Introduction to Neuropathology & General Aspects
Special Features of the CNS

- Complex and diverse topography
- Complex and diverse cytology
- Axoplasmic transport
- Myelin
- 3 classes of intermediate filaments – neurofilaments, glial fibrillary acidic protein, vimentin
- Neurotransmitters
- Separate population of interstitial cells-glia
- Blood brain barrier
- Cerebrospinal fluid
- Absent lymphatic vessels and lymph nodes
- Special aspects of cranial cavity (intracranial pressure)
Neuropathology – in a broader sense

**Neurology of the**

Central Nervous System  
(Brain and spinal cord, incl. their coverings)

Peripheral Nervous System  
(and its coverings)

Skeletal Muscle

**Neuropathology in a limited sense**

Neuropathomorphology
General Neuropathology =

Neuropathology-related Special Features

Cell Pathology

General „Organ Pathology“

General Principles of neuropathologic disease groups
Neuropathology of

<table>
<thead>
<tr>
<th>Nerve cells</th>
<th>blood brain barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glial cells</td>
<td>peripheral nerves</td>
</tr>
<tr>
<td>Oligodendroglia</td>
<td>skeletal muscle</td>
</tr>
<tr>
<td>Astroglia and Ependyma</td>
<td></td>
</tr>
<tr>
<td>Microglia</td>
<td></td>
</tr>
</tbody>
</table>
Keyhole Neuropathology

- Brain biopsy
- Nerve biopsy
- Extracerebral biopsy in neurodegenerative diseases
  - in adults
  - in children
General Principles of Neuropathologic Groups of Diseases

Neurodegenerative Diseases
   Neurometabolic Diseases

Inflammatory Diseases
   Infections
   Autoimmune processes

Toxic Diseases

Malformations

Tumors
Circulation Diseases
I. Pathologic Reactions in the CNS

II. Brain Edema
Neuronal Reactions
Pathology of Neuronal Processes

Dendrites

Axons
13-year-old girl with Jansky-Bielschowsky type. Purkinje cell with severely stunted dendritic apparatus. NADH$_2$-diaphorase.
Axonal Transport

Anterograde / Orthograde

**Fast:**

I  
100 - 400 mm/day  
-  
Polypeptides

II  
20 - 70 mm/day  
-  
Polypeptides

III  
3 - 20 mm/day  
-  
Polypeptides

**Slow:**

IV / V  
0.1 - 4 mm/day  
-  
Components of cytoskeleton and membrane skeleton and associated proteins incl. cytoplasmic enzymes

Retrograde
Pathology of Neuronal Processes

Wallerian degeneration
Retrograde reaction
Anterograde transneuronal degeneration
Retrograde transneuronal degeneration
Wallerian Degeneration
Anterograde transneuronal Degeneration

- Loss of eye
- Lesion of optic nerve → Lateral geniculate body

- Lesions of fornix → Mamillary bodies

- Loss of sensory fibers in posterior spinal columns → Gracilis and cuneate nuclei

- Loss of cortico-pontine fibers → Pontine nuclei
(Central) Chromatolysis – „axonal“ Reaction

- rounding of perikaryon
- loss of central Nissl bodies
- peripheral displacement of nucleus
- retraction of presynaptic terminals
Retrograde Transneuronal Degeneration

Lesions of the optic radiation and calcarine region → degeneration of retinal cells ganglion
Factors which impair Regeneration of CNS Axons

Lack of matrix-proteins,
  e.g. laminin and fibronectin

Lack of growth factors,
  e.g. GAP 43

Formation of inhibitory proteins,
  e.g. oligodendroglial glycoproteins

Formation of glial scars
reactive
degenerative
axonal changes
regenerative
dystrophic
Neuroaxonal Dystrophies
Pathology of the Neuronal Perikaryon

retrograde reaction

vacuolisation

cell death

atrophy

aggregation of
  proteins
  lysosomal substrates
  viruses
Cell Death
Types of Cell Death

- necrosis
- apoptosis
- autophagy
- „loss“
STAGES OF HYPOXIC NEURONAL DAMAGE

I. Microvacuolation
II. Ischemic cell change
III. Incrustations
IV. Homogenizing cell change
V. Bare pycnotic and fragmented nuclei
VI. Neuronophagy
Necrophanerosis
Elective Parenchymal Necrosis

= 

selective neuronal necrosis
Causes of elective Parenchymal Necrosis

- Anoxia / Hypoxia
- Cardiac arrest
- Anaemia
- CO intoxication
- Pulmonary disease
- Hypoglycaemia
Regions of elective Parenchymal Necrosis

