Alzheimer Disease

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No conflict of interest or conflict of commitment
Objectives

• Definition of Alzheimer Disease
• Epidemiology of Dementia and AD
• Clinical presentation of Alzheimer’s Disease
• Pathophysiology of Alzheimer
• Management of Alzheimer
• Cases and questions
Alzheimer Dementia

- Is a neurodegenerative dementing disease
- Is a syndrome consisting of progressive loss of recent and then older memories
- Alzheimer’s disease is a subtype of dementia
- Degenerative dementias begin insidiously and follow a ceaselessly progressive course.
Forms of Dementia

- Early Onset Alzheimer Disease (EOAD)
- Late Onset Alzheimer Disease (LOAD)
- Posterior Cerebral Atrophy
- Primary Progressive Aphasia (logopenic)
- Primary Progressive Aphasia (semntic)
- Fronto-Temporal Dementia (ALS spectrum)
- AIDS dementia Complex (HIVE, HIND)
- Dementia with Parkinson (executive dementia)
- Dementia with LBD
- Dementia associated with CTE
- Dementia in Psychiatric disorders
Clinical Presentation

• Dementia is characterized by loss of memories
• Clinical presentation of dementia, depends on the sum of locations of pathology in the cerebral cortex.
• Phenotype of dementia = location in the cerebral cortex
Neurology of Dementia: localization

- Memory does not have a specific address
- It is distributed throughout the brain
- Explicit memory is localized to the cerebral cortex.
- Type of dementia depends on the location of brain lesion that causes loss of specific memories
Disease Progression: other types of dementia
Imaging: Memory is ‘stored’ in the cerebral cortex: PET Scan
PET imaging of different dementias

NORMAL AGING

ALZHEIMER’S

PICK’S
Epidemiology of Dementia

- Estimated 25 million people with dementia in developed world
- 70% of these are AD
- Regionally, in population > 60 yr:
  North America has the highest prevalence (11%, and 34% in people >85), followed by western Europe then E. Europe, Africa (1.6%; 3.5/1000)
- Dementia has a complex set of etiologies
Dementia and Alzheimer Disease: Epidemiology USA

- It is a disease of the elderly, and currently about 4 million people in the US are afflicted with AD, 5.5 mil dementia
- Two third of all dementias in the developed world is caused by AD
- The economic burden of dementia in the US alone is estimated to be over 50 billion dollars annually.
Alzheimer Disease

- A chronic deterioration of intellectual and ‘cognitive function’ characterized by loss of ability to **form new memories** and a gradual loss of ‘insignificant’ memories.

A Alzheimer and Auguste Deter
AD: Clinical Presentation

• A chronic deterioration of sequential set of intellectual and ‘cognitive functions’
• Loss of recent memory
• Loss of insight into the disease
• Loss of visual-spatial orientation
• Loss of executive function
• Loss of social graces, oppositional behavior
Disease progression (AD): What is lost?
What Memories are lost? = tree rings
Quantity of memory loss

- Normal
- MCI
- AD

Functional Decline
Gross brain: Early and late dementia
It is all about volume=cell loss
Also, decreased function and activity
Risk factors for Alzheimer’s diseases

Genetic Factors
- Early onset/Familial AD
  - Chromosome 21, abnormal amyloid precursor protein (APP)
  - Chromosome 14, abnormal Presinilin 1
  - Chromosome 1, abnormal Presinilin 2
- Genetic Risk Factor/Sporadic late onset AD
  - Chromosome 19, Apolipoprotein E (APOE)
  - APOE ε2, ε3, ε4

Environmental Factors

Activation of the apoptotic pathway

Cell Death
Genetic Factors:

• Early onset/Familial AD
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Other risk factors for dementia
Alzheimer Disease

Genetic Factors

Other Risk Factors

Activation of the apoptotic pathway

Cell Death
Risk Factors for dementia

- Age
- Family history
- Depression
- Diabetes
- Midlife high BP
- Midlife high cholesterol
- Head injury
- Sleep Deprivation

- Apo e4
- Down’s syndrome
- Family Hx of Down’s
- Level of Education?
- Homocysteine
- Macroglobulin
- CYP46

From Brodaty, 2003
Dementias are often mixed: Continuum of Alzheimer and vascular dementia

**Mixed**
- AD/CVD
  - Amyloid plaques
  - Genetic factors
  - Neurofibrillary tangles
  - Stroke/TIA
  - Hypertension
  - Diabetes
  - Hypercholesterolemia
  - Heart disease

**Vasc. Dementia**
- Stroke/TIA
- Hypertension
- Diabetes
- Hypercholesterolemia
- Heart disease
- Smoking

AD

Genetic factors:
- Amyloid plaques
- Neurofibrillary tangles

Pathophysiology of Alzheimer’s Disease (AD)

• The exact sequence of how cells die is not known.
• The main pathological feature of AD comprises amyloid plaques, neurofibrillary tangles and loss of neurons by Apoptosis
• Lewy bodies can be another pathological feature.
Amyloid plaque and Neurofibrillar tangles
Maturation of Amyloid Plaque

A

B

C

D
How are the plaques deposited in the brain?

