Overview of Dementia

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April 4, 2024

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Outline

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- Introduction
- Definitions
- Causes of cognitive impairment and dementia
- Current management of dementia
- Conclusions

Introduction

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- 10% of Americans age 45 and older report subjective cognitive decline
  - But 54% of these people have not sought evaluation for this
- After 65, risk of cognitive impairment increases
  - 1 in 9 people >65 has Alzheimer’s disease in the US
- Incidence rate of AD is decreasing (new cases per year)
  - Likely due to improvement in risk factors, especially vascular
- Total number of cases continues to rise, however
  - Impact of COVID-19 unknown but likely will contribute

Definitions

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- Memory changes, trouble with memory, cognitive changes, etc – subjective trouble with memory or other cognitive tasks

- Mild cognitive impairment
  - Subjective complaints of cognitive changes and objective measure of cognitive impairment, but not overtly affecting daily function

- Dementia
  - Non-reversible process causing deterioration in cognition beyond what is expected in normal biological aging that interferes with daily living
  - What does "interferes with daily living" mean?

Is it dementia?

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- Medications
  - Benzos
  - Opioids
  - Hypnotics
  - Anticholinergics
  - Barbiturates
  - Seizure meds, muscle relaxers
  - Antipsychotics
- Other medical issues, deficiencies, toxicities
  - Vitamin deficiencies – B12, B1, folate
  - Endocrine dysfunction – thyroid
  - Chronic liver or kidney disease
  - Severe lung disease, heart failure
  - Inflammatory/autoimmune disease
  - Infections
- Sleep disruption
  - Obstructive sleep apnea
  - Insomnia
- Depression, anxiety
- Other neurological causes
  - Longstanding MS
  - Epilepsy or seizures
  - Traumatic brain injury
  - Stroke
  - Tumors or other masses
- Pain
- Hearing and/or vision loss

Workup for cognitive impairment

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- History
- Screen for sleep apnea
- Screen for depression, anxiety
- Physical exam
- Cognitive screening tests
  - MMSE
  - MoCA
  - SLUMs
- Basic labs
  - CBC
  - Metabolic panel
  - Thyroid function
  - B12, other vitamins
- Imaging
  - CT
  - MRI
- Neuropsychological testing

Causes for dementia

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- Alzheimer’s disease
- Vascular dementia
- Dementia with Lewy bodies and Parkinson’s disease dementia
- Frontotemporal dementia
- Less common – PSP, Huntington’s disease, CTE, LATE

Alzheimer's disease

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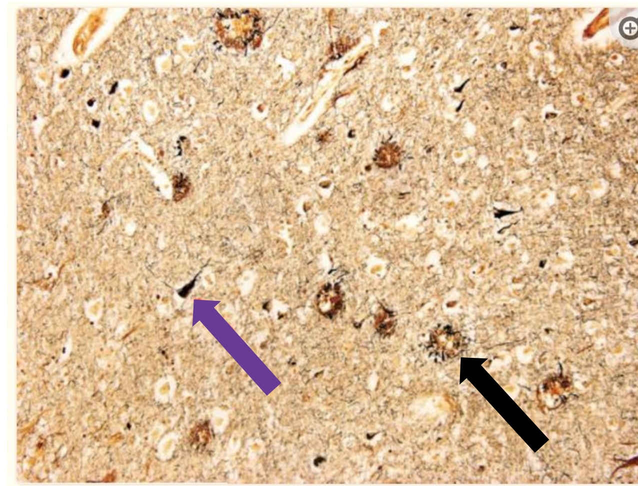
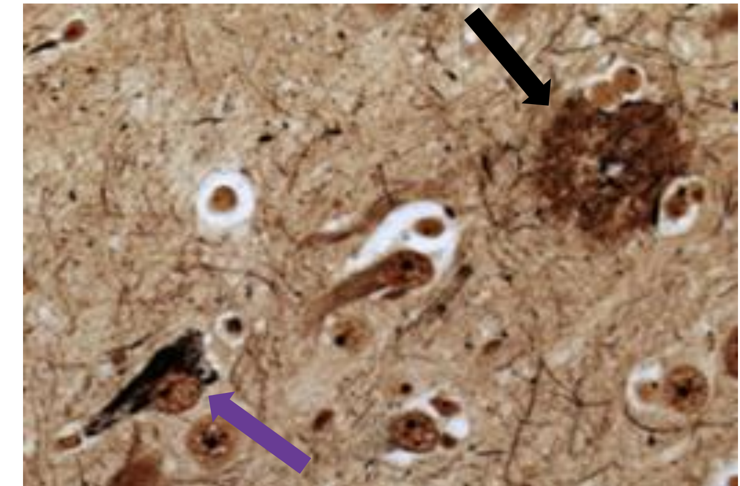
- Most common cause of dementia in the US and in the world
- Estimated prevalence of 6.5 million people over age 65 living with AD in the United States
  - 1/9 people over 65
  - 73% of these people are over age 75
- Due to accumulation of **amyloid-beta plaques** & **neurofibrillary tangles** of p-tau



