Genetic Risk and Prevention of Alzheimer’s Disease

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Outline

• Cognitive changes with normal aging
• Definition of dementia
• Basics of Alzheimer’s Disease
• Genetics of Alzheimer’s Disease
• The pre-clinical state of Alzheimer’s Disease
• Prevention of Alzheimer’s Disease
• The Generation 2 Study
Effects of age on physical performance

World record women’s 100m dash: 
10.49 sec

World record age 90-95: 
23.18 sec

World record women’s shot put: 
74.3 feet

World record age 90-95: 
16.1 feet

Olga Kotelko, 91-year-old track star
Cognitive changes with normal aging

<table>
<thead>
<tr>
<th>Decline</th>
<th>Maintain or improve</th>
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<td>Attention</td>
<td>Language</td>
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<td>Word-finding</td>
<td>Visuospatial function</td>
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<td>Short-term memory</td>
<td>Executive function</td>
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<td>Long-term memory</td>
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- Key is that activities of daily living remain unimpaired (patients can compensate)
- Tip of the tongue phenomena, misplacing keys are common
Definition of dementia

Memory impairment

Plus

(a) language disturbance
(b) difficulty with complex motor activities
(c) failure to recognize or identify objects

OR

(d) problem with planning, organizing, or problem solving

Significant impairments in social or occupational functioning, a significant decline from previous level of functioning
Dementia is a “syndrome”

- A broad category or description
- Like “headache” or “cancer”
- There is an underlying cause or type of “dementia”, just as there is for “cancer”
Frequency of Dementia Subtypes

- Alzheimer's Disease: 62%
- Vascular Dementia: 17%
- Mixed: Alzheimer's & Vascular Dementia: 10%
- Lewy Bodies: 4%
- Parkinson's Disease: 2%
- Fronto-temporal: 2%
- Other: 3%
Mild cognitive impairment (MCI)

• Memory complaint (by patient or other)
• Testing indicates deficits in one or more areas of cognition
• *Not impacting occupational or social functioning*
• MCI may represent “early dementia” and may progress with time
• Some patients with MCI remain MCI indefinitely or return to normal
The continuum of Alzheimer’s disease

Cognitive function

Asymptomatic

Early symptomatic

Preclinical

MCI

AD Dementia

Years

Generation 2 Study

Sperling et al Alzheimer & Dementia 2011
NIA-AA Preclinical Workgroup
Alzheimer’s Disease

• Pathology: cerebral atrophy, amyloid plaques, and neurofibrillary tangles
• Death of neurons (brain cells)
• Eventually, leads to death of the individual (6th leading cause of death in the U.S.)

FIGURE 1
Neuropathology of Alzheimer’s disease: A. β-amyloid (Aβ) deposits in the form of senile plaques (SP) in a section of the cerebral cortex. Deposits appear as brown patches and are widely distributed, especially in the cerebral cortex (β-amyloid immunohistochemistry). B. Neurofibrillary tangles (NFT) in the cerebral cortex appearing as inclusion bodies within neurons (tau immunohistochemistry).
FIGURE 1
ALZHEIMER’S DISEASE DOUBLES IN FREQUENCY EVERY 5 YEARS AFTER 60 YEARS OF AGE

Typical early signs of Alzheimer’s Disease

• Gradual in onset
• Short term memory – forgetting conversations, appointments, bills, medications, shopping lists
• Word-finding difficulty (names or things)
• Getting lost
Progressive signs of Alzheimer’s Disease

- Poor judgement e.g. being unaware of danger
- Difficulty with tasks: cooking, dressing, bathing, using the toilet
- Trouble recognizing familiar people
- Mood swings
- Loss of motivation
- Changes in sleep
- Hallucinations (an abnormal sensation)
- Delusions (a false belief)
- Trouble walking
- Trouble swallowing
Current treatments for Alzheimer’s disease

