CNS Pathology - II

Pathology of Dementia

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Pathology of Dementia - contents

- Dementia – definition, clinical features
- Causes of dementia
- Dementia secondary to other pathologies
  (vascular, expansion infection, intoxication, metabolic…)
- Neurodegenerative diseases (prionoses, m. Alzheimer, m.Pick, m. Parkinson, m. Huntington…)
- Multiple sclerosis
Dementia

Def.

decrease of individual intelectual abilities under the formerly reached niveau

It is estimated that more than 45 million people worldwide are living with dementia and this number is expected to increase to more than 130 million people by 2050 (http://www.alz.co.uk/research/world-report-2016).
Dementia

Clinical features (variable)

Disturbances of

- memory (mnestic)
- cognitive functions (gnostic)
- adaptative behaviour (practice)

Impairment of episodic memory, aphasia, apraxia, agnosia and executive dysfunction.
First trousers. THEN Shoes!!!
Dementia

Onset
mostly inapparent

Course
reversible
stationary
progredient
Dementia - causes (1)

- THERAPY
- INTOXICATION
- INFECTION
- METABOLIC DISORDERS
- PROGRESSIVE DEGENERATIVE DISEASES
- MALNUTRITION
- VASCULAR EXPANSION
- AFFECTIVE DISORDERS
Dementia - causes (2)

- THERAPY polypragmasia
- INTOXICATION Mn, Cu, Pb, CO, CS2, Hg, etanol.....
- INFECTION viral, bacterial, protozoan, mycotic
  (HIV, PME, Whipple disease, Lues, toxoplasmosis, cryptococcosis, ...)
Ethylismus - Brain
Wernicke’s encephalopathy
Ethylismus chronicus

Cerebellum

Corpora mammilaria
Abscessus cerebri
Abscessus cerebri
Prionoses - morphology

- neuronal loss
- spongiosis
- gliosis

ATROPHY
CJD

Atrophia loborum frontalium cerebri
CJD
Dementia - causes (3)

- METABOLIC DISORDERS
  - chron. liver or kidney failure,
  - thesaurismoses
  - hepatolenticular degeneration

- MALNUTRITION
  - avitaminosis B1
  - Wernicke-Korsakoff encephalopathy with dementia
Storage Diseases

Def.: inborn errors of metabolism (*mostly single gene abnormality*) leading to an
- enzyme defect with subsequent
- accumulation of the substrate (&
- lack of the product) in tissues or organs
## Lipid Storage Diseases -1.

<table>
<thead>
<tr>
<th>Disease</th>
<th>E- def</th>
<th>Accum. Lipid</th>
<th>Tissues Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs</td>
<td>Hexosaminidase A</td>
<td>GM2 ganglioside</td>
<td>Brain, retina</td>
</tr>
<tr>
<td>Gaucher</td>
<td>β-Glucosidase</td>
<td>Gluco cerebrosid</td>
<td>Liver, spleen, bone marrow, Brain</td>
</tr>
<tr>
<td>Niemann-Pick</td>
<td>Sphingo myelinase</td>
<td>Sphingo myelin</td>
<td>Brain, liver spleen</td>
</tr>
</tbody>
</table>
## Lipid Storage Diseases – 2.

<table>
<thead>
<tr>
<th>Disease</th>
<th>E- def</th>
<th>Accum. Lipid</th>
<th>Tissues Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metachromatic Leucodystrophy</td>
<td>Arylsulfatase A</td>
<td>Sulfatid</td>
<td>Brain, kidney, liver, peripheral nerves</td>
</tr>
<tr>
<td>Fabry’s</td>
<td>α-galactosidase</td>
<td>Ceramid trihexosid</td>
<td>Skin, kidney</td>
</tr>
<tr>
<td>Krabbe’s</td>
<td>Galactosylceramidase</td>
<td>Galactol cerebroside</td>
<td>Brain</td>
</tr>
</tbody>
</table>
## Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Disease, inheritance course</th>
<th>E- def</th>
<th>Accum. Mucopoly saccharide</th>
<th>Tissues Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler AR, severe</td>
<td>$\alpha$-l-iduronidase</td>
<td>Heparan sulfate, dermatan sulfate</td>
<td>Skin, cornea, bone, heart, Brain, liver, spleen</td>
</tr>
<tr>
<td>Hunter X, rec. moderate</td>
<td>l-iduronosulfate sulfatase</td>
<td>Heparan sulfate, dermatan sulfate</td>
<td>Skin, bone, heart, ear, retina</td>
</tr>
<tr>
<td>Sanfilippo</td>
<td>Many types</td>
<td>Heparan sulfate</td>
<td>Brain, skin</td>
</tr>
</tbody>
</table>
MPS VI