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



Keene CD et al. *UptoDate* 2023

Alzheimer’s disease symptoms

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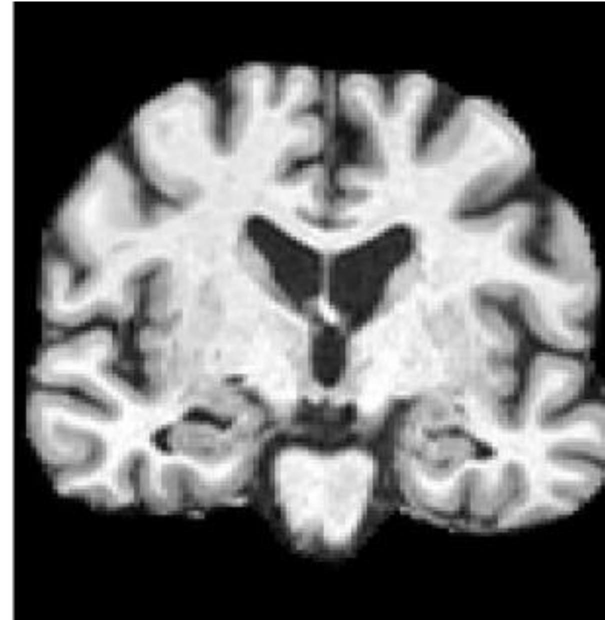
- **Short term episodic memory loss**
  - Forgetting recent events, conversations, asking repetitive questions
  - Misplacing objects, forgetting to pay bills or take medications
- Executive dysfunction
  - Difficulty making decisions, multitasking
  - Driving
  - Difficulty with finances and taxes
- Difficulty completing familiar tasks
  - Hobbies
  - Household chores, cooking
  - Using technology and utilities
- Visual and spatial relationship difficulties
  - Getting lost driving in familiar places
  - Wandering
- Language difficulties
  - Word finding
- Changes in judgement, behavior, personality
  - Decision making, basic ADLs
  - Leaving the stove on, car running
  - Financial decisions
  - Worsening irritability or mood lability
  - Aggressive behaviors
  - Delusions and hallucinations

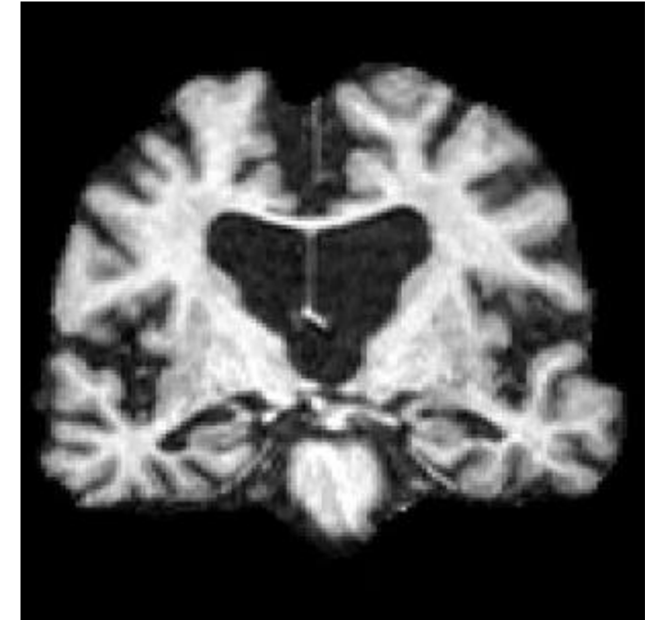
Alzheimer's disease diagnosis

- Normal neurological exam
- Cognitive testing – memory predominant deficits
- MRI/CT with atrophy especially mesial temporal and parietal

