The Neurobiology of Alzheimer Disease

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Summary of Presentation

• Alzheimer disease (AD) is a dementing disorder, typically in the elderly.
• It is important to rule out other conditions for people experiencing problems with memory.
• The incidence of AD qualifies it as an oncoming epidemic.
• The brains of people with AD show characteristic features.
• These changes and new genetic evidence point to a number of possible disease mechanisms.
• Effective treatments for AD are sorely needed.
• Additional research is needed to discover them.
LEAR:

“I fear I am not in my perfect mind. Methinks I should know you, and know this man; Yet I am doubtful: for I am mainly ignorant What place this is; and all the skill I have Remembers not these garments; nor I know not Where I did lodge last night. Do not laugh at me …”

*Shakespeare: King Lear, 1606*
Alzheimer’s Disease: A challenge for humanity

Alzheimer’s disease robs patients of their intellect and personality. Because the risk of the disorder increases with age, and because people are living longer, many more individuals will be affected in the future. Research is directed at attempting to avoid what could be an epidemic of Alzheimer’s. Nevertheless, effective treatments continue to be elusive. For success, we must understand underlying mechanisms that cause this illness.
Questions

1. What is Alzheimer’s disease?
2. Why are so many concerned about it?
3. Why is it viewed as an ‘oncoming epidemic’?
4. What do we know about the pathogenesis of AD?
5. What new treatments can be envisioned?
Glossary

- **Neuron** – Information processing cell of the brain
- **Synapse** – Point of contact between two neurons
- **Neurodegeneration** – Disease in which dysfunction and death of neurons leads to neurological disability
- **Dementia** – Decline of memory and other cognitive function sufficient to interfere with usual activities.
NEURONAL CIRCUITS MEDIATE ALL BRAIN FUNCTIONS

INFORMATION

DENDRITE → SYNAPSE → AXON

CELL BODY ➔ NEURON 1 ➔ NEURON 2 ➔ NEURON 3 ➔ CHANGE IN FUNCTION

RECEIVE ➔ PROCESS ➔ SEND
ALL NEUROLOGICAL DISORDERS ARE DUE TO DISRUPTED CIRCUITS
Glossary

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Memory Complaints of Healthy Elderly

Percentage of Elderly

- Recalling names/words: 83%
- Recalling where you put things: 55%
- Knowing you have told someone something: 49%
- Forgetting a task after starting it: 41%
- Losing the thread of conversation: 40%

Bolla et al., Arch Neurol 1991
<table>
<thead>
<tr>
<th>Complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trouble with new memories</td>
</tr>
<tr>
<td>• Need to rely on memory helpers</td>
</tr>
<tr>
<td>• Difficulty finding words</td>
</tr>
<tr>
<td>• Struggling to complete familiar tasks</td>
</tr>
<tr>
<td>• Confusion about time, place or people</td>
</tr>
<tr>
<td>• Misplacing familiar objects</td>
</tr>
<tr>
<td>• Onset of new depression or irritability</td>
</tr>
<tr>
<td>• Making bad decisions</td>
</tr>
<tr>
<td>• Personality changes</td>
</tr>
<tr>
<td>• Loss of interest in important responsibilities</td>
</tr>
<tr>
<td>• Seeing or hearing things</td>
</tr>
<tr>
<td>• Expressing false beliefs</td>
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</tbody>
</table>
What is Mild Cognitive Impairment (MCI)?

- Subjective memory complaint
- Objective memory impairment for age and education
- Largely intact general cognitive function

Petersen et al., 1999
What causes MCI?