- Purkinje cells (cerebellar cortex)
- Pyramidal cells of cortex, incl. hippocampus (cerebral cortex)
- Striatal neurons
- Thalamic neurons
Tissue Death
Types of Tissue Necrosis

- Coagulation necrosis
- Hemorrhagic necrosis
- Liquefaction necrosis
- Caseating necrosis (TB)
- Gummous necrosis (Syphilis)
- Fibrinoid necrosis (arteries)
Infarct

focal tissue necrosis owing to insufficient local blood supply

= Ischemia
Coagulation necrosis
Antemortem brain death
Dissociated (brain) death
Complete infarct of the brain
Antemortem autolysis of the brain
Respirator brain
Morphological Criteria for:

**Necrosis**
- Passive process

**Apoptosis**
- Active process
## Morphological differences between necrotic and apoptotic cell death

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Necrosis</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>cell</td>
<td>swells</td>
<td>shrinks</td>
</tr>
<tr>
<td>nuclear chromatin</td>
<td>disintergrates</td>
<td>condenses, strand breakage</td>
</tr>
<tr>
<td>other organelles</td>
<td>swell</td>
<td>normal</td>
</tr>
<tr>
<td>cell membrane</td>
<td>ruptures, blebs</td>
<td>remains intact, later: budding phagocytosis</td>
</tr>
<tr>
<td>surrounding tissue</td>
<td>inflammation</td>
<td></td>
</tr>
<tr>
<td>Phases of Apoptosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation phase:</td>
<td>different stimuli</td>
<td></td>
</tr>
<tr>
<td>Effector phase:</td>
<td>common to all cells</td>
<td></td>
</tr>
<tr>
<td>Degradation phase:</td>
<td>metabolic enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>activated</td>
<td></td>
</tr>
</tbody>
</table>
Demonstration of APOPTOSIS:

TUNEL technique (terminal deoxynucleotidyl transferase-mediated dUTP biotin end labeling)

ISEL (in situ end labeling)

pro-Apoptosis
- bax (bcl-2-associated X protein)
- ICE (interleukin-1β converting enzyme)
- APO-1/Fas

anti-Apoptosis
- bcl-2
- bcl-xL
## PROTEINS of the Bcl-2 family involved in Apoptosis:

**Inducing:**
- Bax
- Bak

**Suppressing:**
- Bcl-2
- Bcl-\( x_L \)
- Bcl-w
- Mcl-1
- A1

**Virus proteins:**
- BHRF1 (*Epstein-Barr virus*)
- LMW5 HL (*African swine fever virus*)
- E-1B 19K (*Adenovirus*)

**Location:**
- Endoplasmic reticulum
- Nuclear membrane
- Outer mitochondrial membrane
- Dimeric partners
  - Bcl2 — Bax
  - Bcl-\( x_L \) — Bak
Apoptosis in Neuropathology

Axotomy – retrograde
Motor Neuron diseases
Alzheimer disease
Parkinson disease
Huntington disease
Ischemia
loss of neurons
Ageing
A → B Improved housing, sanitation, antiseptics
B → C Public health, hygiene, immunization
C → D Antibiotics, improved medical practice, nutrition, health education
D → F Recent biomedical breakthroughs

Percent survivors

Age (years)

Ancient time to early 19th century
Cell Biology of Aging

programmed aging

defective DNA-repair

degeneration of extracellular matrix

damage by free radicals

insufficiency of protein degradation

cumulating cell damage
Aging and CNS

Loss of brain weight:
  parenchyma, water content

shrinkage of large neurons (loss?)

dendritic proliferation

cellular gliosis
NEUROPATHOLOGICAL CHANGES OF AGE IN THE CNS
(excl. blood flow, metabolic, neurochemical data)
(Creasy and Rappaport, Ann Neurol 17:2-10, 1985)

- Loss of weight (7-8%)
  (incl. infratentorial parts)

- Atrophy of gray and white matter
  gray-to-white ratio: 1.28 (age 20 ys)
  1.13 (age 50 ys)
  1.55 (age 100 ys)

- Dilatation of ventricles

- Selective neuronal loss
  (Golgi type II neurons of layers II and IV)
  superior frontal
  superior temporal
  precentral
  striatum
  hippocampus
  Purkinje cells
  locus caeruleus
  amygdala
  thalamus
  substantia nigra

- Reduction in neuronal size

- Loss of specific growth factors

- Loss of nucleolar volume, RNA content

- Accumulation of lipofuscin, amyloid

- Senile plaques

- Neurofibrillary tangles

- Granulovacuolar degeneration
Age changes of human isocortex

Dendritic changes of pyramidal cells

Meganeurites of layer IIIa pyramidal cells

Cytoskeleton abnormalities

Tangles Threads

Plaques

Loss of intrasaccular myelin

Development of meganeurites

Loss of non-pyramidal cells
Granulovacuolar Degeneration Simchowicz
Intraneuronal (intragalial) Aggregation