Maroteaux - Lamy
Atrophia cerebri senilis (91 anni)
Dementia – causes (4)

- VASCULAR
  - hypertensive encephalopathy, MID

- EXPANSION
  - subdural hematoma, hygroma, neoplasia, hydrocephalus

- AFFECTIVE DISORDERS
  - depression
Status cribrosus
normal brain  atrophy
Haematoma subdurale
Dementia - causes (5)

PROGRESSIVE DEGENERATIVE DISEASES

- dementia – *the only one symptome:*
  m. Alzheimer, m. Pick (FTLD)

- dementia – *combined with neurology symptomes:*
  m. Parkinson, m. Huntington, ALS, PP
Neurodegenerative Diseases

- Genetic abnormality
- Modified protein
- Pathologic structures
- Loss of neurons
Neurodegenerative Diseases

I. Polyglutamine diseases
   (multiple Cytosin–Adenin–Guanin CAG complexes)
   m. Huntingtoni
   (+ family of other triplet repeat expansion dis.)

II. \(\tau\)–pathies, \(\alpha\)–synucleinopathies
    m. Alzheimeri, m. Parkinsoni (Lewy bodies)
M. Alzheimeri - incidence

> 65 yrs  5%
> 80 yrs  20%

population
Michel Goedert, Cambridge, UK:
Oskar Fischer and the study of dementia.


- Born in Slaný (25 km northwest of Prague) 1876
- MD degree in Prague in 1900
- two years in Path. anatomy dept. of German University
- Dept. of Psychiatry – directed by Arnold Pick
- Description of neuritic plaques 1907
- Died in Terezin 1942
ATROPHIA CORTICIS CEREBRI ASYMETRICA
M. Alzheimeri

Extracellular

- β-amyloid plaques
- dystrophic dendrites
- axons
- activated microglia
- reactive astrocytes

Diffuse plaques - Aβ42
Mature plaques - Aβ42 and Aβ40
M. Alzheimeri

Intracellular

- neurofibrillar deposits
- hyperphosphorylated proteins τ (pair helical filaments)
- glycosaminoglycans admixture (heparin)
Morbus Alzheimeri
# M. Alzheimeri-genetic factors

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene defect</th>
<th>Age of onset</th>
<th>Aβ phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>β APP mutations</td>
<td>50s</td>
<td>Production of total Aβ&lt;sub&gt;42&lt;/sub&gt; peptides</td>
</tr>
<tr>
<td>19</td>
<td>apo E4 polymorphism</td>
<td>60 and older</td>
<td>Density of Aβ plaques and vascular deposits</td>
</tr>
<tr>
<td>14</td>
<td>presenilin 1 mutations</td>
<td>40s and 50s</td>
<td>Production of Aβ&lt;sub&gt;42&lt;/sub&gt; peptides</td>
</tr>
<tr>
<td>1</td>
<td>presenilin 2 mutations</td>
<td>50s</td>
<td>Production of Aβ&lt;sub&gt;42&lt;/sub&gt; peptides</td>
</tr>
<tr>
<td>17</td>
<td>τ - protein - pair helical filaments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trisomia 21 – m. Downi
M. Alzheimeri - diagnosis

age matched

neuritic plaques

quantity & tangles

NIA / Khachaturyan - 1985
CERAD / Mirra et al. - 1991
NIA / Reagan Inst. - 1997
BrainNet Europe Consortium - 2008
m. Alzheimer

Hippocampus - tangles

Neocortex - neuritic plaques
In the non-amyloidogenic pathway APP is mostly cleaved by alpha-secretase within Ab, which precludes the production of Ab.

