Alzheimer's Disease

A mind in darkness awaiting the drink of a gentle color.

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
Alois Alzheimer

- Case of Auguste D., 50 year old woman in Germany - 1906
- Her disruptive behavior prompted her husband to see Dr. Alzheimer.

insight: dementia is physical

- Alzheimer examined Auguste D.’s brain.
- Discovered plaques and tangles.
- At the time it was thought that dementia was normal aging.
DEGENERATION GENERATION

The prevalence of Alzheimer’s disease is expected to rise sharply in the United States as its population ages.

People with Alzheimer’s disease (millions)

- Upper estimate
- Lower estimate

EARLY ONSET:

Memories begin failing in one’s 40s, occasionally as early as 32.

By 47, on average, full-blown Alzheimer’s develops.

New York Times, The Vanishing Mind 2010
A Clouded Inheritance

A group of 25 families in Colombia has inherited a genetic mutation from common ancestors, making members prone to early-onset Alzheimer's.

At right, Alzheimer's cases among the founding members of the clan and some of their early descendants, who number in the thousands today.

KEY

- No Alzheimer's
- Suspected cases
- Known cases

PAISA MUTATION
The inherited disease is caused by a mutation of the presenilin 1 gene on chromosome 14.

Note: the chart has been simplified and does not show all children or descendants.

TODAY
Carlos Alberto Villegas, his wife and their siblings descend from a common ancestor, circled above, who had the Paisa mutation.

Source: University of Antioquia

New York Times, The Vanishing Mind 2010
The Vanishing Mind

In the mountains of northwest Colombia, many members of a sprawling extended family suffer from a genetic mutation that makes them begin to forget in their early 40s. | Related Article
Early onset familial Alzheimer disease (eFAD)

- Dominant genetic trait
- One parent had eFAD
- Siblings: 50%

- eFAD and late-onset AD is essentially the same disease (mostly)
Early-Onset Alzheimer Disease in Families With Late-Onset Alzheimer Disease

A Potential Important Subtype of Familial Alzheimer Disease

Kiri L. Brickell, MBChB; Ellen J. Steinbart, RN, MA; Malia Rumbaugh, MS, CGC; Haydek Payami, PhD; Gerard D. Schellenberg, PhD; Viviana Van Deerlin, MD, PhD; Wuxing Yuan, MS; Thomas D. Bird, MD
## Autosomal Dominant Forms (eFAD)

<table>
<thead>
<tr>
<th>Protein/Precursor</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Precursor Protein (APP)</td>
<td>21</td>
</tr>
<tr>
<td>Presenilin-1 (PS1)</td>
<td>14</td>
</tr>
<tr>
<td>Presenilin-2 (PS2)</td>
<td>1</td>
</tr>
</tbody>
</table>

Accounts for most eFAD
Members of 25 extended families, with 5,000 members, develop early-onset Alzheimer’s, usually before the age of 50, if they harbor an aberrant version of a particular gene.

PAISA MUTATION
The inherited disease is caused by a mutation of the presenilin 1 gene on chromosome 14.
12 to 15 fold increase risk for AD

<table>
<thead>
<tr>
<th>Not autosomal dominant (ApoE)</th>
<th>ApoE4 is thought to lower the age of onset by a decade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE4</td>
<td></td>
</tr>
</tbody>
</table>
• eFAD
• Test drugs before symptoms

• Many recent drug candidates have failed in trials.
• Perhaps because the drugs were given too late.

• When a person loses their memory – it is too late.
• The disease has been present for a long time by the time there are symptoms.

• Preventative or delay strategies.
Francisco Lopera
## Treatment plan eFAD

<table>
<thead>
<tr>
<th>Delay or stop Assessing treatment by tracking AD specific biomarkers.</th>
<th>Administered 7 years before average age of diagnosis</th>
<th>Alzheimer’s Prevention Initiative</th>
</tr>
</thead>
</table>

- **Amyloid accretion**
  - 5 – 20 years before diagnosis of Alzheimer’s dementia
  - Damages synapses

- **Tau buildup**
  - 1 – 5 years before diagnosis
  - Tau protein detaches from the microtubules.

- **Brain shrinkage**
  - 1 – 3 years before diagnosis
  - Cell death shrinks the brain.
Amyloid Accretion
5–20 years before
diagnosis of Alzheimer’s
dementia

neuron

Amyloid-beta plaques

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
Amyloid-beta blocks neurotransmitters from reaching the post-synaptic receptors.
PET scans show increasing retention in the brain’s frontal lobes of the amyloid-beta tracer Pittsburg imaging compound-B (PIB) over the course of two years in a 74-year-old, even while the subject remained cognitively normal.
Disintegrating microtubule

Enzyme adding phosphate groups to tau

Toxic tangles formed by tau

Microtubules held together by tau proteins

Neuron

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
• Spinal tap
• Measures levels of tau protein
Healthy brain

Alzheimer’s brain

Hippocampus

Extreme shrinkage of hippocampus

Scientific American (June 2010)

Alzheimer’s: Forestalling the Darkness
Computer graphic of slices through a normal brain and an Alzheimer’s brain, derived from volumetric magnetic resonance imaging, shows considerable shrinkage (right) from degeneration and death of nerve cells.
Does changing amyloid beta levels really improve cognition?

One needs to apply a cognitive test along with a biomarker measure in order to make sure that the treatments are helping.
Inhibitors of enzymes that produce amyloid-beta

Vaccines/Antibodies

Vaccines induce the body to produce antibodies that bind to amyloid and clear them from the brain.