Proteins
Viruses
Lysosomal substrates
Lipofuscin (Lipopigment)

Age pigment
Wear and tear pigment
<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological neuronal:</td>
<td>lateral geniculate body, inferior olive, dentate nucleus</td>
</tr>
<tr>
<td>Aging:</td>
<td>large neurons (pyramidal neurons)</td>
</tr>
<tr>
<td>Pathological:</td>
<td>neuronal ceroid-lipofuscinoses, Vitamin E deficiency</td>
</tr>
<tr>
<td>Experimental:</td>
<td>Feeding unsaturated fatty acids</td>
</tr>
</tbody>
</table>
Marinesco body
Alzheimer Disease

NFT  neurofibrillary tangles

PHF  paired helical filaments
Lewy body
Lewy body
Protein Distribution

Classification of proteins identified in cortical Lewy bodies. Pie chart depicting the 296 proteins characterized by LC-MS/MS. Functional classification of a given protein was based on the one that is best known, although typically, multiple functions may have been associated with that particular protein. Notably, a significant portion of the proteome is novel without known functions.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Proteins</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer diseases</td>
<td>NFTs/PHFtau</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Amyotrophic lateral</td>
<td>Spheroids/NF subunits</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLB Disease</td>
<td>LBs/NF subunits, (\alpha)-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>LBVAD (AD+DLBD)</td>
<td>NFTs/PHFtau</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>LBVAD (AD+DLBD)</td>
<td>LBs/NF subunits, (\alpha)-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>MSA</td>
<td>GCIs/(\alpha)-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>PD</td>
<td>LBs/NF subunits, (\alpha)-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Tauopathies</td>
<td>NFTs/AD-like PHFtau</td>
<td>Intracytoplasmic</td>
</tr>
</tbody>
</table>
# Neurodegenerative diseases with filamentous proteins

<table>
<thead>
<tr>
<th>Disease</th>
<th>Proteins</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal intranuclear inclusion disease</td>
<td>Inclusions/expanded polyglutamine tracts</td>
<td>Intranuclear</td>
</tr>
<tr>
<td>Tri-nucleotide repeat diseases</td>
<td>Inclusions/expanded polyglutamine tracts</td>
<td>Intranuclear</td>
</tr>
<tr>
<td>AD</td>
<td>SPs/Aβ, NonAβ-components</td>
<td>Extracellular</td>
</tr>
<tr>
<td>LBVAD (AD+DLBD)</td>
<td>SPs/Aβ, NonAβ-components</td>
<td>Extracellular</td>
</tr>
<tr>
<td>Prion diseases</td>
<td>Amyloid plaques/prions</td>
<td>Extracellular</td>
</tr>
</tbody>
</table>
Fig. 1. Schematic diagram of βAPP showing the transmembrane region, the boundaries of Aβ, the α-secretase site, the position of the Kunitz protease inhibitor insert, and the regions probed by antibodies.

JAN L. DE BLECKER, et al. 1996
## Amyloid (osis)

<table>
<thead>
<tr>
<th>Type</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ specific</td>
<td>generalised</td>
</tr>
<tr>
<td>Hereditary</td>
<td>acquired</td>
</tr>
<tr>
<td>Primary/Systemic</td>
<td>secondary</td>
</tr>
</tbody>
</table>
Viral inclusions in nerve cells

Nucleus (Cowdry type A)
- Herpes simplex / zoster virus
- Papova/JC (progressive multifocal leukoencephalopathy)
- Paramyxovirus (measles)
- Cytomegalovirus

Cytoplasm
- Negri / Lyssa bodies (Rabies)
<table>
<thead>
<tr>
<th>Oligodendroglial Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral replication</td>
</tr>
<tr>
<td>Protein aggregation</td>
</tr>
<tr>
<td>lysosomal activation</td>
</tr>
</tbody>
</table>