• There is currently no cure for Alzheimer’s disease

• 4 medications are FDA approved to treat symptoms

• Cholinesterase inhibitors for mild-moderate
  Donepezil (Aricept)
  Rivastigmine (Exelon) patch
  Galantamine (Razadyne)

• Memantine (Namenda) for moderate-severe
Risk factors for Alzheimer’s disease

• Age
• Genetics – having a first degree relative with Alzheimer’s disease raises risk by a factor of 3 (some of which is mediated by ApoE4 gene)
• Low education
• Head trauma
• Cardiovascular risk factors – high blood pressure, diabetes, high cholesterol, smoking
Autosomal-dominant (Familial) Alzheimer’s Disease is rare

- Less than 1% of people with AD have “familial AD”
- Autosomal dominant (you have a 50% chance of receiving the gene if your parent has it)
- Early-onset – dementia in 40s or 50s
- Mutation in APP, PS1, or PS2, which are all genes involved in production of amyloid-beta (plaques)
- Colombia kindred – seen on 60 Minutes
THE ALZHEIMER'S LABORATORY

An extended family in Colombia with a genetic mutation of Alzheimer’s may help scientists prevent the disease.

The following script is from “The Alzheimer’s Laboratory,” with Lesley Stahl as the correspondent. Shari Finkelstein, produce of the documentary, speaks with Nobel-prize-winning Colombian novelist Gabriel Garcia Marquez in the middle of the jungle whose residents suffer from an illness that erases their memories. Today, in a region of Colombia called Quebrada, scientists try to find out if Alzheimer’s disease may be preventable.

Resources

For more information, visit the Alzheimer’s Prevention Registry. People age 65 or older can sign up for it. It provides news about Alzheimer’s and other diseases that people may qualify to participate in. It’s led by the nonprofit Alzheimer’s Association.

View a list of ongoing Alzheimer’s studies, including the study in Antioquia.

Antioquia is home to the largest concentration in the world of people who carry a rare genetic mutation that makes them 100 percent certain to develop Alzheimer’s disease. And as devastating as Alzheimer’s is anywhere, this is a particularly cruel version—it strikes when people are in their mid-40s and leads to death about a decade later. It is a tragic situation, but a perfect scientific laboratory. And it’s now the home of a multimillion dollar, NIH-backed study trying to find out for the first time whether Alzheimer’s disease may be preventable.

These are the Andes Mountains and lush countryside of Antioquia, Colombia, whose capital city, Medellin was once famous for murder and the drug cartel of Pablo Escobar. Today Medellin — or “Medejerin” as it’s pronounced here — is peaceful. But for some families here, there’s still a battle going on, a battle against an insidious disease. This family, mother Cecilia, her seven children, and grandchildren, lost its patriarch, Alonso.
Alzheimer’s disease *risk factor* genes

• Several have been identified, however the most common is APOE
• APOE is a lipid transport protein, why it affects AD risk is not fully known
• 3 versions of APOE: E2,E3,E4
• 1 copy from each parent
• APOE is associated with risk of AD
Approximate Lifetime Risk (%) of Alzheimer's Disease Based on ApoE Genotype*

- $\varepsilon2/\varepsilon2$ or $\varepsilon2/\varepsilon3$: 10%
- $\varepsilon3/\varepsilon3$: 20%
- $\varepsilon2/\varepsilon4$: 30%
- $\varepsilon3/\varepsilon4$: 40%
- $\varepsilon4/\varepsilon4$: 60%
APOE and risk of Alzheimer’s disease

• You can have APOE e4/e4 or e3/e4 and never get Alzheimer’s disease
• You can get Alzheimer’s disease and not carry any copies of APOE e4
• Currently knowledge of APOE status does allow us to directly intervene
• General AD prevention measures apply whether you are an APOE e4 carrier or not
• I do not generally recommend this genetic test, except for research
Purpose of Clinical Research

• Healthy older people are monitored over time to understand changes in cognition with aging
• New Alzheimer’s disease tools, technology, and interventions are being developed to:
  – Detect
  – Diagnose
  – Slow
  – Treat
  – Prevent
Need for earlier intervention in Alzheimer’s disease