Healthy control



Alzheimer's disease

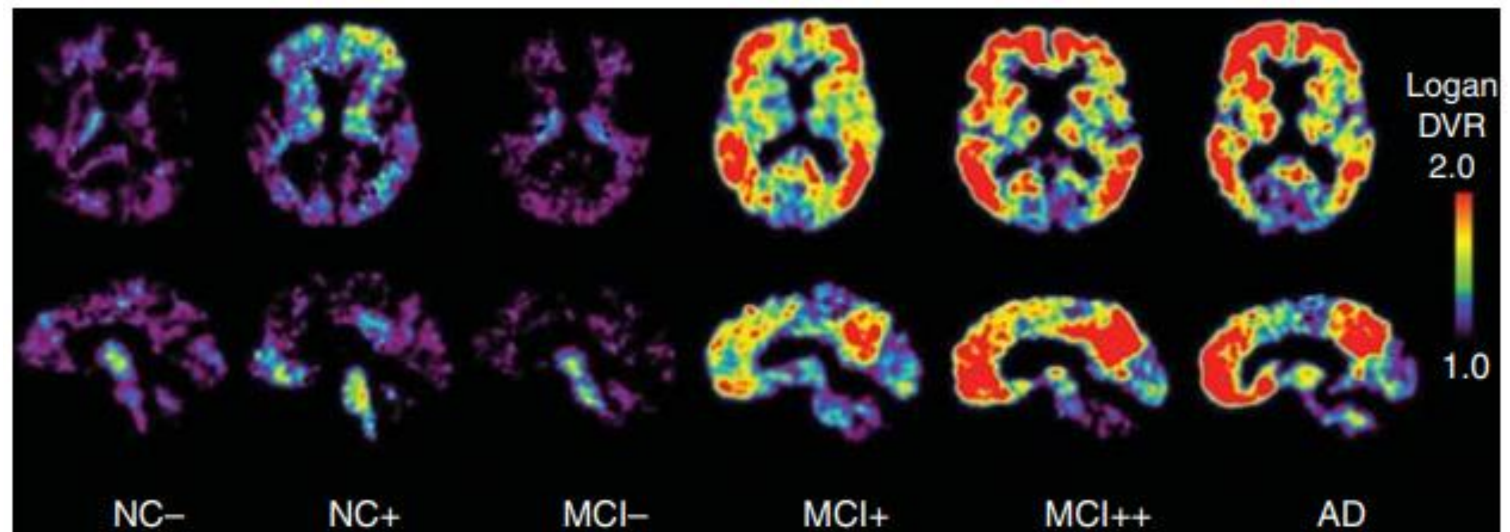


Ledig et al. *Scientific Reports* 2018; 8:11258

Alzheimer’s disease biomarkers

- Spinal fluid and serum amyloid and tau levels – decreased A-beta42, increased total and p-tau
  - Ratios often used - P-tau/Abeta42 or Abeta42/40 ratios
  - CSF testing – Athena ADmark®
  - Serum testing - PrecivityAD®

- PET scan
  - Amyloid/tau shows accumulation of tracer
  - Medicare coverage!



Vascular dementia

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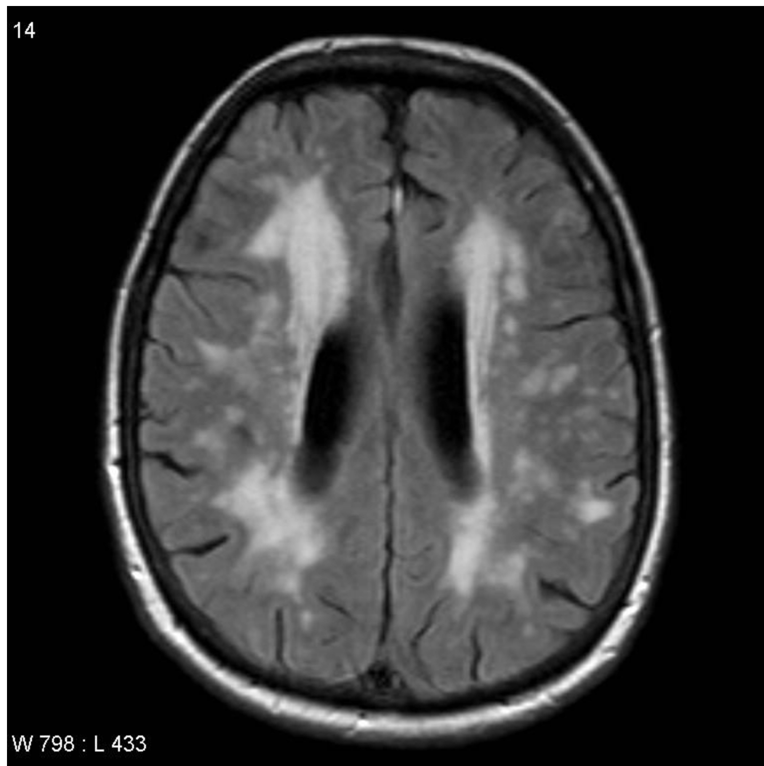
- Cognitive impairment due to vascular brain injury
  - Ischemic stroke, hemorrhage, microvascular disease
- Second most common dementia type – 15-20% of diagnosed patients
- Two main types:
  - Slowly progressive over time due to microvascular disease – “Binswanger’s disease”
  - Stepwise worsening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

