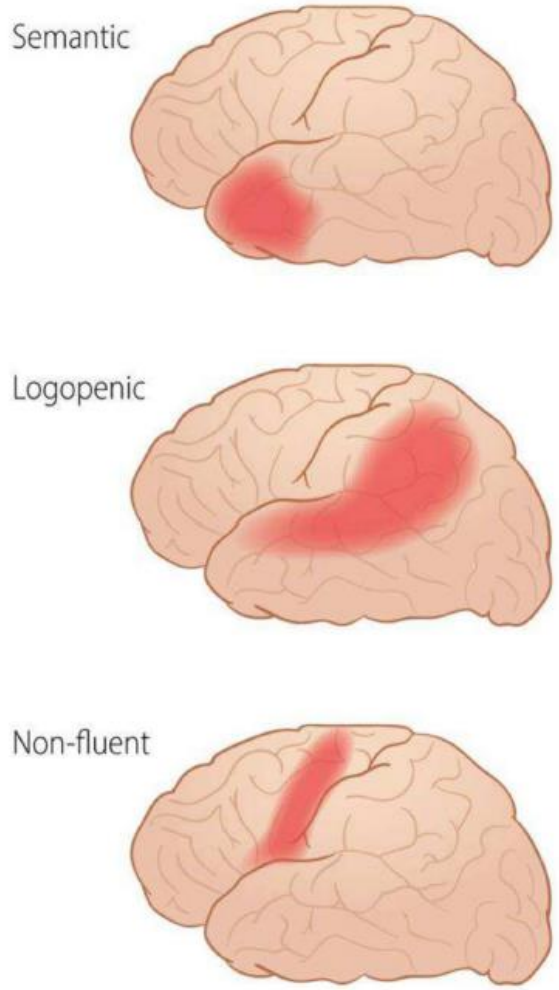
- Progressive loss of language functions due to a neurodegenerative process

- Three variants
  - Semantic variant PPA
  - Non-fluent agrammatic PPA
  - Logopenic PPA



Mirbod et al. *Ann Nuc Med* 2024;38:673

FTD - Primary progressive aphasia

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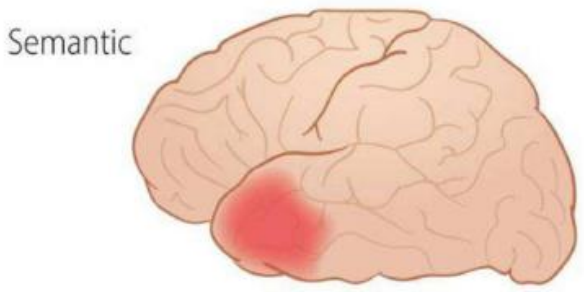
- Semantic PPA – svFTD
  - Most commonly due to TDP-43 Type C, other TDPs and Pick's disease (tau)



Mirbod et al. *Ann Nuc Med* 2024;38:673

- Impaired confrontational naming and single word comprehension
- Dyslexia, dysgraphia
- Impaired object knowledge esp for low-frequency words
- Repetition intact
- Speech production intact (fluent)
- Grammar intact

FTD - Primary progressive aphasia

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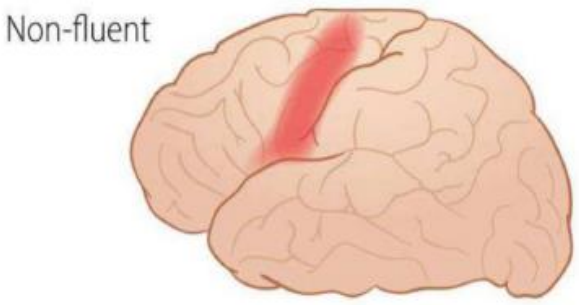
- Agrammatic nonfluent PPA – nfvFTD
  - Tau pathology, can also be Pick's disease or TDP-43



Mirbod et al. *Ann Nuc Med* 2024;38:673

- Agrammatism
- Effortful, halting speech with apraxia of speech
- Impaired comprehension of syntactically complex sentences
- Spared single word comprehension
- Spared object knowledge