• Many Phase III clinical trials in AD dementia have failed over the past decade
• Intervention prior to dementia (widespread irreversible brain cell loss) may likely have better chance of changing the course of disease
• Think about what happens in cancer, atherosclerosis, osteoporosis… if we wait to treat until after symptoms appear?
Florbetapir PET

- PET scan that can detect beta-amyloid in the brain
- Approved April 12, 2012 by FDA
- Insurers and Medicare are not yet covering
PET Amyloid Imaging

Harvard Aging Brain Study

Sperling, Johnson NeuroMolecular Med 2010
The continuum of Alzheimer’s disease

Cognitive function

Asymptomatic
Early symptomatic
Preclinical
MCI
AD Dementia

Years

Generation 2 Study

Sperling et al Alzheimer & Dementia 2011
NIA-AA Preclinical Workgroup
About the Generation Program

✓ Made up of two clinical trials: Generation Study 1 and Generation Study 2 in cognitively normal people aged 60–75 years

✓ Looking for participants with a specific form of a gene that can increase the risk of developing Alzheimer’s

✓ Each study will compare results of the investigational treatment versus placebo

✓ Each trial will last for 5-8 years

✓ The investigational treatment may be able to prevent the onset of Alzheimer’s
Enrolling Volunteers Now

Step 1

Eligibility

✓ People with normal memory and thinking ability
✓ In general good health
✓ Age 60-75
✓ Willing to learn or already know their APOE genetic test results
How it all works

Step 2

Genetic testing

✓ Identify those who have an increased risk of Alzheimer’s through a quick cheek swab
✓ You may be invited to learn your genetic test results
✓ You can refuse to receive your results if you no longer want to participate in the study
✓ Before learning your results, you’ll be able to speak to a genetic counselor
✓ Only people with the genetic results we are looking for can take part in the Generation Program
What will happen if I participate?

✔ The trial will run between 5 and 8 years
✔ You will receive an investigational treatment or a placebo
  • Placebo is an inactive form of the drug, which is vital to ensure the reliability of the results

✔ Need to visit the study site at regular intervals
  • Take tests to measure efficacy and safety of investigational treatment
  • Reasonable travel costs will be reimbursed

✔ Participation is voluntary - you can withdraw from the program at any time
Consider Signing Up

- Normal memory and thinking ability
- General good health
- Age 60-75
- Willing to learn or already know their APOE genetic test results

OHSU
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The people behind the program

The Generation Program is a collaboration between a group of leading research organizations.

A global healthcare company that provides solutions to address the evolving needs of patients worldwide.

One of the world’s leading companies, Amgen is a values-based company, deeply rooted in science and innovation to transform new ideas and discoveries into medicines for patients with serious illnesses.

A world leading non-profit organization in Alzheimer’s research and care, dedicated to preventing the disease as soon as possible.
The Generation 2 Study

• A pioneering, multi-center study of Alzheimer’s disease prevention
• To test an anti-amyloid compound in healthy adults with increased genetic risk of Alzheimer’s disease (APOE e4 carriers)
• Who also may have “elevated amyloid” on brain PET scans
The Generation 2 Study

• Randomized, double-blind, placebo-controlled study
• In 2000 healthy older adults, between age 60-75 years
• Who are willing to learn or already know their APOE genetic test results
• Who have one copy of APOE e4 and elevated amyloid by PET scan or lumbar puncture or who have two copies of APOE e4
• To test whether daily pills of CNP-520
• Over 5-8 years
• Will slow progression of cognitive decline
Participants in the Generation 2 study

- Are 60 to 75 years old
- Have normal thinking and memory abilities
- Have an study partner – someone who has regular contact with you who can answer questions about your thinking and memory abilities and daily live
- Are willing and able to receive oral pills of the investigational treatment or placebo for 5-8 years
- Are willing to have your health monitored throughout the study using assessments such as:
  - Memory and thinking tests
  - ECGs (a look at your heart)
  - PET scan (a way to look for the plaques associated with AD) or lumbar puncture
  - MRI scans (a way to take a picture of your brain)
  - Blood and urine tests
You are *not eligible* to join if you...