- Risk factors – cardiovascular
  - Hypertension
  - Hyperlipidemia
  - T2 diabetes
  - Smoking
  - Atrial fibrillation
  - Coronary artery disease

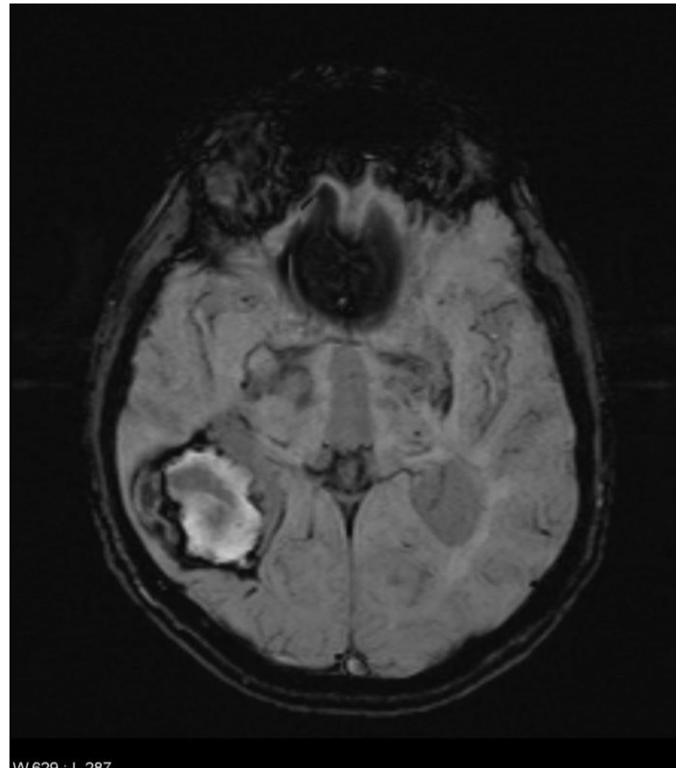
Vascular dementia

Microvascular disease



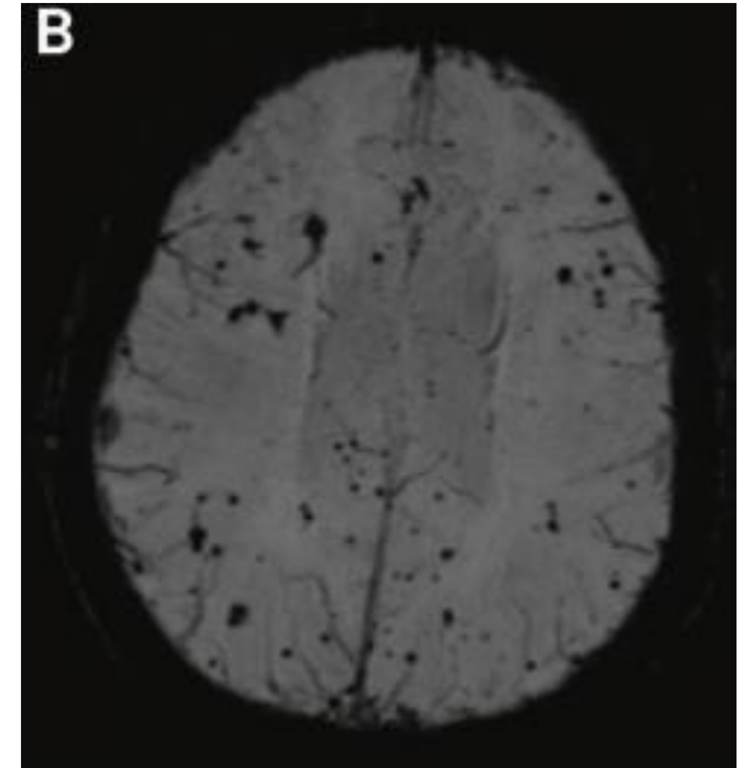
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 10674