Primary progressive aphasia

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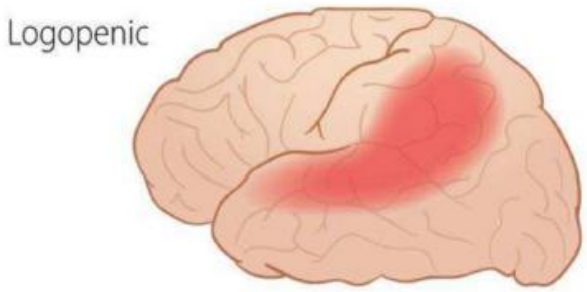
- Logopenic PPA
  - 86-90% due to AD pathology



Mirbod et al. *Ann Nuc Med* 2024;38:673

- "Word finding difficulties" – impaired single-word retrieval in spontaneous speech
- Phonemic paraphasias – saying "blant" for "plant"
- Spared single word comprehension and object knowledge
- Repetition impaired, even for simple sentences
- Fluency intact, no trouble with motor speech or grammar

Atypical Alzheimer's disease

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- Typical Alzheimer's pathology
- Atypical symptoms, atrophy, ?location of pathology, and demographics
- Tends to occur in younger patients with AD
  - Estimated to be around 3% of AD patients
- Three main forms:
  - Logopenic primary progressive aphasia (PPA)
  - Frontal variant – behavioral or dysexecutive
  - Posterior cortical atrophy

Frontal variant AD

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- Rare – 2% of AD
- 7-20% of “FTD” diagnoses clinically are found to have AD pathology
- Dysexecutive variant – trouble with planning, multitasking, organizing, completing projects
  - Not really associated with personality changes aside from prominent apathy
- Behavioral variant – resembles FTD
  - Disinhibition, lack of empathy, disregard of societal norms, obsessive-compulsiveness, occasional hyperorality
  - Can also have delusions and hallucinations – rare in FTD

Posterior Cortical Atrophy

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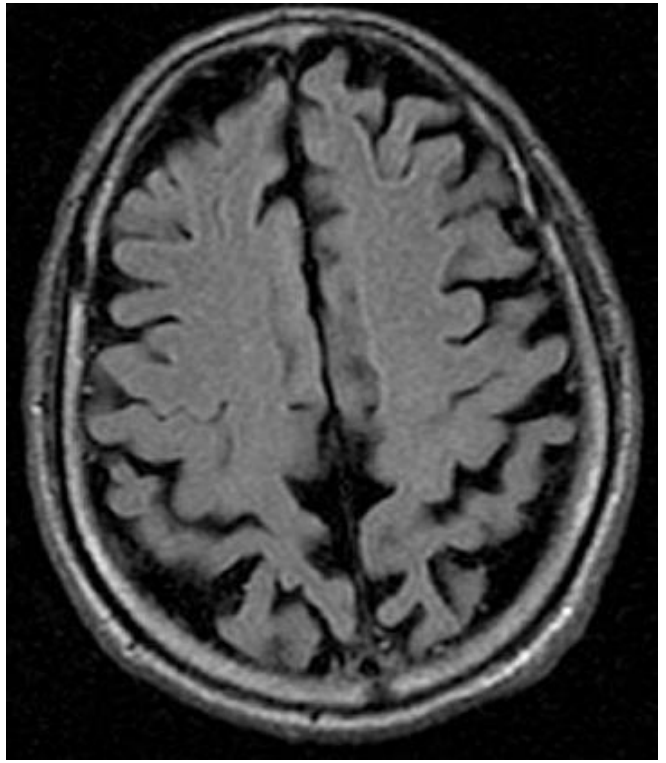
- 96% due to AD pathology
- Mean age of onset of 58.9 yrs, 80% had onset before age 65
- Female > Male

Posterior cognitive dysfunction:

- Complex visuospatial abnormalities
- Apraxia
  - Limb apraxia
  - Dressing apraxia
  - Constructional apraxia
- Prosopagnosia
- Alexia
- Cortical vision loss



Case courtesy of Royal Melbourne Hospital Neuropsychiatry Unit, Radiopaedia.org, rID: 24746

PCA symptoms

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- Trouble finding objects in plain sight
- Trouble with driving
- Navigation difficulties esp complex or uneven surfaces
- Loss of dexterity
- Trouble with dressing or putting objects together