• Amyloid plaques are made of deposits of Aβ proteins (39 – 42 aa)

• Aβ is a product of the metabolism of amyloid precursor protein (APP)

• APP is a normal protein and can behave as a growth factor or a cell adhesion molecule.
Sequence of proteolysis of APP

- Three enzymes: *Alpha, Beta and Gamma Secretases*
- Alpha or Beta secretase enzymes cleave APP first
- Gamma comes in later
- Presinilins 1 and 2 are parts of gamma secretase
Cleavage sites and action sequence of various enzymes
Folding of AB fibril = plaque
Neurofibrillary tangles

- Neurofibrillary tangles comprise aggregates of highly phosphorylated form of a normal neuronal protein, Tau.
Neurofibrillary Tangles
Pathophysiology of AD

a Normal brain
- Excitatory neuron
- Inhibitory neuron
- Synapse
- Astrocyte
- Microglia

b Predromal AD
- Circuit disruption
- Amyloid fibril
- Mild synapse loss

b Late-stage AD
- Hyperexcitability
- Paired helical filament
- Amyloid plaque
- Inflammation
- Deficits in autophagy
- Loss of inhibitory tone
- Synapse loss
The prion idea
Flouro-Deoxy-glucose

(a) 

$^{18}$F-FDG 

Low uptake  
High uptake 

Normal aging  
Late-onset AD
Vizamyl PET images of healthy brain and an Alzheimer’s brain
Non-Pharmacological Treatments

- Physical activity
- Cognitive activity
- Taking statins
- HRT
- NSAIDS
- Wine?
- Seafood?
- Caffeine
- Vitamin E, Vitamin D
- Vitamin C
- B12, folate
- Ginkgo
- Leisure activity

From Brodaty, 2003
Pharmacological Treatment of Alzheimer’s Disease (AD):

• Loss of cholinergic neurons is believed to account for some of the learning and memory deficits.

• Therefore, drugs that boost cholinergic transmission are used as treatment for memory problems.
Cholinergic Systems
Pharmacological treatment of Alzheimer Disease

- Galantamine
- Donezepil
- Tacarine
- Pyridostigmine
- Memantin
Acetylcholine Metabolism
Treatment of other symptoms

• Psychosis
• Sleep behavior, disturbance
• Daily behavioral issues
• Feeding
• Family counseling – avoiding nursing home, pharmacological treatments
Treatment of AD with monoclonal antibodies to different proteins
<table>
<thead>
<tr>
<th>Feature of AD</th>
<th>Progression</th>
<th>Treatment strategies</th>
</tr>
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</table>
| Amyloid-β plaques                 | ![Brain](image1.png) | • Immunization  
• Small-molecule-based therapy |
| Neurofibrillary tangles           | ![Brain](image2.png) | • Immunization  
• Small-molecule-based therapy |
| Inflammation                      | ![Brain](image3.png) | • Immunization  
• Small-molecule-based therapy |
| Network disruption                | ![Brain](image4.png) | • Small-molecule-based therapy  
• Deep-brain stimulation |
| Cognitive dysfunction             | ![Brain](image5.png) | • Cognitive training  
• Lifestyle changes |
Dementia Case 1

• A 68 year old woman with history of hypertension and high cholesterol brought in by the family to her physician’s office with complaints of forgetfulness.

• Patient ‘denies’ memory problems. When asked to give an example of memory problems, the family relates that she can not remember the name of her new born grand child, loses her keys often; she went to supermarket to purchase a turkey for thanksgiving, came back empty handed. However, she remembers scattered details of distant past with clarity and accuracy.
Case 1 (Cont.)

- On physical examination, the patient is awake, alert and oriented to self and place, but not to time. She is well groomed and well mannered. Physical and neurological examination was non-focal.

- On mental status exam, she was not oriented to time. Speech was sparse. She did not remember what she ate for breakfast. She watched her favorite ball game the night before, but did not know who played and what was the score.

- However, she distinctly remembered the color and details of her wedding dress (40+ yrs ago), and where she was when president Kennedy was shot in 1963 and she remembers events of 9/11.
Case 1. Question

• With regard to this patient:
  • A. She has Alzheimer disease
  • B. This condition can be treated by removing plaques from the brain
  • C. She has a ‘primary dementia’ that can be exacerbated by diabetes and HTN
  • D. She has vascular dementia
Discussion for Case 1

• What is the disease process?
• What other clinical findings may be associated with this disease?
• Where is the starting location of disease in the brain?
• What would be the imaging findings, if any?
• What are the histo-pathological features of this disease?
• What are the molecular and anatomical pathways that lead to this disease process?
• What are the treatment options?
Disease progression in AD

Temporal lobe (hearing, advanced visual processing)
Dementia Case 2

- A 63 year old man with history of hypertension brought in by the family to her physician’s office with odd behaviors. Patient ‘denies’ memory problems or any other issues.

- When asked to give an example of the problems, the family relates that ‘he is not himself’, ‘acting strange and inappropriate’, ‘speech is stuttering’. Recently, at a restaurant he started eating with his hand from other people’s plates and had an unnecessary argument with the waiting staff. He walks around the house with only his underwear. There is no complaints of severe memory deficits
Case 2 (Cont.)

• On physical examination, the patient is awake, alert and oriented to self, place and time. He is mildly disheveled and restless. Physical and neurological examination was non-focal.

• On mental status exam, he was oriented, speech was fluent. During the interview he interrupted the questioning, and often his answers to questions were not fully relevant.

• However, he had minimal problems remembering recent and remote events.

• A biopsy of frontal lobe was performed, neuropathology identifies only few tau deposits.
Questions for case 2.

• With regards to case #2
• A. Cell death and cortical atrophy starts in the frontal lobe area
• B. The patient has fronto-parietal dementia
• C. The pathological marker for this condition is intranuclear inclusion that stains for Ubiquitin.
• D. The clinical manifestations are related memory disorder
• E. Memory will be eventually affected
• All of the above
Disease progression in FTD and FPD cortical association areas?

Temporal lobe (hearing, advanced visual processing)