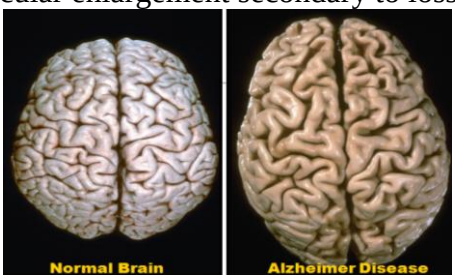
Unit VIII – Problem 10 – Pathology: Alzheimer's Disease (AD)

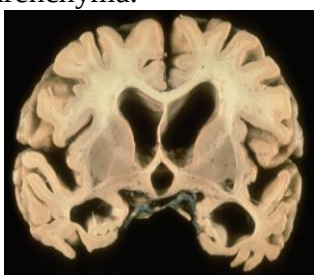
- **What is dementia?**
  - It is a general term that describes a brain syndrome characterized by problems with:
    - ✓ Memory.
    - ✓ Judgment.
    - ✓ Language.
    - ✓ Orientation.
    - ✓ Executive functioning.

    Notice that consciousness is not clouded in dementia.
- **Alzheimer's disease (AD) is the most common cause of dementia** -by causing progressive degeneration of brain tissue- in people above 65 years old (elderly). It is characterized by loss of neurons and synapses in cerebral cortex and certain subcortical regions.
- **Genetics of AD:**
  - **99% of cases are sporadic** and the most important genetic risk factor is the **(ApoE)** genotype which is present on chromosome 19. There are 3 forms of ApoE (ApoE2, ApoE3 and ApoE4):
    - ✓ Persons who are homozygous for the ApoE4 allele develop AD at a mean age of 70 years (ApoE4 has been detected in neurofibrally tangles and Aβ-plaques in cases of AD).
    - ✓ Persons with other ApoE phenotypes develop the disease later.
  - **Genetic factors in AD:**

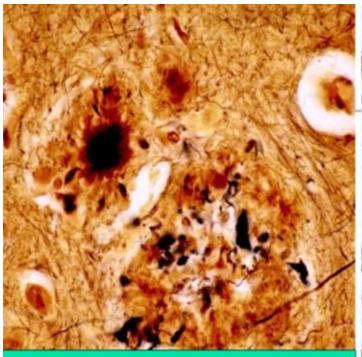
Gene	Chromosome	Disease association
Amyloid Precursor Protein (APP)	21	Associated with early onset familial AD
Presenilin-1 (PS1)	14	Associated with early onset familial AD
Presenilin-2 (PS2)	1	Associated with familial AD
ApoE	19	Associated with younger age of onset of both inherited and sporadic forms of late onset AD

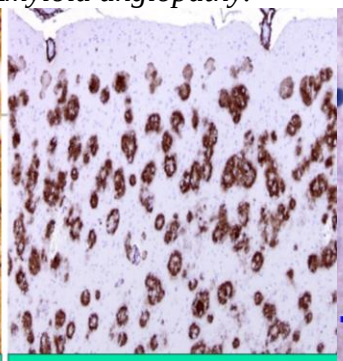
- **Pathogenesis of AD:**
  - APP which is present on the surface of cell membrane is critical for neuron growth, survival and post-injury repair.
  - **APP is degraded by secreteases** (there 3 types of them: alpha, beta and gamma).
  - In AD, APP will be degraded into **Aβ-fragments which will accumulate outside the cells** (in the form of oligomers) resulting in the formation of **senile plaques**. In addition, there will be activation of kinases intracellularly causing **hyperphosphorylation of tau-protein** and formation of **neurofibrillary tangles (NFTs).**
    - ✓ Note: Aβ plaques causes selective neurotoxicity for the hippocampus and entorrhinal cortex while sparing cerebellar neurons.
- **Morphology of AD:**
  - **There are 3 important gross features in AD:**
    - ✓ Cortical atrophy.
    - ✓ Widening of cerebral sulci (frontal, temporal and parietal).
    - ✓ Ventricular enlargement secondary to loss of parenchyma.