- Preserved insight
- Sparing of other cognitive domains

Gerstmann syndrome

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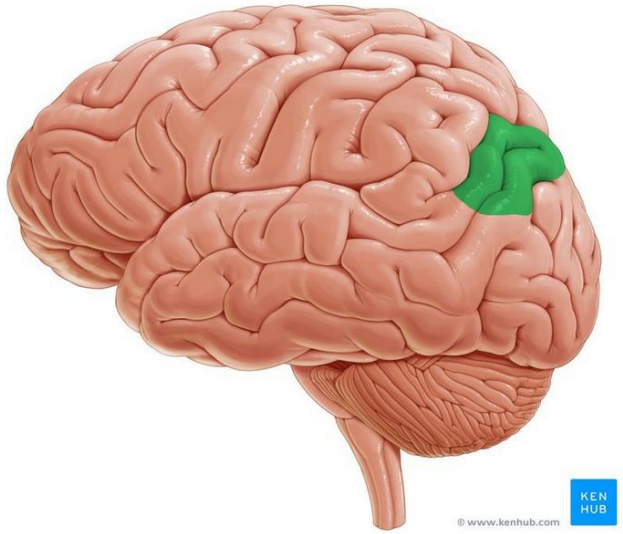
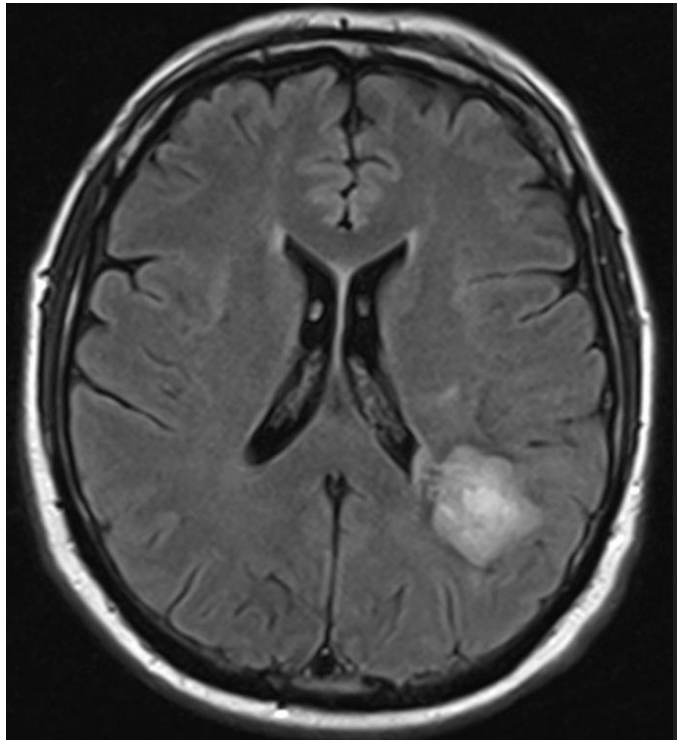
- Injury to the left angular gyrus

Symptoms:

- Left-right disorientation
- Finger agnosia
- Dyscalculia
- Dysgraphia



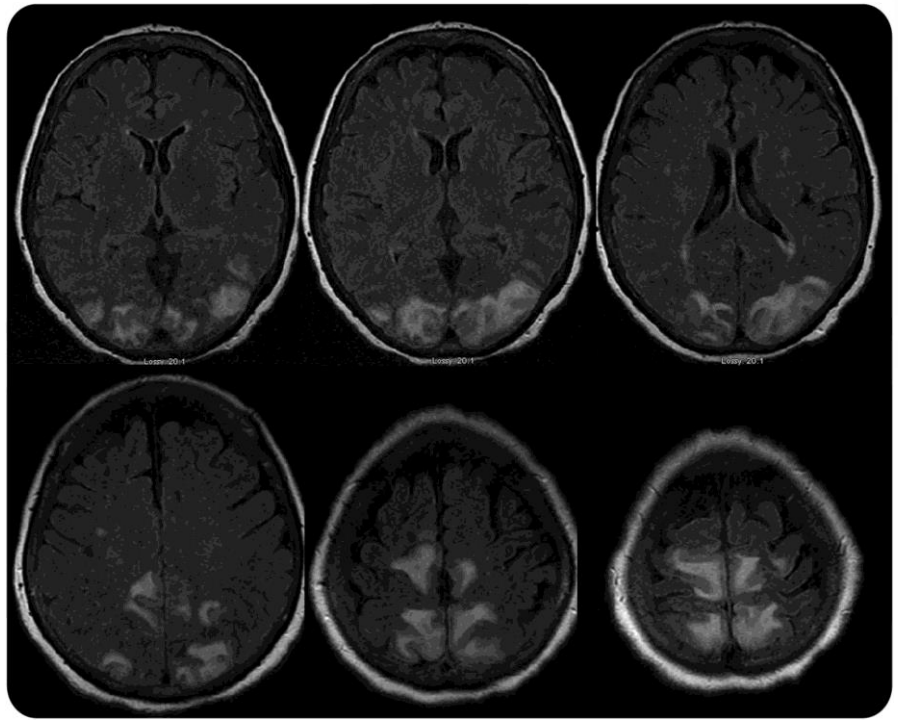


https://www.eurorad.org/case/14092

Balint syndrome

- Injury to bilateral parietal lobes

- Simultagnosia
- Optic ataxia
- Oculomotor apraxia



Espay and Allen. *Neurology* 2014;82:1844

Atypical parkinsonism causing dementia

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- Lewy body dementia
- Progressive supranuclear palsy
- Corticobasal syndrome

Progressive supranuclear palsy (PSP)

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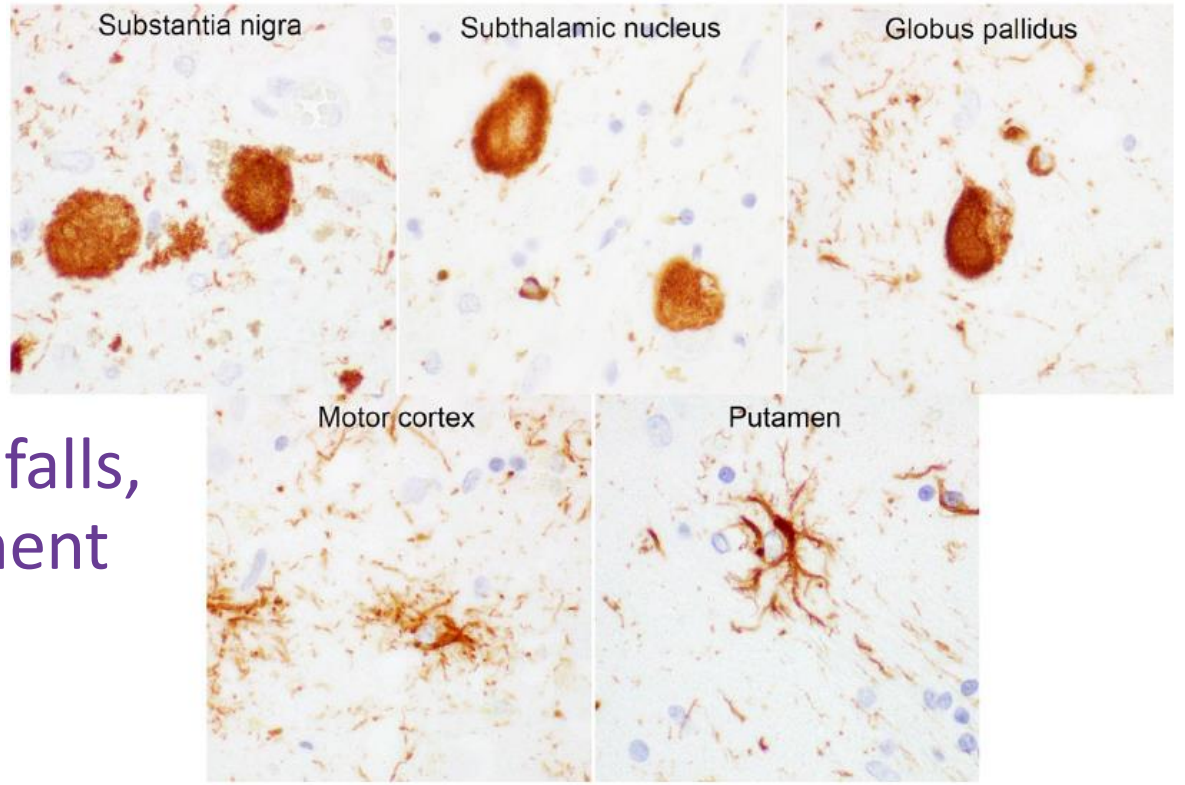
- Tauopathy – 4-repeat tau
- Traditional syndrome of downward gaze palsy, axial parkinsonism with early falls, dysphagia, and frontal cognitive impairment
  - Richardson's syndrome
- Mean age of onset 65, very rare before age 40
- Many variants and subtypes



