Degenerative, Toxic, and Metabolic Disorders of the Central Nervous System

MHD – Neuroscience Module

Ewa Borys, MD
Assistant Professor, SSOM
Department of Pathology, LUHS

Objectives

• List the most common treatable causes of dementia
• For each of the following diseases, describe (as appropriate): etiology/pathogenesis of lesions, locations of lesions, clinical features and course of the disease, diagnostic tests, inheritance pattern and genetic mechanism, gross pathology, and microscopic pathology:
  – Alzheimer's disease
  – Pick's disease
  – Dementia with Lewy bodies
  – Huntington's disease
  – Parkinson's disease
  – Amyotrophic lateral sclerosis
  – Friedreich's ataxia
• Describe histopathologic hallmarks of metabolic encephalopathy
• Describe gross and microscopic CNS findings in ethanol toxicity

Outline

• Neurodegenerative disorders
  – Alzheimer's disease
  – Lewy body disease
  – Parkinson's disease
  – Frontotemporal dementia
  – Huntington's disease
  – Multiple system atrophy (MSA)
  – Amyotrophic Lateral Sclerosis (ALS)
  – Friedreich's ataxia
• Toxic disorders
  – Ethanol toxicity
  – Methanol toxicity
  – Carbon monoxide poisoning
• Metabolic disorders
  – Subacute combined degeneration
  – Central pontine myelinolysis
  – Metabolic encephalopathy
  – Wilson disease
Dementia

- Gradual decline in cognitive function
  - Memory deficits
  - Aphasia (inability to communicate)
  - Apraxia (difficulty to perform voluntary movements)
  - Agnosia (difficulty in visual and auditory recognition)
  - Loss of abstract thought
  - Behavioral/personality changes
- 5% of people >65, 20% >80
- Differential diagnosis (potentially treatable causes):
  - Stroke
  - Infections (CJD, syphilis, HIV)
  - Neoplasms
  - Drugs and toxins (barbiturates, alcohol, heavy metals)
  - Metabolic (hypothyroidism, liver failure)
  - Vitamin deficiencies (Thiamine, Niacin, Cobalamin)

Neurodegenerative Disorders

I. Diseases primarily affecting cerebral cortex
   A. Alzheimer’s disease
   B. Lewy body disease
   C. Frontotemporal dementias

II. Diseases of basal ganglia
   A. Idiopathic Parkinson’s disease
   B. Huntington’s disease

III. Diseases of cerebellum and spinal cord
   A. Multiple system atrophy
   B. Amyotrophic lateral sclerosis
   C. Spinal muscular atrophy
   D. Friedreich’s ataxia

I. Diseases primarily affecting cerebral cortex
I/A. Alzheimer’s Disease

- Most common cause of senile dementia over age of 65 years
  - Prevalence ~2.5 % of people over 65 years of age
- Familial (early-onset): 10% of cases
  - Autosomal dominant inheritance
- Sporadic (late-onset): 90% of cases
  - Etiology unknown (genetic? environmental?)
  - Major risk factor is age
  - Same neuropathology as familial form

Genetic background

- Early onset:
  - Amyloid precursor protein (APP) – Chromosome 21
    - Patients with Down syndrome (Trisomy 21) if they live into their 40's and 50's usually develop clinical and microscopic features of AD
    - Presenilin-1 (PSEN-1) – Chromosome 14
    - Presenilin-2 (PSEN-2) – Chromosome 1
- Late onset:
  - ApoE4 (Chr. 19) – increased risk
  - ApoE2 - protective

<table>
<thead>
<tr>
<th>Table 10-1: GENETICS OF ALZHEIMER DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constom</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>
Brain atrophy:
- Narrowing of gyri and widening of sulci throughout
- Decreased brain weight
- Average weight women 1200 grams
- Average weight men 1350 grams

Normal brain

Dilated ventricles (hydrocephalus ex vacuo)
Hippocampal atrophy (blue arrow)

AD PATHOLOGY

- **Amyloid PLAQUES**
  - Extracellular deposits of beta-amyloid protein
  - Cause neuronal injury through:
    - Disruption of cell signaling
    - Neuroinflammation
    - Other mechanisms ??

- **Neurofibrillary TANGLES**
  - Tau – microtubule associated protein inside the cell
  - Becomes insoluble and forms tangled aggregates when abnormally phosphorylated
  - Causes neuronal death through apoptosis
Amyloid precursor protein (APP) is a transmembrane protein that can undergo a series of proteolytic cleavage by secretase enzymes.

