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Outline

- Types of Dementia
 - Description
 - Symptoms
 - Treatment
 - OVERLAP / Unique Features
- Case Study
- Advances in Alzheimer's disease Research



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Dementia

Dementia: A group of symptoms affecting thinking and social abilities severely enough to interfere with daily functioning.

The difference depends the cause and location of the brain has been damaged.

Introduction/Background

- Vascular Dementia
- Lewy Body
- Frontotemporal
- Alzheimer's disease

Alternative Causes

- Medications
 - Chemotherapy
- Depression
- Fever / Infection
- Nutritional deficit
- Surgery
- Alcoholism
- HIV

Diagnosis

- Consensus Dx (ADRCs)
 - Neuropsychologists, neurologists, cognitive scientists, geneticists, geriatricians, RNs, etc...
- Cognitive testing (MMSE)
- Neuroimaging
- Genetics / family history
- Abeta testing in CSF

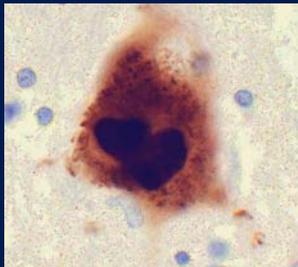
Why the Need to Correctly Diagnose?

- Different projected path
- Different Medications
- Planning for the patient and caregiver

Lewy Body Dementia

- In Lewy body dementia, protein deposits, called Lewy bodies, develop in nerve cells in regions of your brain involved in thinking, memory and movement (motor control).
- Lewy bodies are also found in the brains of people with Parkinson's disease

Lewy Body Dementia



Lewy Body Dementia

- Visual hallucinations / having conversations with deceased loved ones.
- Significant fluctuations in alertness and attention, daytime drowsiness / staring into space.
- Rigid muscles, slowed movement and tremors.
- Rapid eye movement (REM) sleep behavior disorder that involves acting out dreams.

Lewy Body Dementia

- No cure yet
- AD medications (cholinesterase inhibitors)
- Memantine
- Anti-Parkinson's drugs, though could exacerbate hallucinations.
- Neuroleptics are dangerous

Vascular Dementia

- 2nd second most common type of progressive dementia after Alzheimer's disease, causes a progressive decline in mental abilities.
- Problems with reasoning, planning, judgment, memory and other thought processes caused by brain damage from impaired blood flow to your brain.



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Vascular Dementia

Most common after a stroke

- Multi-infarct dementia
- Whether a stroke affects your thinking depends the stroke's severity and location. Can result from other conditions that damage blood vessels and reduce circulation, depriving your brain of vital oxygen and nutrients.
- Factors that increase your risk of heart disease and stroke — including high blood pressure, high cholesterol and smoking — also raise your vascular dementia risk. Controlling these factors can help lower your chances of developing vascular dementia.



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Vascular Dementia Risk Factors

- history of stroke, high blood pressure (50%), high cholesterol, diabetes or sleep apnea
- lack of physical activity, alcohol, smoking, eating a fatty diet,
- family history of stroke or cardiovascular disease
- an Indian, Bangladeshi, Pakistani, African or Sri Lankan background - differences in vascular risk factors (such as heart disease) in these communities may contribute to the increased risk



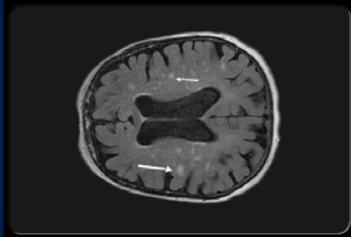
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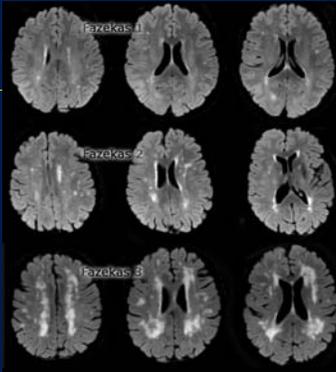
Vascular Dementia