Roemer et al. *Acta Neuropathol*. 2022;144:603

Dementia in PSP

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- Frontal cognitive impairment early in course
  - 70% of PSP patients will develop dementia during course
  - 10% initially present for evaluation of cognitive changes

- Speech apraxia and non-fluent aphasia
- Executive dysfunction, trouble with sequencing

Dementia in PSP

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- Disinhibition and perseveration
  - Positive applause sign
  - Emotional lability, pseudobulbar affect
  - Compulsive behavior, inappropriate behavior
- Attention/immediate memory
  - Up to 1/3 of patients with episodic memory and/or visuospatial deficits
- Prominent apathy and bradyphrenia

MRI findings – midbrain atrophy

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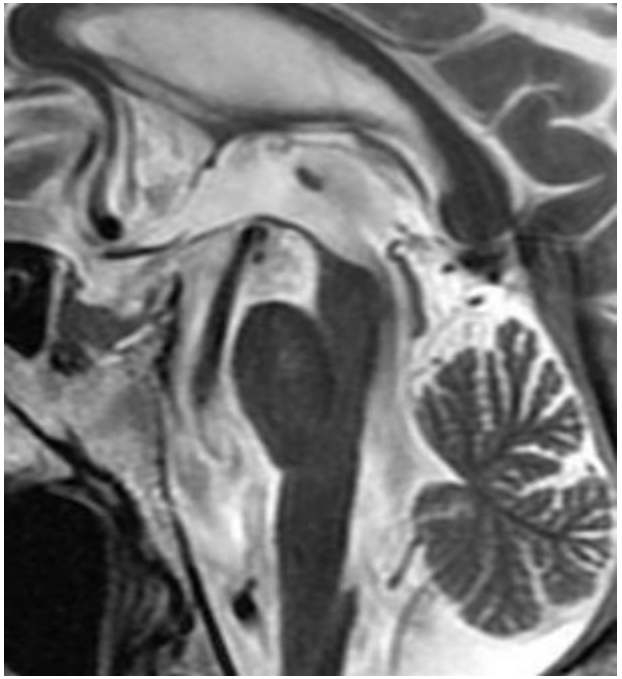
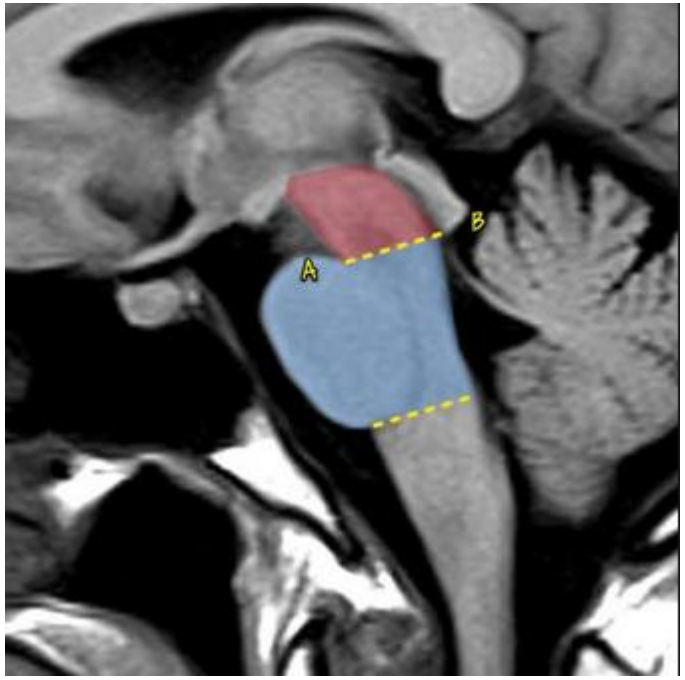
Variant PSP may not always show these findings

