I Can't Recall: Memory and the Impact of Neurological Disorders

Community Medical School
December 2, 2014
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Overview Of Today’s Presentation

• Memory, aging and dementia
• Alzheimer’s disease (AD)
• Public health impact of dementia and AD: challenges
• AD: causation and pathogenesis
• Differential diagnosis
  – Frontotemporal Lobar Degenerations
  – Diffuse Lewy Body Disease
  – Vascular Dementias
• New concepts: opportunities
• Final thoughts
Some Views About Memory

• “The world will little note nor long remember what we say here”  Abraham Lincoln
• “Happiness is nothing more than good health and a bad memory”  Albert Schweitzer
• “There are a lot of people who mistake their imagination for their memory”  Josh Billings
• “Creditors have better memories than debtors”  Benjamin Franklin
What Is Memory?

• Memory is the ability of the brain to:
  – Learn or remember new information
  – Place that information into long term storage
  – Recall it from storage when needed
How Is Memory Formed And Used?

- Step 1: **information gathering** from the environment (somatosensory inputs)
- Step 2: **registration** in the hippocampus which creates a short term memory
- Step 3: save or delete?
- Step 4: **storage** into long term memory in the cerebral cortex
- Step 5: **remembering** which allows an individual to become increasingly efficient at interpreting life’s experiences, making decisions, and communicating one’s thoughts and feelings
How Is Memory Affected By Aging?

- As we age, the brain loses some of its abilities that can lead to forgetfulness
  - This is normal, and begins after the age of 40
  - Not progressive
  - No decline in activities of daily living
  - Productive and satisfying life
Dementia

The development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive function.

The cognitive deficits must be sufficiently severe to cause impairment in the occupational or social functioning of the patient and must represent a decline from a previously higher level of functioning.

What Is Dementia?

- When memory loss and related symptoms affect our ability to function on a day-to-day basis, and are progressive, this is called dementia. Common symptoms of mild to moderate dementia include:
  - Progressive short term memory loss
  - Forgetting names of familiar people
  - Difficulty finding words
  - Mild, usually transient, disorientation
  - Changes in personality
  - Decreased reasoning ability, poor insight, lack of judgment
Is It Dementia Or Something Else?

• Other factors that interfere with normal memory function and related symptoms:
  – Stress (physical/emotional)
  – Lack of sleep
  – Substance abuse
  – Depression
  – Metabolic disorders (e.g., thyroid problems)

• Symptoms of dementia require a careful medical evaluation
Aging American Population

3% of the population 65-74 yrs of age; 20% of the population 75-84 yrs of age; 30%-50% of the population > 85 yrs of age
Prevalence of Dementia (%)

- > 65 yrs: 3%–15%
- > 85 yrs: 32%–47%

Age (yrs)

Prevalence of Dementia (%)
Differential Diagnosis Of Dementia

Vascular dementias:
- Multi-infarct dementia
- Binswanger’s disease

Other dementias:
- Frontotemporal lobar degenerations
- Creutzfeldt-Jakob disease

Lewy body dementias:
- Parkinson’s disease
- Diffuse Lewy body disease
- Lewy body variant of AD

AD and Lewy body dementias

Overview Of Alzheimer’s Disease

Alzheimer’s disease (AD) is a degenerative disorder of the brain that is (by far) the leading cause of dementia in elderly people in the United States and throughout the world. AD causes a progressive loss of cognitive abilities that is associated with a decline in a person’s capacity to be independent and care for one’s own needs. Behavioral disturbances are almost always present. There currently is no cure for AD, and the benefit of current treatment is limited.
Someone in the United States develops AD every 67 seconds
Challenges
Public Health And Personal Impact Of AD

- Over 5.5 million people are affected in US
- Prevalence rate as high as 10% over age 65
- Cost/year for AD patient care: $20-80,000/pt
- Average disease duration: 7-8 years
- Health care cost: over 600 billion dollars annually worldwide
- US health care cost: over 214 billion dollars in 2014
  - 150 billion in costs to Medicare and Medicaid
  - Expected to reach 1.2 trillion in 2050
- Third most expensive disease after heart disease and cancer (US health care $’s)
- Fifth leading cause of death over 65; sixth leading cause overall
Death Due To AD

• In 2010, underlying cause for 83,494 deaths
• Contributing cause for an additional 26,488
• Mortality from AD has steadily increased during the last 30 years-6th leading cause of death in U.S. overall, and 5th for people over 65
• Death from AD increased 38% between 2000 and 2010
• AD is the only cause of death among the top 10 in America that cannot be prevented, cured or even slowed
Alzheimer’s disease mortality increased compared with selected major causes of death.

