Neurological Diseases: 
Alzheimer’s Disease & Dementia

07.18.2020

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Recap of last week

Join at [www.kahoot.it](http://www.kahoot.it) (phone, tablet, or computer are OK)

With Game PIN 8993465

We will start the game when everyone has joined
Recap answers

86 BILLION neurons, over 100 trillion synapses

Electrical signals flow one direction. This is called an action potential
Outline for today

What is Alzheimer’s Disease?

- Stages, symptoms, and risk factors
- Changes in the brain

Biology of AD

- Amyloid beta and tau hypothesis
- Laboratory models of AD
- Clinical trials

New possible treatment from MIT
Alzheimer’s disease (AD)

Most common cause of dementia

Associated with age

Life expectancy after diagnosis: 3-9 years
Age is the biggest AD risk factor
Early stages of AD

- General forgetfulness
- Impaired short-term memory
- Confusion in unfamiliar places or situations

I forget things almost instantly. It runs in my family.

To find out more information on Alzheimer's, visit: alz.org
Middle stages of AD

- Substantial memory impairments
- Difficulty performing everyday tasks
- Problems with speech, coordination, and attention
- Personality changes
Late stages of AD

- Complete dependence on caregivers
- Near total loss of speech
- Loss of mobility and muscle mass
Anatomy of AD progression

Mild Cognitive Impairment
- Duration: 7 years
- Disease begins in Medial Temporal Lobe
- Symptoms: Short-term memory loss

Mild Alzheimer's
- Duration: 2 years
- Disease spreads to Lateral Temporal & Parietal Lobes
- Symptoms include: Reading problems
- Poor object recognition
- Poor direction sense

Moderate Alzheimer's
- Duration: 2 years
- Disease spreads to Frontal Lobe
- Symptoms include: Poor judgment
- Implausivity
- Short attention

Severe Alzheimer's
- Duration: 3 years
- Disease spreads to Occipital Lobe
- Symptoms include: Visual problems
How is AD diagnosed?

There is no conclusive test for AD. It can only be conclusively diagnosed after death.

Potential methods to diagnose AD are being developed and tested:

- MRI and PET imaging
  - Structure
  - Brain activity
  - Metabolism
  - Amyloid/tau presence

- Cerebrospinal fluid (CSF) sampling
The biology of AD
Large-scale changes in AD
Neurodegeneration

The progressive loss of structure or function of neurons

- Reduced cell number (**cell death**)
- Reduced brain volume (**atrophy**)

Region-specific degeneration can cause specific cognitive deficits.
Molecular signature of AD

Plaques

Amyloid beta

Neurofibrillary Tangles

Tau
Role of amyloid in AD

Extracellular amyloid beta deposits contribute to neuronal damage in AD.
Why do we have amyloid?

Amyloid beta could have a protective anti-microbial function:

- Binds to cell wall of microbes
- Blocks microbes from sticking to healthy host cells
- Traps bacteria within a resistant matrix
Role of tau in AD

Healthy tau:
- Normally found in axons
- Stabilizes cytoskeleton

Neurofibrillary tangles:
- Tau separates from cytoskeleton
- Tau aggregates within NFTs
- Cytoskeleton becomes unstable
Spread of amyloid, tau, and neurodegeneration

Stage A

Stage B

Stage C

Stage I and II

Stage III and IV

Stage V and VI

Amyloid plaque

Neurofibrillary tangle

Severity
Spread of amyloid, tau, and neurodegeneration

Biomarkers
- Amyloid-β
- Tau-mediated neural injury

Clinical symptoms
- Cognitive impairment
- Social dependence
- Quality of life
- Motor abnormalities
Genetic risk factors for AD

Related to amyloid

- PSEN 1
- PSEN 2
- APP
- APOE4 (2 copies)
- TREM 2
- APOE4 (1 copy)
- MS4a CR1
- PICALM BIN1 CLU
- CD2AP CD33 EPHA1
- ABCA 7

Risk for Alzheimer's disease:
- High risk
- Medium risk
- Low risk

How many people have the gene?

Very Rare to Very Common
AD is mostly NOT inherited

Familial AD (fAD)
- Inherited (genetic) cause

Sporadic AD (sAD)
- No family link
- Likely caused by genetics and lifestyle

Early onset
(<10% of cases)
- Before age 65
- Genetic causes
- More likely to be fAD

Late onset
(>90% of cases)
- After age 65
- More likely to be sAD
Breakdown of AD cases

Autosomal dominant
- Early Onset Age <65
  - Familial 54%
  - Sporadic 40%

- Late-Onset Age >65
  - Familial 27%
  - Sporadic 70%

Early onset 13%
Late onset 87%
Modeling AD in the lab

Knowledge of amyloid and tau has allowed scientists to create models of AD to study potential mechanisms and treatments for AD.
Treatments for AD

Exercise, memory training, and social engagement can lower risk and improve quality of life.

Two classes of approved drugs:
- Acetylcholinesterase (AChE) inhibitors
- NMDA receptor (NMDAR) antagonists

These treat disease symptoms, but don’t slow/stop AD.

Memantine: \[\text{NH}_2\]

Donepezil:
Clinical trials in the US

A typical drug costs $1B to get approved. An AD drug costs $5.7B.
Many try, but few succeed

Nature Reviews | Drug Discovery
Potential new treatments
Questions?