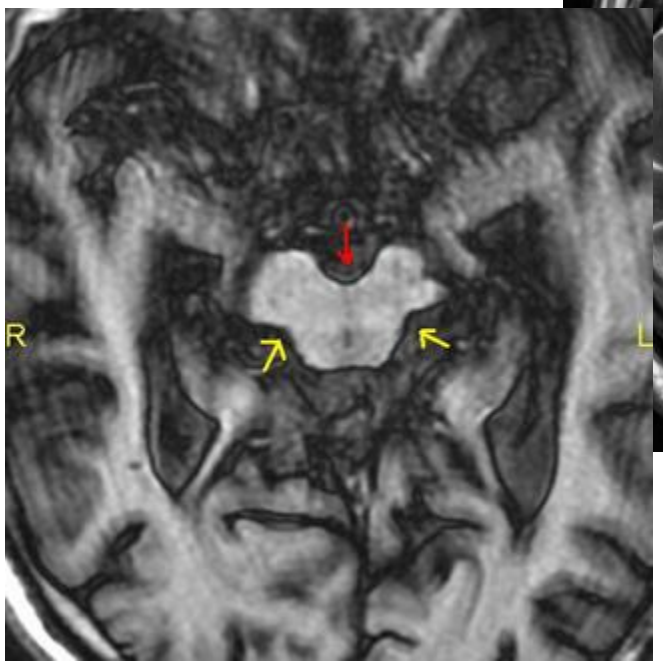


Hummingbird sign
Penguin sign

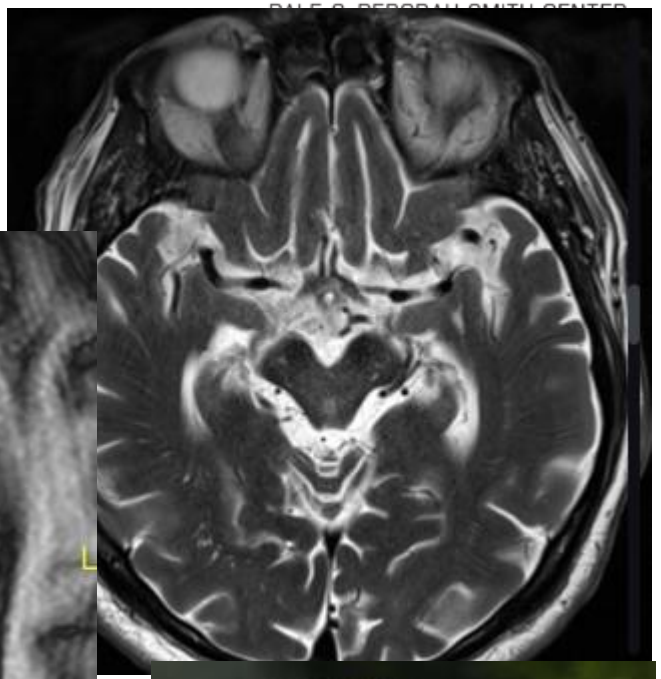


Midbrain-to-pons ratio

Normal is ~0.24
PSP <0.16



Mickey mouse sign



Morning glory sign

Corticobasal syndrome

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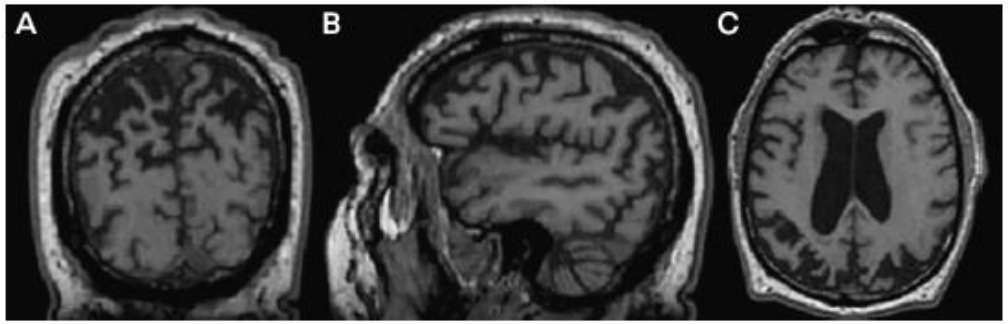
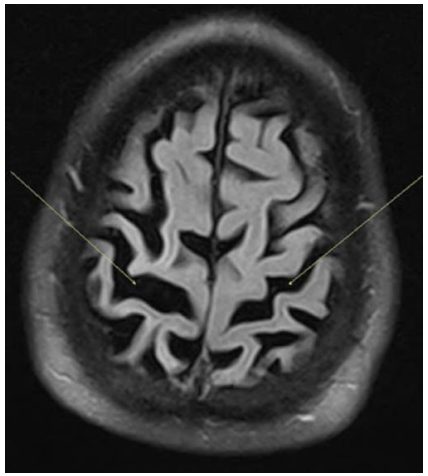
- Clinical presentation
  - Asymmetric parkinsonism with focal dystonia and cortical findings



