Alzheimer’s disease and Down syndrome
What is Alzheimer’s Disease?

- An **irreversible** and **progressive** neurodegenerative disorder characterized by gradual loss of memory and other cognitive functions, deficits in activities of daily living, behavior, personality and judgment. Accounts for the majority of dementia cases among people age 65 and older.

William Utermohlen 1967

1 year later of diagnosis of Alzheimer’s Disease

5 years later
Alzheimer’s Disease Symptoms

- Gradual memory loss
- Decline in the ability to perform routine tasks
- Disorientation
- Difficulty in learning
- Loss of language skills
- Impairment of judgment and planning
- Personality changes
Alzheimer’s Disease Progression

Mild Cognitive Impairment

AD Progression

Death from pneumonia and/or other comorbidities

Mild
Loss of recent memory
Faculty judgment
Personality changes

Moderate
Verbal and physical aggression
Agitation
Wandering
Sleep disturbances
Delusions

Severe AD

Severe
Loss of all reasoning
Bedridden
Communication disability

Preclinical AD
Mild Cognitive Impairment (MCI)

- Prodromal Alzheimer’s disease?
  - Memory complaint corroborated by informant
  - Measurable, greater-than-normal memory impairment detected with standard memory assessment tests
- Normal general thinking and reasoning skills
- Maintained ability to perform normal daily activities
- Several subtypes (amnestic subtype most likely to progress to AD)

Sperling et al. 2011
Alzheimer’s Disease

healthy brain

advanced alzheimer's
Inside the brain

- The brain has billions of neurons, each with an axon and many dendrites.
- To stay healthy, neurons must communicate with each other, carry out metabolism, and repair themselves.
- AD disrupts all three of these essential jobs.
Alzheimer’s Disease Pathology

- **Amyloid plaques**
  - Insoluble extracellular deposits which accumulate in the cortex and hippocampus.
  - Composed of amyloid – beta (Aβ) protein fragments: Aβ40 and Aβ42.

- **Neurofibrillary tangles**
  - Bundles of insoluble helical fibers within neurons.
  - Composed of hyperphosphorylated tau proteins that are normally associated with microtubules.

- Intensive loss of synaptic contacts and neurons. Cortical atrophy: loss of 1/3 of brain mass
- Other factors may contribute such as inflammation
Amyloid plaque formation

APP is cleaved by β-secretase and γ-secretase to form the neurotoxic $A\beta_{42}$ fragment that aggregates into the amyloid plaque that is a hallmark feature of AD. Amyloid plaques form when there is an imbalance between accumulation and clearance of $A\beta$ from the brain.
Tau and microtubules
Changes in tau in Alzheimer’s

Tau proteins stabilize microtubules (MT) in neurons, particularly in axonal processes. MT main functions are to provide structure, organize the cytoplasm of the cell, and serve as tracks for the transport of cellular elements form the cell body to the axonal terminals (synapses).
Reduced functionality in AD brains

PET scans in Alzheimer's patients show reduced brain glucose metabolism

AD brain have a significant reduction of functionality throughout the entire brain
Treatment for Alzheimer’s Disease

- **No treatment or cure.** Only symptomatic relief and only for a short period of time. Dementia is progressive.

- **Acetylcholinesterase inhibitors:**
  - Tacrine
  - Rivastigmine
  - Galantamine
  - Donepezil

- **NMDA receptor antagonist:**
  - Memantine

  Increase amounts of acetylcholine in synapses by inhibiting its breakdown

  Reduces glutamate excitotoxicity
Down syndrome facts

- A genetic condition that causes delays in physical and intellectual development.
- Occurs in approximately one in every 800 live births.
- Individuals with Down syndrome have 47 chromosomes instead of the usual 46.
- It is the most frequently occurring chromosomal disorder.
Three types of Down syndrome

- **Trisomy 21**: caused by a faulty cell division that results in fetus having three #21 chromosomes instead of two.
Three types of Down syndrome

- **Translocation**: accounts for only 3% to 4% of all cases. In translocation a part of chromosome #21 breaks off during cell division and attaches to chromosome #13.
Three types of Down syndrome

- **Mosaicism:**
  - Trisomy occurs after fertilization leading to a mixture of somatic cells (some with 46 chromosomes & some with 47 chromosomes).
  - 1-2% percent of all Down syndrome cases

Mosaic trisomy 21
Down syndrome characteristics

- >60% spontaneously aborted
- 20% stillborn
- Developmental abnormalities
- Learning difficulty (IQ usually <50)
- Congenital heart malformations (40%)
- Many other associated features
Down syndrome diagnosis

- Diagnosis based on physical characteristics
- Confirmed by full karyotype analysis
Risk and maternal age

- Risk of Down syndrome goes up with maternal age
Down syndrome brain development

- Brain reduced in size
- Altered in configuration and connectivity (some underconnected and some overconnected)
- Altered cortical lamination
- Diminished synaptic formation
- Glial dysfunction and microglial activation
- By age 40 nearly all DS cases show neurological deficits similar to those observed in Alzheimer’s disease
- Most show cognitive decline by age 60
Down syndrome and Alzheimer’s

- PET scans show similar amyloid plaque density to AD

Nelson et al. *JAMA* 2011
Amyloid pathology in DS infants

- Evidence of amyloid pathology as early as infancy

Brain section of an infant with DS age 4 months.
(Anti-Abeta1-16 immunostaining in free floating formic acid pretreated 50MM thick formalin-fixed sections)
Why is DS associated with AD?

- APP is coded by a gene on chromosome 21

- Since people with Down syndrome have an extra chromosome 21, they also have an extra copy of the gene that encodes APP.

- Having this extra gene may lead to increased accumulation of neuritic plaques.