- Depression
  - Memory function may improve with treatment of depression

- Medical Illness (e.g. Hypothyroidism)
  - Memory function may improve if corrected

- Traumatic injury (e.g. Head injury)
  - Memory function often stabilizes after a period of recovery

- Vascular disease (e.g. Stroke)
  - Memory function may stabilize or progress

- Degenerative processes (e.g. Alzheimer’s disease)
  - Memory function declines over time
MCI Increases Risk for Dementia

Years of Follow Up

Proportion Dementia Free

Normal Controls

1-2% per year

MCI Subjects

10-15% per year
Questions

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Prevalence of Dementia
Memory Impairment PLUS Other Cognitive Deficit

Dementia (Jorm et al., 1987)

Alzheimer (Bachmann et al., 1992)
Alzheimer Dementia

- Alzheimer dementia (AD) affects about 5 million Americans\(^1\)

- Most are 65 years of age and older, with prevalence reaching nearly 50% at age 85 and older\(^1\)

- AD patients typically live about 7 to 10 years after diagnosis\(^2-4\)

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Dramatic increase in aged populations
AD: An Oncoming Epidemic: The World

Current and projected numbers for people with Alzheimer's or another dementia worldwide (in millions):

- Today: 35.6
- 2030: 65.7
- 2050: 115.4

Alzheimer Disease

- A dementing disorder of insidious onset – there is impairment in short- and long-term memory.
- There is also impairment of abstract thinking, judgment or other cognitive tasks.
- There may be a change in personality.
- There is no disturbance of consciousness.
- The disorder has its onset between the ages of 40 and 90, most often after 65.
Typical Clinical Course (7 to 10 years)

Early Stage:

• Symptoms begin insidiously and are progressive
• Increasing forgetfulness, decreased spontaneity
• Insight may be impaired
Middle Stage:

- Memory is worse – frequent repetition of questions, items are misplaced
- Language skills decreased (e.g. poor word-finding)
- Difficulty in performing complex tasks, difficulty in handling appliances
- Poor calculation, difficulty with finances
- Getting lost, wandering
- Passivity vs. restlessness
- Apathy vs. aggression
Advanced Stage:

- Only fragments of memory remain
- Verbal output is poor or nil
- Loss of ability to care for themselves
Very Advanced Stage:

- Bedridden
- Mute
- Unresponsive
- Weight Loss
- Terminal illness is with pneumonia, other infection, sepsis, or pulmonary embolism
Self-portraits by artist William Utermohlen chronicle his experience with Alzheimer's disease.

The first (top left) was painted just prior to diagnosis.
Diagnosis of AD

The criteria for the clinical diagnosis of “probable Alzheimer disease” include:

- Dementia established by clinical examination and confirmed by neuropsychological tests
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65
- Absence of systematic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition.
AD Treatments in 2011

- Cholinesterase inhibitors
- Weak antagonists of NMDA receptors
- Trials of vaccines against Aβ, results pending
- Several recent failed trials
Diagnosis and Care Comes Too Late?

Too Little Insight into Cause?
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Pathology of Alzheimer’s Disease

Gross Exam:
- Brain Atrophy

Microscopic Exam:
- Plaques
- Tangles
- Loss of Synapses
- Loss of Neurons
  - Cortex
  - Hippocampus
  - Basal Forebrain Cholinergic
Brain Atrophy is Marked
Volumetric MRI Report
Pathology of Alzheimer’s Disease

Gross Exam:

Brain Atrophy

Microscopic Exam:

Plaques
Tangles
Loss of Synapses
Loss of Neurons
  - Cortex
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Neuritic plaque
PET Imaging to Detect Amyloid

Amyloid imaging detects fibrillar deposits of Aβ in plaques. These arise years before people develop memory loss. About 30% of people aged 70 have positive scans.
Biomarkers to Aid in Diagnosis and Treatment

**Structure:**
- MRI
  - whole brain atrophy
  - regional atrophy
  - connectivity - DTI

**Function:**
- fMRI
  - ↓ activation/ default network
- PET, SPECT
  - ↓ glucose use

**Biochemistry:**
- CSF
  - Aβ42 ↓
  - tau, P-tau ↑
- MRI spectroscopy
- PET
  - amyloid deposition
- Plasma
  - Aβ

Brain atrophy and neuron loss

Amyloid and plaques

Neurofibrillar tangles
FDG PET Scans are Abnormal in AD

Normal

Mild cognitive impairment

Alzheimer’s disease
Pathology of Alzheimer’s Disease

Gross Exam:

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Microscopic Exam:

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AD Pathogenesis

• Features a relatively uniform set of pathological changes - **Endosomal Pathology**
• Is largely sporadic
• But a significant number of cases are present in families or in another clearly genetic context
• The latter include EOFAD, Down syndrome, and cases of gene duplication – all of which implicate the APP protein, its trafficking and processing
Endosomes: A Source of Signals

Rab 5 - controls endocytosis and fusion
Signaling Endosomes Carry Trophic Signals
Endosomal Enlargement is Present in AD and DS

Every person with DS shows the brain pathology of AD by age 40 and most are demented by age 60. Linked to one extra copy of the APP gene.
Endosomal Pathology in AD and DS

• Proteins that regulate endosomes are increased in MCI/AD/DS.
• Increased Rab5 correlates with cognitive decline.
• Increase in Rab5 positive endosomes and increased endocytosis are early changes.
• How to link EE pathology and NTF signaling -
  – Motility: size or abnormal transport proteins?
  – Signaling: changes in amount or quantity?
AD Pathogenesis - Genetic Factors

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• Is largely sporadic
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Genetics of AD

Amyloid Precursor Protein – via mutation or triplication
  - Presenilin 1 - mutation
  - Presenilin 2 - mutation

More than 200 mutations in these genes - EOFAD

Down Syndrome – via increased APP gene dose
APP and its Aβ Product
APP Processing: Important Steps Occur In Neuronal Endosomes
Genetics of AD

Amyloid Precursor Protein – via mutation or triplication
Presenilin 1 - mutation
Presenilin 2 - mutation
Down Syndrome – via increased APP gene dose

More than 200 mutations in these genes - EOFAD

ApoE 4 - dose-related increased risk of AD.

Other genes: GAB2, ATXN1, CD33, GWA 14q31, PCDH11X, CLU (APOJ), CR1, PICALM, BIN1, EXOC3L2, MTHFD1L, SORLA, and others.
Alzheimer Pathogenesis

**Suggested Molecular Mechanisms**

1) Toxic peptide or protein
2) Protein misfolding/aggregation
3) Abnl protein-protein interaction
4) Loss of critical synaptic function
5) Glutamate toxicity
6) Deranged intracellular Ca regulation
7) Excessive ROS/ free radicals
8) Mitochondrial dysfunction
9) Inflammation
10) Trophic Deprivation
Alzheimer Pathogenesis: The Players

- APP Mutation/Dose
- PS Mutation
- APOE4
- Aβ42/ Aβ40
- Aβ Oligomers
- Plaques/Tangles
- Neurodegeneration
- Endosomes
- Aging
Are we just treating too late? Or do we need to think differently?
How is Aβ42 Toxic?

• Aβ42 is the whole story. It exerts toxicity by interacting with one or more ‘receptors’/acceptors to compromise neuronal function:

• **AND/OR**

• Aβ 42 increases are due to failure of other cell functions. One possibility is that it points to decreased processing through γ-secretase activity and that toxicity results from the inability of this enzyme to process its many substrates.
Increased APP Gene Dose (DS)

Increased Endosome Size

Defective Axonal Trafficking

Neuronal Dysfunction

Neuronal Death

FAD/Typical AD

Aβ 42

Aβ 42
Alzheimer Pathogenesis

Suggested Molecular Mechanisms

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9) Inflammation
10) Trophic Deprivation
Signaling Endosomes Carry Trophic Signals
Scaling endosome to the size of an automobile:
- travel through a tube 60 feet in diameter
- at ~ 250 mph
- on an undulating roadway
- confronting a multitude of obstacles
- some of which are moving at 250 mph in the opposite direction
- and using as a source of fuel organelles that are also moving

Sources of Vulnerability:
- Structural Features
- Molecular Complexity
- Functional/Metabolic Demands
Neuronal Circuits Fail in AD and DS

Decreased Trophic Support Leads to Dysfunction and Death of Neurons
Signaling Endosomes Carry Trophic Signals
Sustaining Circuits: A Moving Experience