The sequential processing of APP by b- and g-secretases in the amyloidogenic pathway produces Ab.
Infectious agents and neurodegeneration.

A growing body of epidemiologic and experimental data point to chronic bacterial and viral infections as possible risk factors for neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

Infections of the central nervous system, especially those characterized by a chronic progressive course, may produce multiple damage in infected and neighbouring cells.

The activation of inflammatory processes and host immune responses cause chronic damage resulting in alterations of neuronal function and viability, but different pathogens can also directly trigger neurotoxic pathways.

Indeed, viral and microbial agents have been reported to produce molecular hallmarks of neurodegeneration, such as the production and deposit of misfolded protein aggregates, oxidative stress, deficient autophagic processes, synaptopathies and neuronal death.

These effects may act in synergy with other recognized risk factors, such as aging, concomitant metabolic diseases and the host’s specific genetic signature.

This review: herpes simplex type-1, HIV, influenza viruses, Chlamydofoilla pneumoniae.
Alzheimer's disease (AD) is a complex and heterogeneous neurodegenerative disorder, classified as either early onset (under 65 years of age), or late onset (over 65 years of age).

Three main genes are involved in early onset AD: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2).

The apolipoprotein E (APOE) E4 allele has been found to be a main risk factor for late-onset Alzheimer's disease.

Additionally, genome-wide association studies (GWASs) have identified several genes that might be potential risk factors for AD, including clusterin (CLU), complement receptor 1 (CR1), phosphatidylinositol binding clathrin assembly protein (PICALM), and sortilin-related receptor (SORL1).

Recent studies have discovered additional novel genes that might be involved in late-onset AD, such as triggering receptor expressed on myeloid cells 2 (TREM2) and cluster of differentiation 33 (CD33). Identification of new AD-related genes is important for better understanding of the pathomechanisms leading to neurodegeneration.

Since the differential diagnoses of neurodegenerative disorders are difficult, especially in the early stages, genetic testing is essential for diagnostic processes. Next-generation sequencing studies have been successfully used for detecting mutations, monitoring the epigenetic changes, and analyzing transcriptomes.
Alzheimer’s disease (AD) is a threshold pathology, **multifactorial** and lifelong **developing**…

**Risks and primary prevention:**

6 groups of childhood risk: (1) perinatal conditions (2) early-life brain development (3) early–life body growth (4) early–life socioeconomic conditions, (5) environmental enrichment, and (6) cognitive reserve


**Vascular risks control** – esp. hypertension;

*(screening of the apolipoprotein E genotype in symptomless not recommended)*


**Diet** - Mediterranean type and physical activity – reduced risk of AD


**Partnership**- widowed and divorced – increased risk of AD


**Viruses** – HSV1 in plaques - increased risk of AD, antivirotics? vaccination???


**Nutrition** – underweight (BMI less than 20) increased risk of AD, slight overweight no influence, obezity REDUCED risk of AD

<table>
<thead>
<tr>
<th>věk</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
<td>4</td>
</tr>
<tr>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>85</td>
<td>27</td>
</tr>
<tr>
<td>90</td>
<td>40</td>
</tr>
</tbody>
</table>

Neurodegenerations are NOT inevitable...