- Receive treatment for Alzheimer's disease or are taking AD-related medications
- Are diagnosed with a current serious or unstable illness
- Had cancer within the last 5 years
  - with exceptions of localized nonmalignant tumors, localized basal or squamous cell carcinoma of the skin, or in-situ cervical cancer
Florbetapir PET scan

• Participants must be willing to perform all study procedures
• For participants with only 1 copy of e4, they will undergo florbetapir PET scan and receive the result
• An “elevated amyloid” result does not mean a person has Alzheimer’s disease
• But persons with an “elevated amyloid” may have a higher risk of developing memory problems and Alzheimer’s disease dementia
• For an individual, we cannot quantify that immediate risk
Lumbar Puncture

- Lumbar punctures gather cerebral spinal fluid, which also can measure amyloid
- Lumbar puncture is optional
The study drug: CNP520

BACE Inhibitor (CNP520) reduces cutting of APP to prevent build-up of beta-amyloid
Finances and Confidentiality

• There is no charge to participate in the Generation 2 study
• Participants are compensated for time and travel expenses for visits: $25 - $50 per visit
• Medical information is kept confidential
• Risk of data breach – genetic result or “elevated amyloid” PET scan result may impact a person’s ability to buy life insurance, disability insurance, long-term care insurance (not medical insurance any longer)
Why Participate?

• Help others, including future family generations
  – Meaningful activity and opportunity to give back!
• Receive regular monitoring by professionals
• Gain access to cutting edge technology
  – Genetic testing
  – PET scans
  – Biomarker analyses
• Obtain current and accurate information about Alzheimer’s disease
• *All at NO COST!*
What are the risks?

- Radiation exposure from PET scans – 5 times more than yearly natural exposure. Radiation is associated with a small future risk of cancer.
- Risk of depression/anxiety/worry upon learning results of genetic testing or PET scan
- Risk from CNP-520 – tested on over 300 participants
  - Skin reactions in 18%, mainly itching; theoretical risk of lightening of hair and skin.
  - Allergic reaction
- Studies with other BACE inhibitors (drug class of CNP-50) have shown variable results – some studies have shown small declines in cognition
- Risk of data breach
OHSU Layton
Aging and Alzheimer’s Disease Center

- Federally funded ADRC
- Multidisciplinary team
- Clinical research
- Basic science
- Collaborations nationally and internationally

(503)-494-7647  adresearch@ohsu.edu  www.ohsu.edu
Other Clinical Research

- **T2 Protect**: A Phase 2 Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of BHV-4157 in Patients with Mild to Moderate Alzheimer’s Disease *(Advarra - IAA)*
  
  **OPEN TO ENROLLMENT**

- **ADNI 3**: Alzheimer’s Disease Neuroimaging Initiative 3 *(NIA, NIH)*
  
  **OPEN TO ENROLLMENT**

- **EVALUATE-AD**: Remote data sensing to construct digital biomarkers associated with disease progression in MCI and AD *(NIH, NIA & Merk)*
  
  **OPEN TO ENROLLMENT**
Advice to prevent dementia and maintain cognition

• Try to get three types of exercise daily

  Physical:
  - 30 minutes, 5 days per week

  Mental:
  - reading, puzzles, activities, computer

  Social:
  - friends, family, support groups
Advice to prevent dementia and maintain cognition

- Control diabetes, high blood pressure, high cholesterol
- Avoid smoking
- Eat a well-balanced diet, high in vitamins and antioxidants (fruits and vegetables)
- Check medication list
Thank you!

Any questions?

Email: adresearch@ohsu.edu
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www.ohsu.edu/alzheimers