Figure 1. Percent change in age-adjusted death rates for selected causes of death: United States, 2000 and 2010

- Alzheimer’s disease: 38.7%
- Diabetes mellitus: -4.5%
- Cancer: -31.6%
- Heart disease: -30.5%
- Stroke: -35.8%

Caregiver Costs

• In 2013, 15.5 million caregivers provided an estimated 17.7 billion hours of unpaid care valued at more than $220 billion dollars
Women Are At The Epicenter Of The AD Epidemic

• In her 60’s, a woman’s estimated life time risk for developing AD is 1 in 6. For breast cancer it is 1 in 11
• Almost 2/3’s of Americans with AD are woman
• There are 2.5 times more women than men providing intensive “on-duty” care 24 hours/day for someone with AD
• More than 60% of AD and dementia caregivers are women
By 2050, the number of people age 65 and older with AD may nearly triple to as many as 16 million, barring the development of medical breakthroughs to prevent, slow or stop the disease.
Symptomatic Course And Progression Of AD

MMSE = Mini Mental State Examination
Alzheimer’s Disease: Pathology

[Images of brain tissue and pathology]
Plaques And Tangles

- Plaques are caused by the accumulation and aggregation of a protein called Aβ42 (Aβ peptide, β-amyloid)
- Tangles are caused by the accumulation and aggregation of a protein called tau
Molecular Pathogenesis Of Plaques
Molecular Pathogenesis Of Tangles

**Troubled tau.** This simplified model shows how normal tau (rectangles on microtubules) might be changed to PHF-tau through abnormal accumulation of phosphate groups. PHF-tau then cannot bind microtubules and instead infests the neuron as tangles, harming and killing the cell.
Differential Diagnosis
Dementia Differential Diagnosis

- Alzheimer’s disease – 70%
- Frontotemporal lobar degenerations – 10-15%
- Diffuse Lewy body disease – 10%
- Vascular dementias – 10-15%
Frontotemporal Lobar Degenerations (FTLDs)
Definition of FTLDs

- Clinicopathologic syndromes with prominent behavioral and language symptoms
- Clinically referred to as frontotemporal dementia
- Progressive degeneration of the frontal lobes, anterior temporal lobes, or both
- Significant hemispheric asymmetry associated with earliest presentation
- Degree of frontal versus temporal pathology accounts for variability in the presenting symptoms
FTLDs: Diagnostic Criteria

- Behavioral disinhibition (verbal, physical or sexual)
- Prominent/early language involvement
- Violation of social norms
- Apathy (passivity, inertia and inactivity)
- Hypomania-like behavior (over activity, excessive talking, laughing, singing, sexuality)
- Loss of interpersonal warmth or empathy
- Loss of insight (for their behavioral changes)
- Relative preservation of memory
FTLDs: Classification

- Pick’s disease
- Pick’s complex
- Primary progressive aphasia
- Semantic dementia
- Progressive supranuclear palsy
- Corticobasal degeneration
- Frontotemporal dementia with parkinsonism linked to chromosome 17 with *Tau* gene mutations (FTDP-17T)
- Frontotemporal lobar degeneration with motor neuron disease-type inclusions (FTLD-MND)
- Several others defined by pathologic features (FTLD-U; DLDH)
Alzheimer’s Disease Versus FTLDs

**Alzheimer’s Disease**
- **Age of onset**: > 65
- **First complaint**: Short term memory loss
- **Anatomy**: Medial temporal, hippocampus
- **Family history**: Negative
- **Exam**: Normal
- **Treatment**: ACIs, memantine, psychotropics