Maja Pliseckaja 20.11.1925 – 2.5.2015
Lenka Reiner 17.5.1916 - 27.6.2008
Vladimir Horowitz 1.10. 1903 – 5.11.1989
Pablo Ruiz Picasso 25.10.1881 – 8.4.1973

Rudolf Ludwig Karl Virchow 13.10.1821 - 5.9.1902

Santiago Ramón y Cajal 1.5.1852 – 18.10.1934

Jiří Kudrmann 24.10.1928

Antonín Fingerland 26.2.1900 – 27.12.1999

Petr Helbich 5.11.1929

Jitka Kobilková 13.7.1928
Dementia - *causes* (5)

PROGRESSIVE DEGENERATIVE DISEASES

- dementia – *the only one symptome*:
  m. Alzheimer, FTLD - m. Pick…

- dementia – *combined with neurology symptomes*:
  m. Parkinson, m. Huntington, ALS, PP…
Arnold Pick 1851-1924

Head of the Prague Psychiatry Clinic 1886-1924

Prager medizinische Wochenschrift 1882 – case report of a dementia patient

FTLD – FrontoTemporal Lobar Degeneration - Tau

Pick disease
m. Pick
Atrophia loborum frontalium cerebri
Dementia - causes (5)

PROGRESSIVE DEGENERATIVE DISEASES

- dementia – the only one symptome:
  m. Alzheimer, m. Pick

- dementia – combined with neurology symptomes:
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Paralysis agitans – m. Parkinsoni

James Parkinson (1755-1824)

An Essay on the Shaking Palsy.

Reprinted in Medical Classic, 1938, 2: 946-97

Prevalance 30-190/100 000, increase with age
Paralysis agitans
– m. Parkinsoni (1817)

Clinical features
- Start 40–60 years
- Early stage
  - dysesthesias
  - discrete tremor
- hypertonia–hypokinesia syndrome
  - resting tremor
  - rigidity
  - bradykinesia & loss of automatic movements
- prognosis: quoad vitam good, quoad sanationem ± (L-DOPA, transpl., nicotine, deep ELECTRIC STIMULATION)
Paralysis agitans
– m. Parkinsoni (1817)

Morphology

- **macroscopy** depigmentation of substantia nigra mesencephali
- **microscopy** Lewy bodies, loss of pigmented neurons
m. Parkinsoni
m. Parkinsoni
m. Parkinsoni
Parkinson’s dis. - etiology

- genetic factors recently described:
  - PARK1 – α-synuclein- autos. dom., Lewy bodies
  - PARK2 – Parkin, autos. rec. juv.-no LB
  - PARK3 – late onset
  - ..... 
  - ..... 
  - PARK 11 ...
Parkinsonism - causes

◆ common
  – Parkinson disease

◆ less common
  – drugs
  – multisystem atrophy
  – progressive supranuclear palsy
  – vascular

◆ rare
  – m. Alzheimeri, m. Huntingtoni, m. Wilsoni, toxins MPTP, dementia pugilistica, hydrocephalus, expansive lesions….

MPTP
1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine "synthetic heroin" component
Chorea chronica progressiva
Huntington

- Autosomally dominant (!)
  - 4th chromosome
- Manifestation 25 – 45 years
  - (juvenile form prior to 20 years of age)
- Duration 15 years

The gene is subtelomeric on the short arm of chromosome 4 and codes for the protein called Huntingtin.
CAG triplets normally 9-36 repeats, in HCH 37-100 or more.
Threshold for the dis usually set for 39.
Chorea chronica progressiva
Huntington

Clinical features

- contravolitional uncontrolled dance–like motions
- schizophrenic and depressive personality features
- death from intercurrent infection (bronchopneumonia, cachexia)
Chorea chronica progressiva Huntington

control brain
Chorea chronica progressiva Huntington

Morphology

- **macroscopy** striatum atrophy
  (ncl. caudatus + putamen)
- **microscopy** loss of small GABA neurons (norm. 80% of population)
Neurodegenerative Diseases

- genetic abnormality
- modified protein
- pathologic structures
- loss of neurons
Neurodegenerative Diseases

I. Polyglutamine diseases
   (multiple Cytosin–Adenin–Guanin CAG complexes)
   m. Huntington
   (+ family of other triplet repeat expansion dis.)