- Corticobasal degeneration: specific 4R-tau pathology
  - Only about 50% of cases of CBS show this



- 20-25% due to AD and PSP pathology each
- Average age of onset 64, rare before age 45

Top: Pantelyat. *Continuum (Minneap Minn)* 2022;28:1364
Bottom: https://thirdeye-radiologysite.blogspot.com/2016/11/corticobasal-degeneration.html

Corticobasal syndrome

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Clinical presentation:

- Very asymmetric parkinsonism
  - Often without tremor, not responsive to levodopa
  - Early balance problems
- Dystonia in limbs
- Dysarthria, dysphagia
- Cortical signs
  - Sensory loss
  - Limb apraxia
  - Hyperreflexia
  - Cortical myoclonus
  - Alien limb phenomenon – 20%
- Cognitive impairment

Cognitive impairment in CBS

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- Executive dysfunction
- Behavioral changes
  - Disinhibition
  - Difficult to distinguish from bvFTD
  - Pseudobulbar affect
- Recognizing facial emotions
- Apraxia
  - Limbs, eyelid, gait
  - Speech
- Aphasia – most often nonfluent
- Visual or spatial neglect
- Balint syndrome, Gerstmann syndrome
- Memory loss – especially in pathological AD

Chronic Traumatic Encephalopathy (CTE)

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- Tauopathy – accumulates in a different pattern
  - TDP-43 also positive in hippocampus, amygdala, and other areas
- Related to repeat head injuries
  - Sports – football, soccer, hockey, boxing, wrestling
  - Military service
- Memory, executive dysfunction, and anger control/behavior problems
- Parkinsonism is a later feature

Irv Cross

CTE

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Symptoms at onset:

- **Memory impairment (85%)**
- Executive dysfunction (79%)
- Attention and concentration trouble (73%)
- Sadness/depression (64%)
- Hopelessness (64%)
- **Explosivity (58%)**
- Language impairment (58%)
- Visuospatial difficulties (55%)
- “out of control” (52%)
- Physically violent (52%)
- Verbally violent (49%)
- Impulse control problems (46%)
- Suicidal ideation/attempts (30%)
- Motor symptoms (30%)

LATE
Limbic-predominant Age-related TDP-43 Encephalopathy

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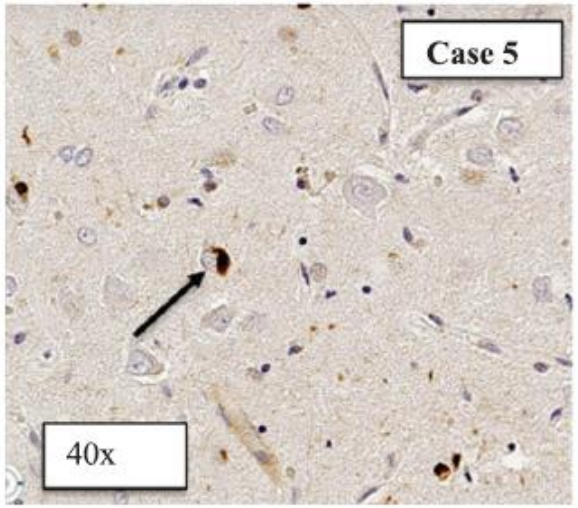
- Named in 2019
- Most prevalent neurodegenerative pathology in the oldest-old
  - Pathologic changes seen in up to 40% of autopsies >85 years old
  - In isolation without other path changes in up to 20%
- Due to the accumulation of TDP-43, especially in the anterior hippocampus
  - With associated atrophy often more severe than seen in AD
- Slower progression than AD and memory-predominant without other cognitive symptoms



Leiby A-M et al. *J Alzheimers Dis* 2023;96:113

LATE clinical features

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- Older age (proposed criteria is ≥75 years)
- Mild symptoms with largely preserved cognition
  - Impaired semantic memory out of proportion to this
- Hippocampal atrophy out of proportion to severity of symptoms
- Slow progression
- If more severely affected, more rapidly progressing, and/or other domains affected, likely copathologies present

