Neurodegenerative diseases
Dementing disorders

Frontotemporal dementia
Pick disease
Chromosome 17-linked dementias

Movement disorders

Parkinson disease (PD)
(30% develop dementia)

Movement disorders & dementia

Dementia with Lewy bodies
Diffuse Lewy body disease (DLBD)
Alzheimer disease Lewy body
Huntington disease (HD)
Usual aging vs. morbidity

Neuronal loss

Aging

Neurofibrillary changes
Neuritic plaques
Hirano body
Granulovacuolar degeneration

Diseases
Usual aging v.s Alzheimer disease (AD)
Neuropathology

74 year-old, Control

89 year-old, AD
Hirano body

10 - 30 µm adjacent or within cytoplasm pyramidal neurons of hippocampus

Granulovacuolar degeneration

Vacuole: 3 - 5 µm
Granule: 1 - 2 µm
Cytoplasmic especially seen in pyramidal neurons of hippocampus

Found in 70 percent of brains of neurologically normal individuals
Neuritic (senile) plaques (Bielschowsky - 640 X)

Neuritic plaque
180 µm diameter
replaces about 100 neurons
& $10^6$ synapses
Amyloid

$\beta$-pleated sheet conformation, insoluble

Congo red stain

Under polarized light

birefringent

Salmon pink

Apple green

Fluorescent with Thioflavine stain
Neurofibrillary tangles of Alzheimer

Usual aging vs. morbidity

Neuronal loss

Neurofibrillary changes

Neuritic plaques

Pick body

Lewy body

Hirano body

Granulovacuolar degeneration

Diseases
Alzheimer disease (AD)

- Irreversible neurodegenerative disease
- Causes memory loss
- Decreases ability to think
- Insidious onset
- Continuous, slow decline in cognition
- Currently, no cure
- Definite diagnosis: Neuropathologic examination
## Alzheimer disease in the US

**Most common cause of dementia**

**90 percent are sporadic; 10 percent are familial**

**Prevalence rate over the age of 60 years (y)**
- 1900-5500 patients per 100,000 population
- > 50 percent of nursing home residents

**Annual incidence rate**
- increases exponentially with advancing age
- 2.4 patients / 100,000 population aged between 40 & 60 y
- 127 patients / 100,000 population aged 80 y & over
Alzheimer disease (AD) in the US

<table>
<thead>
<tr>
<th>In 2000, there were 4.5 million persons with AD (*)</th>
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<tbody>
<tr>
<td>By 2050 -&gt; 13.2 million AD patients (*)</td>
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<tr>
<td>Estimated cost of AD $100 billion / year (1993)</td>
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<td>4\textsuperscript{th} or 5\textsuperscript{th} leading cause of death</td>
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<td>n AD patients will continue to increase unless discoveries contribute prevention of the disease (*)</td>
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</tbody>
</table>

(*) Archives of Neurology, 2003. 60:1119-1122  
Neurology, 2005(Suppl 3). 65:S31-S32
Single photon emission computerized tomography (SPECT)
In AD: Parietal hypoperfusion

From: The Neuropathology of Dementia, M. Esiri & J. Morris
Cambridge University Press. 1997
Alzheimer disease (AD) : Neuropathology

Cerebral atrophy

Atrophy = Widening of sulci + Narrowing of gyri
Permanent loss of predominantly glutamatergic, pyramidal neurons of neocortex

Basal nucleus of Meynert (cholinergic system)
Neurofibrillary tangles

A: Early stage
B: Intermediate stage
C: End stage
Neurofibrillary tangles: ultrastructure

Parried helical filaments 8 - 12 nm, helically wound Insoluble React with silver stains

Hyperphosphorylated Tau ? Abnormal kinase or phosphatase activities

Tau: normal neuronal proteins, bind to microtubules regulate their assembly
Neuritic (senile) plaques (Bielschowsky)
Precuneus
Cuneus
Calcarine
β-amyloid
Substantia nigra pars reticulata (SNr), & compacta (SNC)

Coeruleus
Norepinephrine
Paradoxical sleep
Cortical activation

Dorsal n. X

LHE
Pick disease
Pick body

- Cytoplasmic, round, argyrophilic, tau positive, ubiquitin positive, 10 - 15 µm across
- α–synuclein negative

Pick bodies usually involve:
- Neocortical, pyramidal neurons
- Hippocampal, pyramidal neurons
- Stratum granulosum of dentate gyrus
- Amygdala
- Striatum
- Brainstem
Pick body

Bielschowsky

Tau

Tau positive
Ubiquitin positive
α-synuclein negative
Ballooned neurons

- Pick disease
- Primary progressive aphasia
- Chromosome 17-linked dementia
- Corticobasal degeneration
- Alzheimer disease
- Progressive supranuclear palsy
- Creutzfeldt-Jakob disease
Parkinson disease
And
Dementia with Lewy bodies
**Dementing disorders**

- **Alzheimer disease**
- **Frontotemporal dementia**
  - Pick disease
  - Chromosome 17-linked dementias

**Movement disorders**

- **Parkinson disease (PD)**
  - (30% develop dementia)

**Movement disorders & dementia**

- **Dementia with Lewy bodies**
- **Diffuse Lewy body disease (DLBD)**
- **Alzheimer disease Lewy body variant (ADLBV)**
- **Huntington disease (HD)**
Parkinson disease

1919: Trétiakoff, C.

50,000 Americans / year -> diagnosed with PD
# Parkinson disease (PD)

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<th>Bradykinesia</th>
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<td>Rigidity</td>
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<td>Resting tremor</td>
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<td>Postural instability</td>
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Neuronal loss
Cytoplasmic inclusion: Lewy

Dorsal nucleus of vagus
Nucleus coeruleus
Pars compacta of substantia nigra
Hypothalamus
Substantia innominata -> Mesolimbic cortex

If, in addition,
neurons with Lewy body in cerebral neocortex (-> dementia)

If, in addition,
neuritic plaques or neurofibrillary tangles
or both in cerebral cortex

Parkinson disease
Diffuse Lewy body disease
Alzheimer Disease Lewy body variant
Lewy body

Cytoplasmic inclusion, round, 8 - 30 µm

Brainstem type, discrete
Cortical type, ill-defined

Found in

5% of asymptomatic, elderly subjects
100% of patients with Parkinson disease or with Lewy body dementia
MPTP

1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydropyridine

Not toxic

1-Methyl-4-Phenylpyridinium ion

Toxic
VIDEO
Dementia with Lewy body (LB) Diffuse LB disease

Lewy bodies & Lewy neurites

Neocortex, hypothalamus, substantia innominata, substantia nigra (compacta), coeruleus, dorsal nucleus of vagus

Substantia nigra

Nucleus coeruleus
Huntington disease
Huntington disease

Early stage
CAG repeats

Normal allele

Abnormal allele

May or may not develop the disease

Huntington disease
Huntington disease
Between early and late stages
Ordered and topographic distribution

Coronal plane

Sagittal plane

Dorso-ventral direction

Caudo-rostral direction
Huntington disease
Late stage
Huntington disease
Juvenile onset
End-stage (Grade 4/4)
Excitotoxicity

Glutamate

Receptors

NMDA
AMPA
Kainate
Metabotropic

+ HDIT15
PolyQ

Normal

HD
Nuclear inclusions

Mouse R6/2
145 CAG

14 y.o. w
82/12 CAG
Huntington disease
Late onset
Relatively early stage
Slow progression