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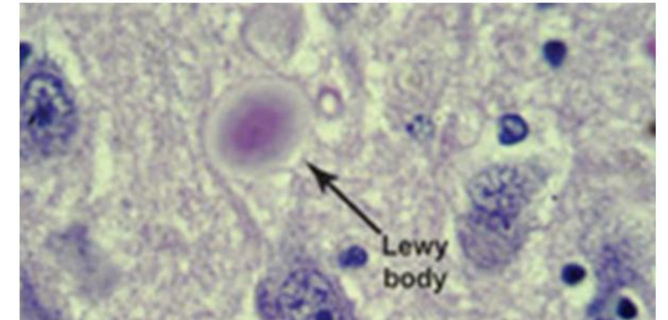
- Due to accumulation of α-synuclein – Lewy bodies = Lewy body dementia (LBD)
- Exist on a spectrum relating to timing of symptoms



https://www.alz.org

Parkinson's disease

Dementia with Lewy bodies

Motor symptoms only

Dementia only

Lewy body dementia symptoms

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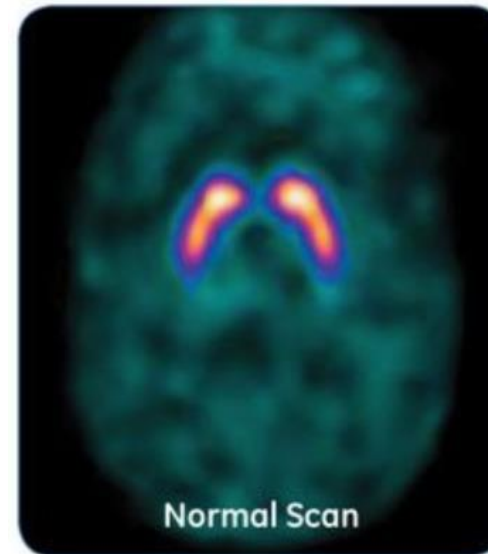
- Cognitive impairment/dementia
  - Executive dysfunction
  - Trouble with attention
  - Bradyphrenia and slowed processing
  - Visuospatial difficulties
- Visual hallucinations
- Prominent fluctuations in cognition – esp in DLB
- REM sleep behavior disorder

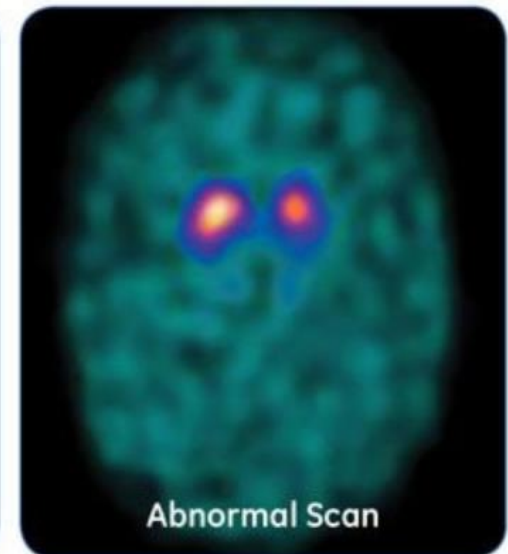
- Parkinsonism – bradykinesia, resting tremor, postural instability, rigidity

Lewy body dementia diagnosis

- History and physical exam critical
- No biomarker scans or labs… yet
- DaT scan positive especially if parkinsonism present
  - Not specific to dementia
  - Usually not needed
- Syn-One Test® - detects α-synuclein
  - Not clearly specific to disease
  - Insurance coverage unclear