Quantum Dot Labeled NGF

Biotin-NGF + Streptavidin-Qdot = Qdot-NGF
Separating Axons from Cell Bodies

A Top view

Side view

B Cell bodies

Distal Axons

PDMS

100 μm

2 μm

Microchannels

Coverslip (24mm x 40mm)

C Cell bodies/Dendrites

Distal Axons

100 μm

D

Chowdary, Che, Cui. Ann Rev Phys Chem, 20
Watching Traffic in Real-Time
A typical run (~10µm) comprises more than 1000 dynein steps. The average distance between varicosities is 10µm.
Might Failure to Traffic Trophic Signals Contribute to Neurodegeneration?
Failed Endosomal Trafficking of NGF in AD/DS

• Decreased levels of NGF in neuron cell bodies and increased NGF levels in targets of axons.
• No evidence for changes in NGF mRNA.
• Defective retrograde transport of NGF in mouse models of DS and AD.
• Defects linked to degeneration of neurons.
• Degeneration linked to increased APP gene dose.
Defining the Genetic Basis for Cognitive Deficits in Mouse Models of Down Syndrome
A Mouse Model of Down Syndrome

These Mice Carry an Extra Copy of Many of the Genes Linked to Down Syndrome Phenotypes

- Gabpa
- APP
- Grik1
- Sod1
- Gart
- Sim2
- Dryk1a
- Ets2
- Mx1

Ts65Dn
Enlarged EE in BFCN terminals of Ts65Dn
Deleting One Copy of App in Ts65Dn Mice Markedly Enhances $^{125}$I-NGF Transport and Prevents BFCN Atrophy

Salehi et al., 2006
APP Gene Dose is Also Linked to Degeneration of LC Neurons
EEA1 Immunostaining of Cultured Hippocampal Neurons from Ts65Dn and 2N mice

DIV7 for 2N and Ts65Dn, 100x
Size distribution of EEA-1 early endosomes in Ts65Dn hippocampal neurons

n = 6 for each 2N and Ts65Dn
Qdot-BDNF Transport in Hippocampal Neurons – Treated with Aβ (1 µM) for 2 hours
QD-BDNF Untreated Control Hippocampal Axon KYMOGRAPHS

Average Speed is ~1.6 \( \mu \text{m/sec} \)

M Maloney, 2009
QD-BDNF 1μM sAβ 2h treated Hippocampal Axon - Kymographs

Average Speed is \(\sim 0.44 \mu m/sec\)

1 min

20 μm

\(\Delta = \) Pause

\(\Rightarrow = \) Reverse

displacement
Increased APP Gene Dose (DS)

- Increased Endosome Size
- Defective Trafficking
- Neuronal Dysfunction
- Neuronal Death

FAD/Typical AD

Aβ42

Increased Rab5 Activity

Aβ42
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APP and its Aβ Product
APP Processing: Important Steps Occur In Neuronal Endosomes
Increased APP Gene Dose (DS) → Increased APP/CTFs → Increased Rab5 Activity → Increased Endosome Size → Defective Trafficking → Neuronal Dysfunction → Neuronal Death

FAD/Typical AD

Aβ 42

Aβ 42
Increased APP Gene Dose (DS)  

Increased APP/CTFs  

Increased Rab5 Activity  
Increased Endosome Size  
Defective Trafficking  
Neuronal Dysfuction  
Neuronal Death  

FAD/Typical AD  

Aβ42  

Decreased γ-secretase activity could explain the increase in CTFs and Aβ42?
Targets to Treat or Prevent AD

• Selectively reduce the effect of increased expression of the gene for APP
  – Through changing processing of APP—e.g. GSMs—
    • New class just discovered at UCSD
  – Through an antibody to reduce Aβ levels—
    • Recent success working with AC Immune
  – Through restoring levels of NE and other neurotransmitters—
    • A trial being planned with Chelsea
Newly Discovered Modulators of $\gamma$-secretase Impact A\(\beta\) Peptide Production

GSMs also appear to enhance activity of $\gamma$-secretase on $\beta$-CTFs
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The Investigators

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Mike

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