Neuropathology of Aging And Neurodegenerative Disease

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• What is normal brain aging?
• The Neurodegenerative Changes
  Alzheimer’s Disease
  Neuropathology
  Parkinson’s (Lewy Body) Disease
  Cerebrovascular disease
  Preventive measures
Aging changes in the human brain:

- Brain weight – range – 1450-1150 gm
- Lipofuscin
- Hirano bodies
- Corpora amylacea
- Vascular changes
- Plaques and tangles
GENERAL FEATURES OF NEURODEGENERATIVE DISORDERS

- Progressive loss of neurons and secondary white matter changes
- Affected groups of neurons with functional relationships
- Presence of abnormal protein aggregates ("proteinopathies")
  - Resistant to degradation
  - Aberrant localization within neurons (inclusions)
  - Elicit stress response from the cell
- Often directly toxic to neurons
- Progressive neurologic symptoms with impairment of "activities of daily living"
- No clear antecedent or inciting event

What are the “neurodegenerative” changes?

- Aβ-amyloid deposition
  - Neuritic plaques, diffuse plaques
  - Cerebral amyloid angiopathy
- Tau pathology
  - Neurofibrillary tangles, neuropil threads
- Alpha-synuclein pathology
  - Lewy bodies, Lewy neurites, glial cytoplasmic inclusions
- TDP-43, ubiquitin, p62

Alzheimer’s disease (AD)

- Most common form of dementia
  - Age 60-64: 5%
  - Age 85-89: 35%
  - 5.4 million Americans live with AD
  - Projected: 7.3 million by 2025
  - $277 billion dollars
  - National health care spending for AD
- Clinically:
  - Gradual, progressive impairment of higher cognitive functions
  - Deficits in memory, judgment, personality, language
  - Profound disability
  - May be sporadic (most common, older onset) or familial (5-10%, younger onset)
Gross findings: Widened sulci & narrowed gyri
Blunting of lateral ventricular angles
Small hippocampi
Reductions in white matter

Gross findings: Widened sulci & narrowed gyri
Enlarged ventricles
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Alzheimer's disease
Hyperphosphorylated tau (p-tau)

- Neurodegenerative diseases
- Triggered by traumatic brain injury
- Loose ability to bind to microtubules
- Accumulates in neurons and glia

Tau: Cytoskeletal protein - stabilizes microtubules.

- MAPT gene on chromosome 17
- Alternative splicing results in six tau isoforms that may contain either 3 or 4 tandem repeats (TR)
- TR regions correspond to microtubule binding sites on protein

Neurofibrillary tangles

- Cytoplasmic “flame-shaped” accumulations of paired helical filaments
- Composed of p-tau
- Remain after death of parent neuron
Alzheimer's disease
Hippocampus

 Tau immunohistochemistry

Braak and Braak Staging: TANGLES
Stage I-II: Entorhinal - Pre-Clinical
Stage III-IV: Limbic - Incipient AD
Stage V-VI: Isocortical - Dementia

Neuritic (senile) plaques

- Extracellular structures composed of “dystrophic neurites”, amyloid core, inflammatory cells:

Amyloid Precursor Protein
Gene: Chromosome 21

Amyloid plaques

Aβ-amyloid: Diffuse and neuritic plaques
Alzheimer's disease: Tissue Sampling

Sampling:
- Cerebral cortex
- Deep nuclei
- Brain stem

Measure:
- Extent of amyloid plaques - (A1 3)
- Neuritic plaque density - (C1 3)

Semi-Quantitative Evaluation of NEURITIC Plaques
FTLD-TDP
“Frontotemporal lobar degeneration with TDP43 inclusions”

- A non-Alzheimer neurodegenerative disorder characterized by TDP-43-immunoreactive inclusions (no tau or A beta amyloid).
- TDP-43 is major disease protein in the FTLD and ALS (amyotrophic lateral sclerosis).
- C9ORF72 mutations (Chromosome 9 open reading frame 72) (hexanucleotide repeat) in autosomal dominant form of FTLD-TDP
- FUS mutations in non-TDP43 FTLD or FTLD-ALS (RNA binding protein)

FTLD-TDP
“Frontotemporal lobar degeneration with TDP43 inclusions”

- TDP-43: Transactive response (TAR)-DNA-binding protein with a molecular weight of 43 kDa
- TDP-43 is an RNA-binding protein with roles in RNA processing and stress responses
  - Normally found diffusely in the nucleus
- Molecular genetics and pathogenesis:
  - Mutations in TDP-43 gene or associated genes
- Gross findings: atrophy of frontal and temporal lobes
Widespread TDP43 inclusions, especially in neocortex and hippocampus AND P62-positive inclusions in the cerebellum.