II. τ–pathies, α–synucleinopathies
    m. Alzheimeri, m. Parkinsoni (Lewy bodies)
Review Article

Neural stem cell-based treatment for neurodegenerative diseases

Seung U. Kim, Hong J. Lee and Yun B. Kim

1Medical Research Institute, Chung-Ang University College of Medicine, Seoul, 2Department of Toxiology, Chungbuk National University School of Veterinary Medicine, Cheungju, Korea, and 3Division of Neurology, Department of Medicine, UBC Hospital, University of British Columbia, Vancouver, British Columbia, Canada
• immortalized cell lines of human NSCs by infecting fetal human brain cells grown in primary culture with a retroviral vector carrying v-myc oncogene and selecting continuously dividing NSC clones.
• both in vivo and in vitro these cells were able to differentiate into neurons and glial cells and populate the developing or degenerating CNS.

There are still many obstacles

(i) it is still uncertain how to generate specific cell types of neurons or glia suitable for cellular grafts in great quantity from NSCs;
(ii) it is required to abate safety concerns related to tumor formation following NSC transplantation; and
(iii) it needs to be better understood by what mechanism transplantation of NSCs leads to an enhanced functional recovery.
Apolipoprotein E (ApoE) protein is the major cholesterol carrier in the brain

- involved in neuronal maintenance and repair
- ApoE binds to several receptors on the cell surface, which are involved in lipid delivery and transport, glucose metabolism, neuronal signaling, and mitochondrial function.
- normally, ApoE binds to A-beta peptide and play a role in its clearance.

**APOE genotyping**

Allele-specific, multiplex PCR has been developed for APOE genotyping of E2, E3, and E4 alleles.

One of the most frequently used kits is the LightCycler® ApoE Mutation Kit by Roche Diagnostics (Basel, Switzerland).


Sclerosis cerebrospinalis multiplex disseminata  MS

*Def.*

chronic autoimmune disease with myelin breakdown

F/M - adult age (20-40 yrs.), incidence 1,5 per mille
Multiple sclerosis – *classif.*

- classic (Charcot type - 1868)
- acute (Marburg type)
- ----------------
- neuromyelitis optica (Devic’s dis.) – newly separated as aquaporin 4- autoantibodies related
- concentric sclerosis (Baló’s dis.)
Sclerosis cerebrospinalis multiplex disseminata  MS

*Clinical features*

Disorders of

- sight
- sensation
- motorics

Course

- cont. progressive
- saw-like
Sclerosis cerebrospinalis multiplex disseminata  MS

Morphological features

– myelinic plaques
  - acute
  - chronic
Sclerosis cerebrospinalis multiplex disseminata
Sclerosis cerebrospinalis multiplex disseminata
Sclerosis cerebrospinalis multiplex disseminata
Sclerosis cerebrospinalis multiplex disseminata
Pathogenesis

- Genetic predisposition: \textit{HLA DR2 association}

- Environmental factors: \textit{vitamin D deficiency, viruses, smoking...}
Sclerosis cerebrospinalis multiplex disseminata – multiple sclerosis - MS

chronic autoimmune demyelinating encephalitis
Current mechanisms of immune dysregulation in the development of MS
Impact of environmental risk factors on immunity
CD4 T-helper (Th) cells have long been implicated as the main drivers of pathogenesis

Multiple sclerosis is largely a heterogeneous disease process

both innate and adaptive immune-mediated inflammatory mechanisms contribute to demyelination and neurodegeneration.

B cells, CD8 T cells, and microglia/macrophages can also play an important role in the immunopathogenesis of multiple sclerosis
Increasing evidence indicates that environmental risk factors
• Vitamin D deficiency,
• Epstein-Barr virus,
• smoking,
• Western diet, and
• the commensal microbiota,
influence the development of multiple sclerosis
Sclerosis cerebrospinalis multiplex disseminata

- immobility/spasticity
- anesthesia
- sight disorders
- incontinency
- cognitive dysfunction
- pain
- depression
Neuromyelitis optica Devic

chiasma opticum demyelination

spinal cord demyelination

control