"Comma"-shaped
Possible essential tremor



"Period"-shaped
Possible parkinsonian syndrome

Image courtesy of the American Parkinson Disease Association https://www.apdaparkinson.org

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

Behavioral variant FTD

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- Progressive deterioration of behavior
  - Disinhibition
  - Apathy
  - Loss of empathy/sympathy
  - Oral fixations and dietary changes
  - Perseverative or ritualistic behavior
  - Cognitive testing – executive dysfunction, sparing of memory and visuospatial tasks

- This is not anxiety, psychosis, depression

Behavioral variant FTD

Age 58 | Age 61 | Age 64 | Age 66

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

Primary progressive aphasia

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- Loss of language functions
- Semantic variant – most rare
  - Loss of knowledge of words
  - Fluent, no issues with grammar
- Nonfluent, agrammatic variant
  - Loss of speech production, fluency
  - Agrammatism
  - Knowledge of words spared
- Logopenic variant
  - Usually due to Alzheimer's pathology
  - Word finding difficulties
  - Cannot repeat even simple phrases
  - Make errors – saying "blant" for "plant"
  - Fluent, no issues with grammar
  - Circumlocution – talking around a subject, unable to get to the specific word or sentence

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

Other types of dementia

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- Progressive supranuclear palsy – PSP
  - Mostly due to tau accumulation
  - Axial parkinsonism with frequent falls, very slow and flat (akinesia), spastic speech and swallowing issues, vertical gaze restrictions
  - 70% of PSP patients will develop dementia
  - Executive dysfunction, apathy, language problems (esp nfPPA)

- LATE – Limbic-predominant Age-related TDP-43 Encephalopathy
  - In the oldest old (>85 years)
  - Due to accumulation of TDP-43, especially in the anterior hippocampus
  - Slower than AD, with memory loss only
  - Still being characterized

Summary of most common types of dementia

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	Alzheimer's disease	Vascular dementia	Lewy body dementia	Frontotemporal dementia
Typical age	Age >65, increases with age	Age >65	Average age of onset 75	Age 45-65, more likely genetic
Typical symptoms	• Short term memory loss • Executive dysfunction, trouble with daily tasks • Later, agitation, delusions	• Symptoms related to location of injury – language, visuospatial, motor skills • Often executive dysfunction	• Dementia – executive dysfunction, visuospatial issues, slowed thought processes • REM sleep behavior disorder, fluctuations, visual hallucinations • Parkinsonsim – slowed movements, rigidity, resting tremor, gait instability	• Behavioral changes – disinhibition, loss of empathy, dietary changes/hyperorality, language problems
Brain changes	• Due to amyloid plaques and tau tangles • Atrophy in the temporal lobe (hippocampus) and pariental lobe	• Due to vascular injuries – ischemia, hemorrhage	• Due to Lewy bodies (aggregates of α-synuclein) in the cortex • Atrophy more generalized in the cortex	• Due to accumulation of proteins, most commonly tau or TDP43 • Atrophy in the frontal and/or temporal lobe
Treatment	• Treat with cholinesterase inhibitors, memantine • Anti-amyloid antibodies available	• Prevent worsening by vascular risk factor reduction • Cholinesteraase inhibitors may be helpful	• Cholinesterase inhibitors (may also improve fluctuations and hallucinations) • Carbidopa-levodopa for motor (parkinsonian) symptoms	• Cholinesterase inhibitors and memantine not indicated, may worsen behavior • Some evidence for SSRIs