- Hard to differentiate from AD
 - Frontal lobe involvement (verbal fluency, recall, bahavior)
- Depression and anxiety
- Symptoms of a stroke (physical weakness, paralysis)
- Seizures
- Periods of severe confusion

Vascular Dementia

- Brain changes: White matter. MRI useful





Vascular Dementia

- Treatment
 - Although the brain damage cannot be reversed, it may be possible to slow the progression of the disease:
 - Medication to treat any underlying conditions, such as stroke, high blood pressure, high cholesterol, diabetes or heart problems
 - adopting a healthier lifestyle by stopping smoking, exercise, eating healthily, and drinking alcohol in moderation
 - receiving rehabilitative support, such as physiotherapy, occupational therapy and speech therapy, to help the person maximize their opportunities to regain their lost functions.

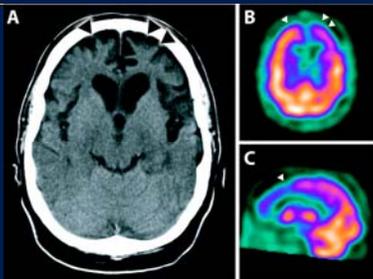
Frontotemporal Dementia



Frontal and temporal lobe atrophy.

- Cause: unknown
- Strong FH link
- MAPT, GRN, C9ORF72
- Does not cause memory problems at first.

FTD



3 Types of FTD

- Behavioral variant Frontotemporal dementia
- Progressive non-fluent aphasia
 - (speech)
- Semantic dementia
 - Vocabulary, grammar, comprehension

Frontotemporal Dementia

- Symptoms vary, depending upon the portion of the brain affected.
 - dramatic changes in personality
 - socially inappropriate
 - Binge eating / impulsive
 - emotionally indifferent
 - inability to use and understand language.
- Less common
- Often misdiagnosed as a psychiatric disorder
- 45-65 yrs

Frontotemporal Dementia

- Preservation (at first) of:
 - Perception
 - Spatial Skills
 - Memory
 - Praxis (engaging / participation)

Alzheimer's disease

- Most common cause of dementia
- Only 100% sure of diagnosis via autopsy (now)
- 65 yrs, more women, genetic, FH and vascular components
- Currently no treatment
 - acetylcholinesterase inhibitors (tacrine, rivastigmine, galantamine and donepezil)
 - and NMDA receptor antagonist (memantine)

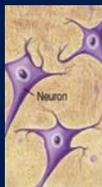
AD Symptoms

- Memory loss that disrupts daily life
- Difficulty with familiar tasks
- Confusion with time and place
- Difficulty with planning and problem solving

AD Neuropathology



Normal

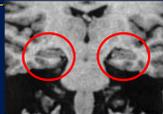


AD

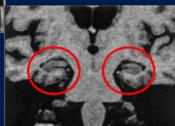


Atrophy of the hippocampus in normal aging, MCI, and AD

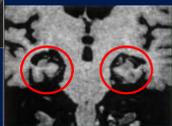
Normal Brain



MCI



Moderate AD



- But in the real world....
- Case Study: Jane X

Clinical Vignette

- 82 year old female, widowed, referred because of rapid decline in cognition
- 2 year history of gradual decline in cognition and function
 - Initially difficulty with memory and higher order tasks
 - 1 year ago episode of sudden confusion with slurred speech, resolved but cognition worse
 - 6 months ago developed mild paranoia, mixing up pills, fire on stove
 - 6 weeks ago worsened confusion with slurred speech, drooped face, signs resolved but cognition worse

Past history:

- Diabetes Mellitus Type II
 - Hypertension
 - Osteoarthritis (knees)
 - Cataracts
- ### Meds:
- Glyburide (diabetes)
 - Metformin (diabetes)
 - Enalapril (high blood pressure)
 - Hydrochlorothiazide (high blood pressure)
 - Aspirin

Cognitive testing:

- MMSE 18/30 (normal ≥ 24), 0/3 recall
- Clock: All numbers spaced on right
- Verbal fluency 4 (normal 10)
- Impaired naming
- Difficulty following complex commands
- Anxious, repetitive, notable word finding problems
- Mild paranoia