**FTLDs**
- **40 to 64**
- **Personality change, behavior, language**
- **Frontal, anterior temporal**
- **Positive in up to 40%**
- **May have motor findings**
- **Psychotropics; ACIs may worsen impulsivity**
FTLDs: Neuroimaging

**FIGURE 3-6** Frontotemporal dementia. Axial magnetic resonance images and positron emission tomography images in a case of frontotemporal dementia. Note the focal atrophy and hypometabolism disproportionately affecting the frontal lobes.
FTLD Pathology: Pick’s Disease
Diffuse Lewy Body Disease
Diffuse Lewy Body (DLB) Disease Core Symptoms

- Dementia
- Fluctuating cognition
- Visual hallucinations
- Extrapyramidal signs (EPS)
- Variation in alertness
# DLB Clinical Features

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Cardinal Manifestations</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Attention, frontal executive, and visuospatial deficits - worse than AD; short term memory - better than AD</td>
<td>100%</td>
</tr>
<tr>
<td>Fluctuating cognition</td>
<td>Variable timing of altered level of attention; distinct from sundowning</td>
<td>60-80%</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>Recurrent; inanimate subjects; variable degree of insight; reminiscent of anticholinergic delirium</td>
<td>50-75%</td>
</tr>
<tr>
<td>Parkinsonian motor signs</td>
<td>Spontaneous; rigidity and bradykinesia most common; intention tremor more common than resting tremor</td>
<td>80-90%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Falls, syncope, transient loss of consciousness; hallucinations and systemized delusions; neuroleptic sensitivity</td>
<td></td>
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Fluctuating Cognition

- Diffuse Lewy body disease – 80-90%
- Vascular dementias – 35-50%
- Alzheimer’s disease – 20%
Lewy Body
Vascular Dementias
Vascular Dementias: Clinical Features

• Clinical diagnosis of vascular dementia:
  – Focal neurological signs, stepwise neurological deterioration, declining cognitive performance that fluctuates considerably day to day
  – Strokes
  – Gait difficulties, urinary incontinence, ‘parkinsonian’ features and pseudobulbar signs
## Hachinski Score

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
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<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Clinical Feature</td>
<td>Score</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2</td>
</tr>
<tr>
<td>Clinical evidence of atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>2</td>
</tr>
</tbody>
</table>
Hachinski Score

- A total score of 4 or less is suggestive of a degenerative cause of dementia such as Alzheimer’s disease.
- A score of 7 or more is suggestive of vascular dementia.
Types And Etiologies

• Vascular dementias
  – Cortical infarct dementia
  – Subcortical ischemic vascular dementia
  – Strategic infarct dementia
  – Hypoperfusion dementia
  – Dementia caused by intracerebral hemorrhage
  – Dementia as a result of specific arteriopathies

• Mixed dementia (vascular dementia and Alzheimer’s disease)

• Vascular mild cognitive impairment (does not meet formal criteria for dementia)
Vascular Dementia

**Supporting clinical features**

- Gait disturbance, falls, and urinary incontinence early

**Features making diagnosis unlikely**

- Early and progressive onset of memory deficit with development of aphasia, apraxia or agnosia

**Pseudobulbar features**

- Lack of neurologic signs other than memory

**Frontal lobe dysfunction**

- Lack of lesions of vascular disease on imaging
New Concepts: Opportunities
We’ve Learned A Lot In 30 Years

• There have been important advances in our understanding of AD

• We now have the ability to detect the patho-physiologic process of AD using biomarkers
  – CSF analysis for certain proteins (discussed later)
  – Positron emission tomography (PET) scan imaging for detection of protein accumulations in the brain
  – PET to detect metabolic activity in the brain
  – Structural MRI scans to detect brain atrophy

• We’ve changed our conceptualization regarding the clinical spectrum of the disease
We Now Know

• The pathologic changes in the brain that underlie the clinical features of AD are present 20-25 years prior to the onset of symptoms

• There is a preclinical stage of AD when there are no symptoms of the disorder, yet pathology is present and can be detected by biomarkers

• There is an early clinical phase of AD when there are no functional limitations or behavioral disturbances (mild cognitive impairment[MCI])
MCI Criteria (amnestic)