LATE

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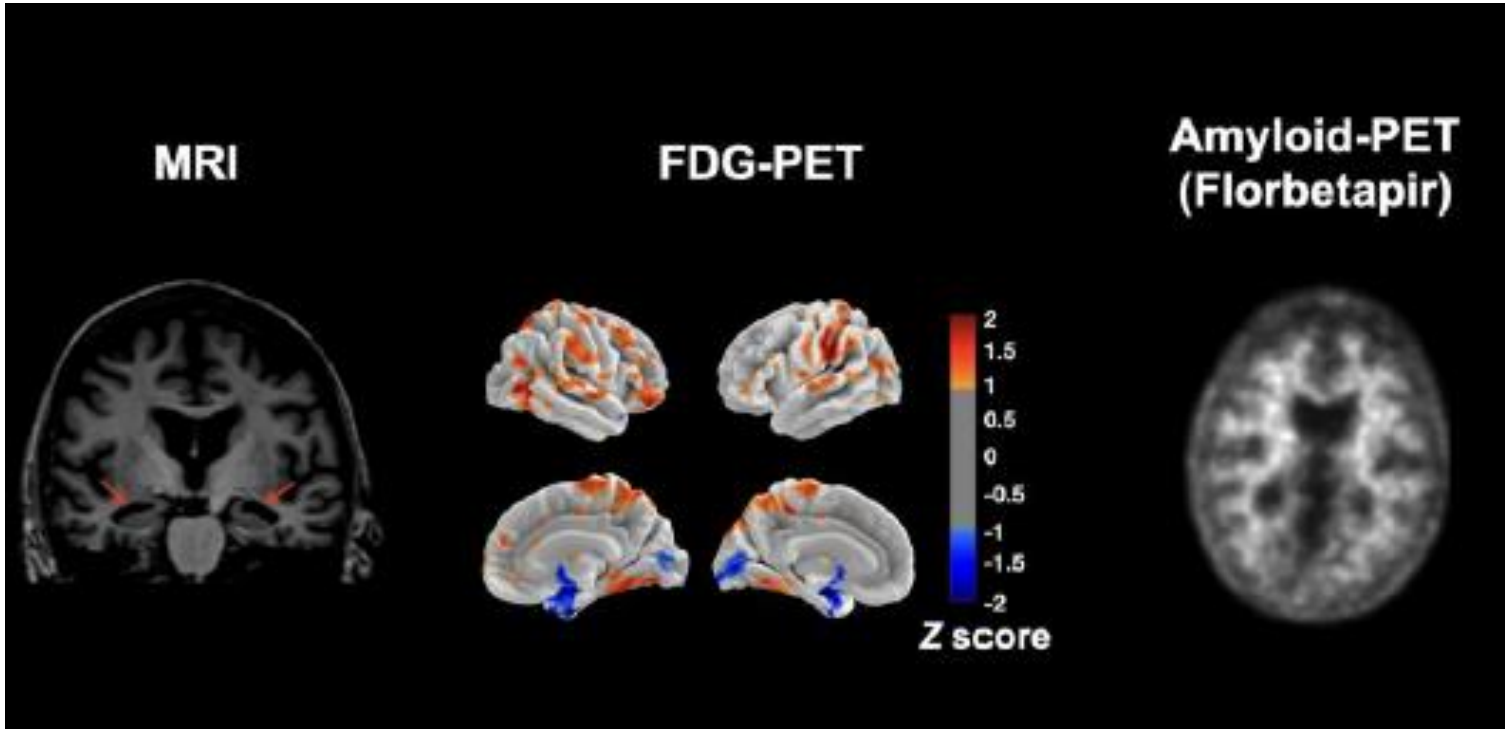
- MRI showing focal hippocampal atrophy
- Amyloid and tau-PET negative
- FDG-PET with medial temporal lobe and limbic hypometabolism
  - Parietal lobes and precuneus region unaffected
- Still being characterized

Corriveau-Lecavalier N et al. *Brain Commun* 2024;6:fcae183



Why does it matter?

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- Many patients will come in with reported “memory” problems
  - A lot of these are not truly memory – executive dysfunction, language, attention
- Comorbidities vary
- Risks and genetics vary
- Diagnostic clarity for patients and families
- Treatments vary
  - Cholinesterase inhibitors – for AD, PD and Lewy body dementia
  - Alzheimer’s disease – anti-amyloid therapy
  - All: supportive care, exercise and activity

Summary

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- Different types of dementia have different pathological causes and different symptoms
- Clinical history, neurological exam, and basic structural imaging are critical to assist with diagnosis
- We need more diagnostic testing for the atypical diseases
- More research is needed in these atypical diseases
- Treatment remains mostly symptomatic and supportive

Thank you!

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