Physical Examination:

- Strength equal throughout
- Reflexes equal throughout
- Increased motor tone bilaterally, no tremor
- Difficulty with rapid alternating movements
- Positive palmo-mental frontal release sign bilaterally
- Gait: slowed, decreased step height, cautious, Romberg negative

CT

- Two very small strokes deep inside the brain
- Brain is smaller than it should be given her age
- Other changes deep inside the brain that tell us it is not getting enough oxygen (white matter ischemic changes)

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Diagnosis

- Mixed dementia
 - Clinical features of Alzheimer's Disease: prominent memory loss, language changes, behavior problems
 - Risk factors for stroke, two suspicious events with possible step-wise decline, CT evidence of strokes
- Rapidity of decline consistent with mixed disease
 - Presence of cerebrovascular (stroke) lesions with AD pathology = more severe disease presentation

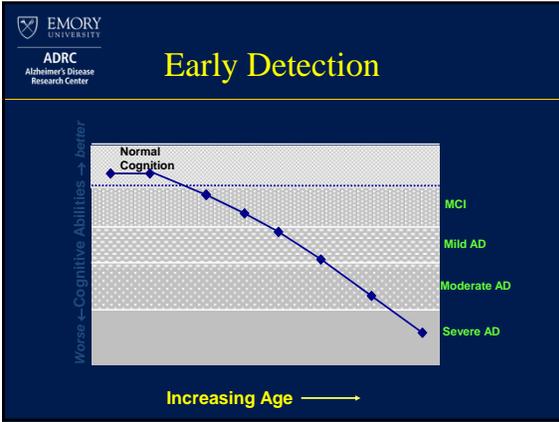
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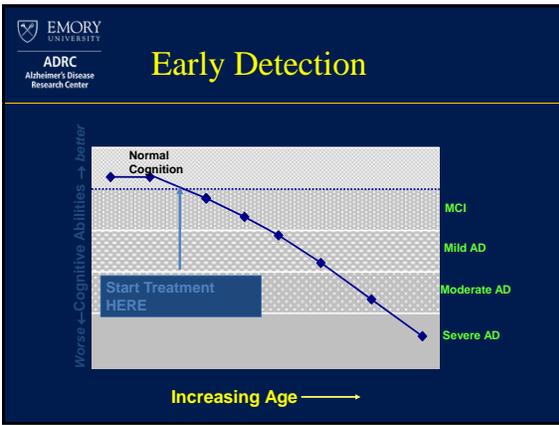
AD Research...

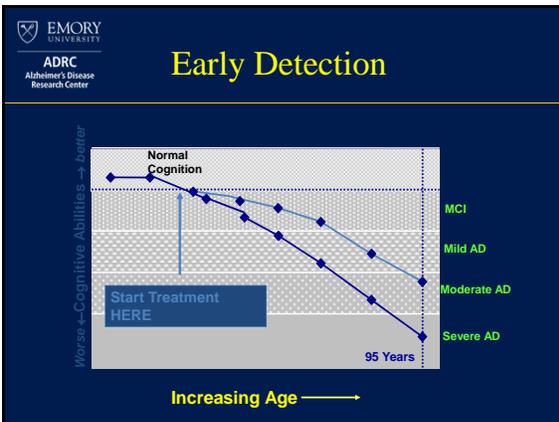
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AD: Disease Progression

The diagram illustrates the progression of Alzheimer's Disease (AD) through three stages: Normal, Mild Cognitive Impairment, and AD. A vertical axis on the left is labeled 'Cognitive Function', with a downward-pointing arrow indicating a decrease in function as the disease progresses. A red diagonal arrow points from the top-left (Normal) towards the bottom-right (AD), representing the disease's trajectory. A yellow curved arrow points from the Normal stage to the Mild Cognitive Impairment stage. A box labeled 'Pathologic hallmarks' is positioned between the Mild Cognitive Impairment and AD stages, with arrows pointing to the corresponding brain images. A box labeled 'CSF biomarkers, Neuroimaging, Cognitive measures' is at the bottom, with arrows pointing to the corresponding brain images. The 'Normal' stage shows a healthy brain and neurons. The 'Mild Cognitive Impairment' stage shows neurons with 'Neurofibrillary tangles' and 'Amyloid plaques'. The 'AD' stage shows a brain with significant pathology and neurons with 'Neurofibrillary tangles' and 'Amyloid plaques'.