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

Treatment of dementia

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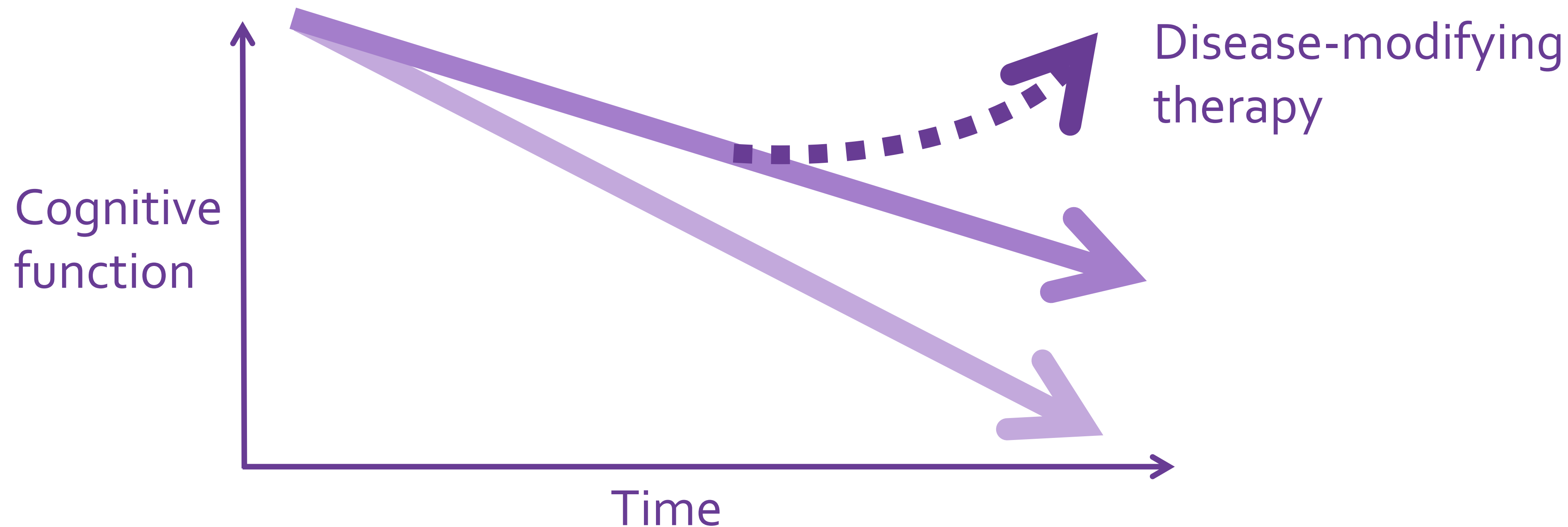
- Pharmacologic of disease
  - Symptomatic
  - Disease modifying therapy
- Other pharmacologic
  - Treating mood, anxiety, behavior
  - Sleep, other symptoms
- Non-pharmacologic
  - Education
  - Assistance
  - Behavior modification

Treatment of dementia

- Pharmacologic
  - Symptomatic
  - Disease modifying therapy
    - Anti-amyloid antibodies – currently FDA approved
    - Many trials for other proteins, none have made it through



Treatment of dementia

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Pharmacologic - symptomatic

- Cholinesterase inhibitors
  - FDA approved for Alzheimer's disease
  - Rivastigmine also approved for PD dementia
  - Used for PDD and DLB, also for amnestic MCI
  - May improve symptoms in vascular dementia
  - **No benefit in FTD**
- Memantine –NMDA antagonist
  - FDA approved for mod-severe AD only
  - Not clearly helpful in PDD or DLB
  - **No benefit in FTD, may worsen function and symptoms**

Donepezil

Rivastigmine

Galantamine

Treating other symptoms

- Depression and anxiety
- SSRIs – sertraline, fluoxetine, citalopram, etc
- SNRIs, bupropion, mirtazapine
- Avoid benzos, tricyclics
- SSRIs and trazodone may improve behavior in FTD patients

- Motor symptoms in parkinsonism
  - Dopamine replacement
    - Carbidopa-levodopa
    - Dopamine agonists
    - COMT, MAOB inhibitors
  - Anticholinergics – amantadine, Artane
    - Avoid in cognitively impaired
- Autonomic dysfunction
  - Orthostatic hypotension
  - Constipation
  - Urinary frequency/urgency

Treating other symptoms

- Sleep apnea
- Insomnia
  - Melatonin
  - Mirtazapine
  - Trazodone
  - Ambien/others not great
  - AVOID TCAs, antihistamines, benzos, antipsychotics
- Vascular risk factor reduction – also important for Alzheimer's and other dementias and overall brain health