- inclusions
- inclusions
- lysosomal storage

**demyelination**
Primary and secondary Demyelination
Types of Demyelination

Diffuse - metabolic, toxic

Focal - unifocal: traumatic, neoplastic

multifocal: inflammatory
<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>Apoptosis of oligodendrocytes</td>
<td>Vartanian et al.,^36^</td>
</tr>
<tr>
<td>Fas or fas ligand</td>
<td>Demyelination or hypomyelination</td>
<td>Corbin et al.,^37^</td>
</tr>
<tr>
<td>Tumor necrosis factor α</td>
<td>Apoptosis of oligodendrocytes</td>
<td>Horowitz et al.,^38^</td>
</tr>
<tr>
<td>Reactive oxygen intermediates</td>
<td>Apoptosis of oligodendrocytes</td>
<td>D’Souza et al.,^39^</td>
</tr>
<tr>
<td>Complement acting alone or through comple-</td>
<td>Apoptosis of oligodendrocytes</td>
<td>Selmaj and Raine^40^</td>
</tr>
<tr>
<td></td>
<td>ment-fixing antibody</td>
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</tr>
<tr>
<td>Complement acting alone or through comple-</td>
<td>Apoptosis of oligodendrocytes</td>
<td>Merrill et al.,^42^</td>
</tr>
<tr>
<td></td>
<td>ment-fixing antibody</td>
<td>Necrosis of oligodendrocytes</td>
</tr>
</tbody>
</table>
CLASSIFICATION OF PRIMARY MYELIN DISEASES

- Allergic and infectious diseases
- Hereditary (metabolic) diseases
- Toxic diseases
- Nutritional diseases
- Traumatic diseases
- Vascular diseases
Glia reactions
Microglia
Astrocytes
(Glial scar)

Mesenchymal reactions
Vessels
Fibroblasts
Scar
Microglia-rapid reaction

phagocytes
MHC I + II positive
express APP, complement receptor
produce cytokines, NO
present antigens
Synaptic stripping by microglia
Kufs Disease
Myelin Basic Protein
Orthochromatic (sudanophilic) Degradation

metachromatic Degradation
General Paresis
Figure 1.54. A diagram of the possible configurations of the astrocytic processes. (From A. Hirano...
Hepatic Glia

Hypertrophy of astrocytic nuclei

Alzheimer type I = Wilson disease (hepato-lenticular degeneration)

Alzheimer Type II = hepatic and uremic encephalopathies
Alzheimer type I glia:

M. Wilson = hepatolenticular degeneration

Alzheimer type II glia:

hepatic encephalopathy
Gemistocytes
normal caudate nucleus

Huntington Chorea
Isomorphic gliosis
Corpora amylacea
Rosenthal fibers: occurrence

reactive
- around craniopharyngeoma
- around MS plaques

neoplastic (?)
- pilocytic astrocytoma

genetic
- Alexander disease
- giant axonal neuropathy
## Types of reaction

<table>
<thead>
<tr>
<th>Cell types</th>
<th>Regressive/degenerative</th>
<th>Progressive/hyper-trophic-hyperplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>neuron</td>
<td>many specific and nonspecific alterations</td>
<td>none</td>
</tr>
<tr>
<td>oligodendroglia</td>
<td>limited</td>
<td>none (limited)</td>
</tr>
<tr>
<td>astrocyte</td>
<td>limited</td>
<td>astrocytosis</td>
</tr>
<tr>
<td>microglia</td>
<td>limited</td>
<td>inflammation phagocytosis</td>
</tr>
</tbody>
</table>
Space occupying Lesions
Contents of the Cranial Cavity

- 70 % brain tissue
- 12 % cerebrospinal fluid
- 15 % blood
## Intracranial Pressure

<table>
<thead>
<tr>
<th>Category</th>
<th>Pressure Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal adult</td>
<td>0-10 mm (upper limit 15 mm)</td>
</tr>
<tr>
<td>5-year old child</td>
<td>0-5 mm</td>
</tr>
<tr>
<td>Newborn</td>
<td>0-3 mm</td>
</tr>
<tr>
<td>Elevated</td>
<td>-25 mm</td>
</tr>
<tr>
<td>Mild</td>
<td>-30 mm</td>
</tr>
<tr>
<td>Moderate</td>
<td>-37.5 mm (electrical activity ceases, ischemia)</td>
</tr>
<tr>
<td>Marked</td>
<td>-60 mm</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
</tr>
</tbody>
</table>
Causes of space-occupying lesions

tumors
haemorrhages
inflammatory processes
blockage of CSF (hydrocephalus)
brain edema
trauma
ischemia / anoxia
TUMORS OF THE CENTRAL NERVOUS SYSTEM

Skull
Falx
entorium cerebelli
Tentorial notch
Foramen magnum
Figure 1. Types of Intracranial Hemorrhage and Brain Herniation. Adapted from Bullock and Teasdale, with the permission of the publisher.
Herniations

Subfalcial herniation
  right and left supratentorial cavities

Uncus herniation
  supratentorial cavities → infratentorial cavity

tonsillar herniation
  infratentorial cavity → spinal canal

Retrograde: cerebellum
  infratentorial cavity → supratentorial cavity
MAINZ