Abnormal cytoplasmic localization of TDP-43

**Parkinsonism**

- Clinical syndrome
  - Diminished facial expression, slowing of voluntary movements, rigidity, “pill-rolling” tremor, stooped posture, abnormalities of gait
  - Damage to dopamine producing neurons
  - Parkinson disease (PD) is the most common neurodegenerative disease to produce clinical parkinsonism

**Dopamine**

L-DOPA

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Parkinson’s disease - treatment

• L-DOPA – Levodopa: Chemical replacement of dopamine

• Deep brain stimulation:
  • Used in pharmacoresistant cases

Gross findings: Left cerebral hemisphere

Post fixation weight: 1107 gns
Gross findings: Hypopigmentation

Parkinson disease
- Idiopathic Parkinson disease: rigidity, tremor, abnormal posture and gait
- Disease of the elderly (75 - 80% are 75 or older)

Parkinson disease
- Pallor of pigmented neurons of the midbrain:
  - SUBSTANTIA NIGRA
Parkinson disease

- Loss of pigmented neurons and associated gliosis
- Lewy bodies: toxic accumulation of α-synuclein

Dementia with Lewy Bodies
Parkinson's disease dementia
Neuropathological Diagnosis

I. Adult brain (pre-fixation weight: 1107 gm)
   A. Lewy Body Disease, Neocortical Type
      1. α-Synuclein-immunoreactive Lewy bodies and neurites
         a. Substantia nigra, locus coeruleus, medullary tegmentum
         b. Deep neocortical layers: frontal and temporal lobes
      1. Aβ-amyloid immunoreactive plaques involving cerebral cortex, deep nuclei, and brainstem tegmentum
      2. Moderate tau pathology: Braak stage III
   C. Cerebrovascular disease
      1. Mild, cerebral amyloid angiopathy
      2. Cerebrovascular atherosclerosis, mild
      3. No lacunar or other ischemic lesions

Neurodegenerative Diseases: “Proteinopathies”

Alzheimer’s Disease  A Beta-amyloid (plaques)  Tau

Frontotemporal Lobar Degenerations:

   Progressive Supranuclear Palsy  Tau
   Pick’s Disease  Tau
   Corticobasal Degeneration  Tau
   FTDP-17 MAPT  Tau
   FTLD-TDP  TDP-43

Parkinson’s Disease  α-synuclein
Dementia with Lewy Bodies  α-synuclein
Multiple System Atrophy  α-synuclein

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Cerebrovascular Disease

- Atherosclerotic CVD
  - Diabetes / Hypertension
  - Smoking / Cholesterol
  - Inactivity
  - Macroscopic infarcts

- “Small vessel” disease
  - Hypertension
  - Older age
  - Multiple lacunar infarcts
  - Microinfarcts

Brain Arteriolosclerosis
“Small vessel cerebrovascular disease”
Hippocampal sclerosis of aging

- > 85 y/o
- Marked neuronal loss in hippocampus
- TDP43 inclusions in limbic structures: Hippocampus, amygdala
- Genetic Risk Factors:
  - ABCC9 – Brain arteriolosclerosis
  - GRN/TMEM106B

106 year old 17 year old

Normal Aging:
At the moment, there are no clinically useful treatments available for Alzheimer’s Disease that modify the long-term clinical outcome.

Preventing Cognitive Decline and Dementia:

- Encouraging education
- Challenging leisure activities
- Learning more than one language
- Avoiding head injuries
- Maintaining good sleep habits
- Making healthy dietary choices
- Aggressively treating cardiovascular risk factors
THANK YOU!!