Non-pharmacologic treatments

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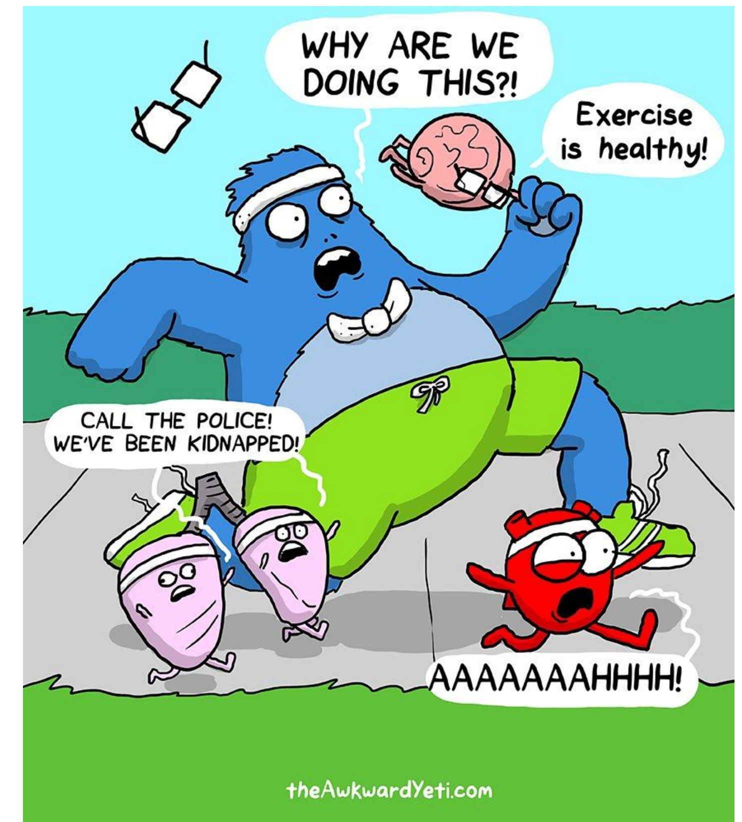
- Prevention of dementia focusing on improving modifiable risks
- Improve cardiovascular health
- Exercise, maintain cognitive and social activity
- Avoid smoking, illicit drugs, limit alcohol
- Improve sleep



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Non-pharmacologic treatments

- Improving behaviors and Coping
  - Communication
  - Review photos, souvenirs, reminisce
  - Organization and routine
  - Home safety
  - Validate feelings
  - Find meaningful activities and interests
  - Senior centers and day centers
  - Music and Art – **Beyond the Medical Center**
  - Limit expectations

Conclusions

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- Cognitive impairment and dementia is a common problem in the aging population, and is going to get worse
- There are many causes of cognitive impairment, some of which are reversible
- The most common types of dementia are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia
- Pharmacologic treatment of the specific disease varies but management of these problems is much more than medication and patients benefit from a multidisciplinary approach

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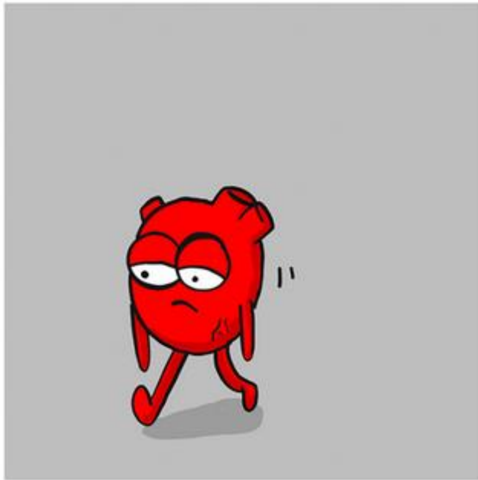
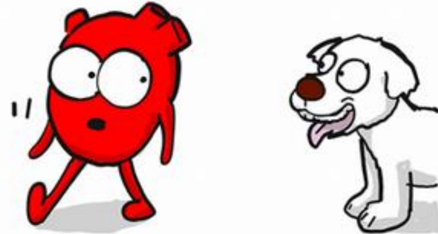
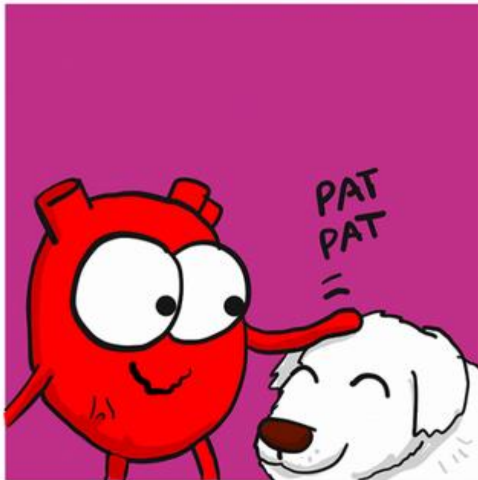
Thank you!







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