How do we clinically shift the curve???

- What factors do we know that....
 - Are linked to cognitive decline and AD
 - Are linked to the pathological hallmarks of AD (plaques and tangles)
 - Occur during Midlife
 - TREATABLE / REVERSIBLE

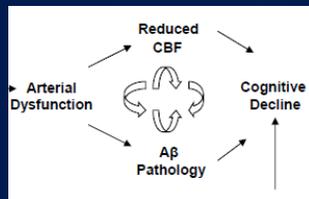
Vascular Risk Factors and Alzheimer's disease

AD has been associated with:

- Increased cholesterol levels in midlife
- Elevated blood pressure in midlife
- Increased levels of inflammation
- Obesity
- Diabetes
- Physical inactivity

Alzheimer's and Vascular risk Factors

- Increased vascular risk leads to AD via increased brain plaques and reduced brain blood flow, leading to brain atrophy and cell death.

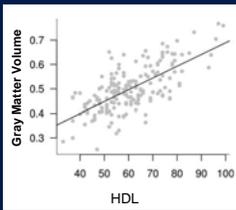


Observational Studies guide Clinical / Mechanistic Studies. Example: Blood Pressure Medication

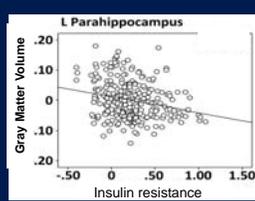
- High blood pressure in midlife is predictive of Alzheimer's disease in later life. Similarly, reductions in BP are associated with protection against AD
- Treatment with some antihypertensive medications is associated with up to a 55% reduction in the prevalence of AD

Modifiable factors also related to "volume"

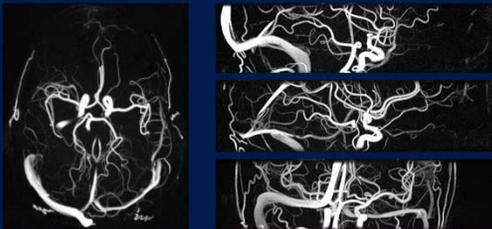
The "good" cholesterol



Low Diabetes risk High



Brain blood flow



Metabolic Syndrome, Brain Blood Flow and AD risk

Results:

Participants at risk for AD, with multiple risk factors connected to metabolic syndrome, including obesity, high blood pressure, high blood sugar and high cholesterol averaged 15 percent less blood flow to the brain than those in a control group

So...

- Based on observational studies, AND taking into account the 'curve' (i.e. midlife intervention, targeting neuropathological factors that are reversible) we can develop studies examining mechanistic specifics to treat / prevent AD.
- i.e. HOW does improved blood pressure relate to AD? Reduced brain blood flow? Increased plaques? Both?

Blood Pressure Studies

- SEAIRA (completed)
- EMBARK (ongoing)
More sensitive, clinically relevant tool assessment.
- ASCEND (recruitment begins 2013)
– Effects of blood flow in the body to blood flow in the brain, plaques, and cognitive testing.

Take Away

- Aging is normal, AD and other dementias are not normal.
- Whole systems approach
- Some of the most difficult symptoms are part of the disease, not the person.
- Refer to specialized memory clinics for correct diagnosis and specialized testing
- Importance of research

Resources

[Thank You!](#)

<http://adrc.wisc.edu/>

- <http://med.emory.edu/ADRC/index.html>
- <http://www.alz.org/>
- <http://www.alzheimers.org.uk/site/scripts/documents.php?categoryID=200122>
