Neurodegenerative diseases

Dementing disorders
- Alzheimer disease
- Frontotemporal dementia
- Chromosome 17-linked dementias

Movement disorders
- Parkinson disease (PD)
- (30% develop dementia)
- Dementia with Lewy bodies
- Diffuse Lewy body disease (DLBD)
- Alzheimer disease Lewy body variant (ADLBV)
- Huntington disease (HD)

Movement disorders & dementia

Prevalence of dementia
Number of patients ALIVE with dementia in a defined population, & time frame

Prevalence is biased by differences in SURVIVAL.

Incidence of dementia
Number of patients that are NEWLY DIAGNOSED with dementia in a defined population, & time frame

Incidence is preferable to prevalence
Increased AWARENESS of dementing illnesses influences the rates of diagnoses, hence of incidence.

Human survival in U.S.

% surviving for each age

U.S. Bureau of Census

Alzheimer disease (AD) in the US

In 2000, there were 4.5 million persons with AD (*)

By 2050 -> 13.2 million AD patients (*)

Estimated cost of AD $100 billion / year (1993)

4th or 5th leading cause of death

Most AD patients will continue to increase unless discoveries contribute prevention of the disease (*)

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)
1900-5590 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

(*) Archives of Neurology, 2003. 60:1119-1122
Neurology, 2005(Suppl 3). 65:S31-S32)
Usual aging vs. morbidity

- Neuronal loss
- Neurofibrillary changes
- Neuritic plaques
- Hirano body
- Granulovacuolar degeneration
- Lewy body
- Pick body

Usual aging vs. Alzheimer disease (AD)

Neuropathology

- 74 year-old, Control
- 89 year-old, AD

Usual aging

Mild cognitive impairment
Occurrence of amnesia without impairment of Activities of daily living (ADL)

Neuritic (senile) plaques (Bielschowsky)

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

Hirano body

- 10 - 30 µm adjacent or within cytoplasm of 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

Neurofibrillary tangles of Alzheimer

Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. Zeitschrift für die gesamte Neurologie und Psychiatrie (Berlin) 1911;4:356-85. (Fig8 “Fortgeschrittene Erkrankung”)
Amyloid

β-pleated sheet conformation, insoluble

- Congo red stain
- Under polarized light
- Birefringent
- Apple green

Fluorescent with Thioflavine stain

Alzheimer disease (AD)

Early stage

- Irreversible neurodegenerative disease
- Destroys memory & ability to think
- Insidious onset
- Continuous, slow decline in cognition
- Currently, no cure
- Definite diagnosis: Neuropathologic examination

Control Alzheimer disease (AD)

Single photon emission computed 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: ultrastructure

- Paired 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.
**Pick disease**

Coeruleus 
Norepinephrine 
Paradoxical sleep 
Cortical activation 
Dorsal n. X 

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**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 

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**Ballooned neurons**

Pick disease 
- Primary progressive aphasia 
- Chromosome 17-linked dementia 
- Corticobasal degeneration 
- Alzheimer disease 
- Progressive supranuclear palsy 
- Creutzfeldt-Jakob disease 

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**Parkinson disease**

Dementia with Lewy bodies
Parkinson disease

1919: Trétiakoff, C.

50,000 Americans / year -> diagnosed with PD

Parkinson disease (PD)

- Bradykinesia
- Rigiidity
- Resting tremor
- Postural instability

- Neuronal loss
- Cytoplasmic inclusion: Lewy body

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

NPSPD: 6 stages


Neuronal loss

Cytoplasmic inclusion: Lewy body

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 (as seen in Alzheimer disease)

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

Parkinson disease

Control
**MPTP**

\[ \text{Ph} \quad \text{NCH, MAO B} \rightarrow \quad \text{Ph} \quad \text{NCH} \]

**MPTP**

\[ 1\text{-Methyl-4-Phenyl-1, 2, 3, 6-} \]

\[ \text{Tetrahydropyridine} \]

**Not toxic**

**Toxic**

**VIDEO**

QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.
**Dementia with Lewy body (LB) = Diffuse LB disease**

- **Lewy bodies**
  Neocortex, hypothalamus, substantia innominata, substantia nigra (compacta), coeruleus, dorsal nucleus of vagus

- **Lewy neurites**
  Hypothalamus, substantia innominata, CA3-2 of hippocampus (minimal) substantia nigra (compacta)

**Huntington disease**

**Huntington disease**

- **Early stage**

**CAG repeats**

- Normal allele
- Abnormal allele

May or may not develop the disease

Huntington disease
Control, 34 y.o.

Huntington disease, 48 y.o.

Coronal plane
Dorso-ventral direction

Sagittal plane
Caudo-rostral direction

Ordered and topographic distribution

Huntington disease
Late stage

VIDEO

Huntington disease
Juvenile onset
End-stage (Grade 4/4)

VIDEO

Control
HD
Dorsal-medial
Ventral
Glutamate

NMDA

AMPA

Kainate

Metabotropic

+ HDIT15

PolyQ

Receptors

Excitotoxicity

Huntington disease
Late onset
Relatively early stage
Slow progression

Nuclear inclusions

Mouse R6/2
145 CAG

14 y.o. w
82/12 CAG

Huntington disease
Late onset
Relatively early stage
Slow progression