- Memory complaint, preferably confirmed by an informant
- Memory impairment is not normal for age and education
- Preserved general cognitive function
- Intact activities of daily living
- Therefore not demented
- Likely that most (?all) aMCI patients progress to AD
Concept Of Preclinical Stage OF Disease

• Multiple examples in other diseases
  – Carcinoma *in situ*
  – Coronary artery disease detected on cardiac catheterization or via coronary calcium

• Symptoms not required to diagnose disease
  – Renal insufficiency or liver cirrhosis often detected by blood test
  – Treatment can prevent emergence of symptoms

• Not all individuals with risk factors or early pathology will manifest symptoms
  – Hypercholesteroleolemia /Atherosclerosis
Clinical Spectrum Of AD

• Preclinical AD
  – No symptoms; cognitively normal
  – Pathology present; but little to no neuronal injury

• Mild cognitive impairment (amnestic)
  – Symptoms limited to memory loss; no functional or behavioral impact
  – Pathology present; early to mild neuronal injury and death

• Dementia due to AD
  – Full blown dementia; impact on function; +/- negative behaviors
  – Pathology present; moderate to severe neuronal injury and death
Can we see the pathologic changes of AD while a patient is still alive?

YES!
Biomarkers For AD Detection

• Biomarkers of Aβ42 accumulation in the brain
  – Reductions in CSF Aβ42
  – Evidence of Aβ42 accumulation in the brain by PET

• Biomarkers of neuronal injury in AD
  – Elevations of tau in CSF
  – Reduced metabolism in the parietal and temporal areas of the brain using radio-labeled glucose and PET (FDG-PET); functional MRI (fMRI)
  – Atrophy on brain structural imaging such as sMRI
As An Example, Consider MCI
Core Clinical Criteria For MCI

• Concern reflecting a change in cognition reported by patient or informant or clinician
• Objective evidence of impairment, typically in memory
• Preservation of independence in functional activities
• Not demented
MCI Due To AD: High Likelihood

- Meets core clinical criteria
- Positive biomarker reflecting Aβ42 accumulation
- Positive biomarker reflecting neuronal injury
MCI Due To AD: Intermediate Likelihood

- Meets core clinical criteria
- Positive biomarker reflecting $\text{A}\beta_{42}$ accumulation with an untested biomarker of neuronal injury; or
- Positive biomarker reflecting neuronal injury with an untested biomarker of $\text{A}\beta_{42}$ accumulation
MCI Due To AD: Low Likelihood

• Meets core clinical criteria
• Negative biomarker reflecting Aβ42 accumulation
• Negative biomarker reflecting neuronal injury
Hypothetical Model Of AD Pathophysiological Cascade

Age
Genetics (causal or susceptibility)

Cerebrovascular risk factors
Other age-related brain diseases

Aβ42 accumulation:
Increased production; or Decreased clearance

Synaptic dysfunction
Tangle formation
Neuronal death

Cognitive decline (Dementia)

Preclinical AD

MCI

Dementia due to AD

Age 45-50
Age 60-70
Age > 70
Final Thoughts
Proof Of Concept: Results From DIAN (Dominantly Inherited Alzheimer’s Network)

- Genetic AD: rare (1-2%); autosomal dominant; mutations involving three loci (chromosomes 1, 14, 21); all related to APP processing
- Inheritance of one of these mutations causes symptomatic AD, with onset at 45 years of age
- DIAN coordinated by investigators at Wash U, St Louis: 400 young adults who are members of genetic AD pedigrees
- Core goal of the study is to understand AD biomarker chronology in asymptomatic carriers
DIAN (Continued)

• Cross-sectional analysis of data on the first 128 DIAN participants showed:
  – 20-25 years before expected onset:
    • Drop in CSF Aβ42
  – 15 years before expected onset:
    • Aβ42 detected by amyloid-PET scan
    • Elevated CSF tau
    • Atrophy in key brain structures by sMRI scan
  – 10 years before expected onset:
    • Decreases in glucose metabolism by FDG-PET scan
    • Subtle impairments on sensitive memory tests
Thank You: Questions?