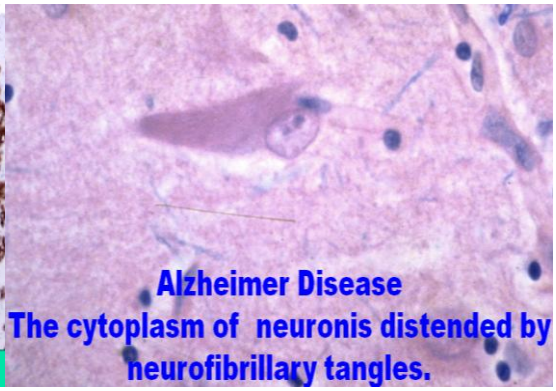




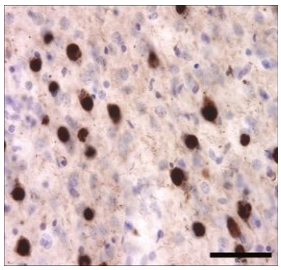
- **Histopathology of AD:**
  - ✓ Extracellular senile plaques → notice that these are specific for AD.
  - ✓ Intracellular neurofibrillary tangles (tau protein) → notice that these can be seen in other degenerative diseases.
  - ✓ Other features which might be seen:
    - ❖ *Granulovacuolar degeneration.*
    - ❖ *Hirano bodies.*
    - ❖ *Amyloid angiopathy.*


Alzheimer plaques-Bielschowski stain

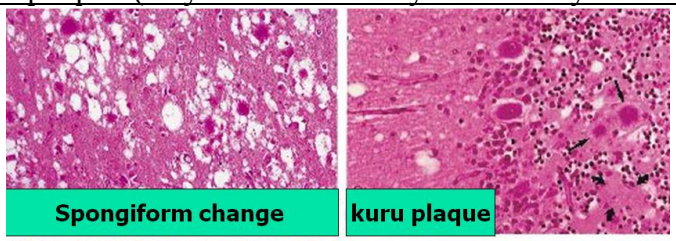

Beta amyloid immunostain



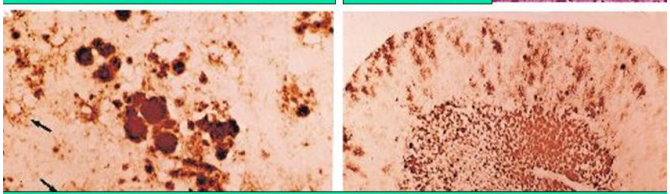
- **Pick's disease:**



  - Causing fronto-temporal lobar degeneration which leads to **fronto-temporal dementia** and **progressive non-fluent aphasia.**
  - **There is no genetic or familial cause.**
  - There is **personality change prior to memory loss** (unlike AD where memory loss presents first).
  - There is complete **absence of senile plaques and neurofibrillary tangles.**
  - **Pathology (see the image): pick bodies** are characteristic of this disease (they are silver-staining, spherical aggregations of tau protein). In addition, there is positive immunohistochemical staining when using anti-tau and anti-ubiquitin antibodies.
- **Prion disease:**
  - **Infectious agent**: prion protein (it is neither a virus, bacteria or rickettsia and contains no nucleic acid). Notice that mutations in PRNP gene causes prion disease.
  - **Etiology**: genetic, sporadic or infectious via ingestion of infected foodstuffs and via iatrogenic means such as blood transfusion.
  - **Features of prion disease:**
    - ✓ Spongiform change.
    - ✓ Neuronal loss.
    - ✓ Astrocytosis.
    - ✓ Amyloid plaque formation.
    - ✓ Kuru plaques (they stain like an amyloid but they are masses of prions).


Spongiform change

kuru plaque


Prion stained with anti-amyloid Ab