Enzymes are involved in precursor steps
Amyloid-beta aggregation blockers

Agents that prevent amyloid fragments from clumping could prevent damage to neurons

Anti-tau compounds

Blocking production of the toxic form of the tau protein
Or
Impeding its aggregation into tangles
Targeting small Aβ oligomers: the solution to an Alzheimer’s disease conundrum?

William L. Klein, Grant A. Krafft and Caleb E. Finch

Amyloid β (Aβ) is a small self-aggregating peptide produced at low levels by normal brain metabolism. In Alzheimer’s disease (AD), self-aggregation of Aβ becomes rampant, manifested most strikingly as the amyloid fibrils of senile plaques. Because fibrils can kill neurons in culture, it has been argued that fibrils initiate the neurodegenerative cascades of AD. An emerging and different view, however, is that fibrils are not the only toxic form of Aβ, and perhaps not the neurotoxin that is most relevant to AD: small oligomers and protofibrils also have potent neurological activity. Immuno-neutralization of soluble Aβ-derived toxins might be the key to optimizing AD vaccines that are now on the horizon.

Klein, W. L. et al (2001), TINS, Vol.24 No.4
Atomic force microscopy of amyloid-β<sub>1-42</sub> forms.

Aβ-derived diffusible ligands

**Fig. 1.** Different assembled states of amyloid β<sub>1-42</sub> (Aβ<sub>1-42</sub>). The assembled forms obtained from incubation of synthetic Aβ<sub>1-42</sub> are highly sensitive to preparation and incubation. Widely differing proportions of insoluble fibrils, soluble protofibrils (PFs) and oligomers are revealed by atomic force microscopy. Typical PF and fibril preparations contain varying levels of small globular molecules, putatively Aβ<sub>1-42</sub> oligomers; Aβ-derived diffusible ligand (ADDL) preparations initiated from monomeric dimethyl sulfoxide stock solutions are fibril- and PF-free, and (uniquely) comprise oligomers. Scale bar, 200 nm. Fibril, PF and ADDL preparations all show neurotoxicity in vitro.

Courtesy of Brett Chromy and Blaine Stine.

Klein, W. L. et al (2001), TINS, Vol.24 No.4
(a) ADDLs are potent neurotoxins that slowly kill hippocampal neurons in mature brain slice preparations. With the live–dead dual fluorescence assay, **ADDLs selectively induce death in hippocampal CA1 neurons**, whereas a subpopulation of CA3 neurons and cerebellar neurons are resistant.

(b) **ADDLs block LTP** in hippocampal slice within 1 hr. In vivo stereotaxic injections give similar results. As seen here, ADDLs do not block pre-tetanic population spikes, nor do they inhibit EPSPs or LTD.
What Causes Alzheimer's?

- Scientists are still not certain.
- Age and family history have been identified as potential risk factors.
- Researchers are exploring the role of genetics.
- Diabetes?
- Sleep problems?
What’s insulin got to do with it?

It is not just in the pancreas!

- **insulin**: Hormone helps store sugar and fat for energy – produced in pancreas.

- **Type 1 diabetes**: When body cannot produce enough insulin

- **Type 2 diabetes**: When body has inadequate insulin response

- **Type 3 diabetes?**: Neurodegenerative diseases? Alzheimer’s, Parkinson’s & Huntington’s
Insulin receptors in the brain!

- Learning and memory
- Snort insulin → better recall
- Memory tasks → increases insulin levels

Suzanne de la Monte
@ Brown University

- Does insulin have a part in Alzheimer’s disease?
- Postmortem study – compare insulin receptors in AD and healthy control brains.

Healthy brains had more insulin...

- Healthy brains had on average 4x higher insulin levels and 10x as many insulin receptors in the learning and memory regions of the brain

Diabetics are...

- 2x more likely to develop AD
- 7x more likely to develop Huntington’s disease
- 50% of Parkinson’s patients have glucose metabolism dysfunction.
AD and T2D share:

- Demographic profiles
- Risk factors
- Clinical features
- Biochemical features
Type 2 Diabetes – metabolic disorder

- > 30 years of age
- 7% global population
- Characterized by a relative insulin deficiency
- Risk factors – high blood glucose, obesity, vascular disease, insulin resistance
- All of these factors, individually and collectively, increase the risk of AD and vascular dementia
Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI

T. den Heijer¹,², S. E. Vermeer¹,², E. J. van Dijk¹,², N. D. Prins¹,², P. J. Koudstaal¹,², A. Hofman¹, M. M. E. Breteler¹

¹Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands
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We observed that people with Type 2 diabetes had more hippocampal and amygdalar atrophy on MRI than people without diabetes. Moreover, in persons without diabetes mellitus, insulin resistance was associated to amygdalar atrophy on MRI. The presence of atherosclerosis or cerebrovascular disease did not explain the associations.

The strengths of our study are its population-based design and the large sample with volumetric MRI. The prevalence of diabetes mellitus in our study was comparable to another Dutch population study [27], leading to a moderate number of people with diabetes mellitus studied in the sample. However, the associa-

![Graph showing hippocampal and amygdalar volumes with standard error](image)
Functional relationship between AD and type-2 diabetes (T2D)

- Elevated levels of insulin
- Cross blood brain barrier
- Compete with amyloid-β for (IDE) insulin-degrading enzyme.

The insulin-degrading enzyme (IDE) has a major role in clearance of both insulin and amyloid-β peptide.