- Produced by proteolytic cleavage from amyloid precursor protein (APP)
- Major component of senile plaques
CEREBRAL AMYLOID ANGIOPATHY (CAA)
- Present in most AD cases (70-100%)
- Beta-amyloid deposition in walls of arterial vessels in subarachnoid space and superficial cortex
- Weakens the vessel wall and increases risk of hemorrhage

Disease progression
- Spread of plaques and tangles follows a predictable sequence:
  - Mesial temporal structures affected first - cortical involvement as the disease progresses
- Loss of short term memory first – motor skills and language – long term memory
- Many cognitively normal people over 60 have some degree of AD pathology
- Definitive diagnosis can only be made on tissue

I/B. Dementia with Lewy Bodies (Lewy Body Disease)
- Second most common type of neurodegenerative dementia
- Initially cognitive symptoms and visual hallucinations followed by symptoms of parkinsonisms (bradykinesia, rigidity, tremor etc.)
- Misfolded protein α-synuclein forms insoluble aggregates inside neurons forming Lewy body inclusions
Lewy Body Disease
- Lewy bodies are present diffusely in both cortex and brainstem (substantia nigra)
- Other neurodegenerative diseases with Lewy bodies (Alpha-synucleinopathies): Parkinson’s Disease and Multiple System Atrophy

I/C. Frontotemporal lobar degeneration (Frontotemporal dementia)
- 3rd most common neurodegenerative cause of dementia (after AD and dementia with Lewy bodies)
- Predominant degeneration of frontal and temporal lobes
- Clinical features:
  - Early changes in personality and behavior (disinhibition, irritability)
  - Language changes
  - Parkinsonism (in later stages)
- Other neurodegenerative disease may coexist (most commonly AD)

Frontotemporal lobar degeneration (FTLD)
- Various inclusions detected by immunohistochemistry:
  - Tau → FTLD-Tau (Tauopathy)
    - Pick’s disease
    - Progressive Supranuclear Palsy (PSP)
    - Corticobasal Degeneration (CBD)
  - TDP-43 (TAR DNA-binding protein 43) → FTLD-TDP
  - Ubiquitin → FTLD-UPS
Pick’s Disease

- Rare (only 1% of all dementia cases over 65 years of age)
- Tauopathy: Pick bodies - inclusions in neurons
- Patients present with
  - Behavioral abnormalities (dissimulation or stereotyping followed by apathy)
  - or Aphasia (reduces speech output, stuttering)

Severe ("knife-edge") atrophy of frontal and temporal lobes (sparing of the superior temporal gyrus)

... “Pick bodies” - globose neuronal cytoplasmic inclusions composed of 3-repeat tau in hippocampus and cortex
II. Diseases of the basal ganglia

II/A. Parkinson’s Disease (PD)
- Progressive movement disorder with onset between 50 and 80 years of age
- Usually sporadic
- Rare familial PD
  - $\alpha$–synuclein and parkin protein mutations
- Clinical definition:
  1. Fluctuating cognition
  2. Visual hallucinations
  3. Features of parkinsonism: resting tremor, rigidity, stooped posture, bradykinesia, shuffling gait, masked facies

Parkinson’s Disease
- Loss of dopaminergic neurons in substantia nigra pars compacta
- **Lewy bodies** — Intracellular inclusions composed of $\alpha$–synuclein
Atrophy and pallor of substantia nigra

Micro: loss of pigmented neurons with clusters of pigment-laden macrophages (extraneuronal pigment deposition) and gliosis (microglia)

II/B. Huntington’s Disease
- Autosomal dominant – abnormal expansion in CAG triplet repeat
- Gene for protein huntingtin on chromosome 4p
- Normal gene contains 10-35 CAG triplet repeats
- Number of CAG repeats (>35 abnormal) is inversely correlated with the age of onset
Huntington’s Disease

- **Anticipation phenomenon**: subsequent generations have more repeats and earlier disease onset

Symptoms

- Males and females between the ages of 20 to 50
- Loss of neurons in the striatum (caudate and putamen)
- Striatum controls movement through inhibitory outputs
- **Clinical features**:
  - Choreiform movements, psychiatric symptoms progressing to dementia and cachexia

Left: patient with HD - severe atrophy of caudate and putamen, discoloration of the grey matter
- “concave” caudate nucleus in severe cases
Right: normal

Left: patient with HD - severe atrophy of caudate and putamen, discoloration of the grey matter
- “concave” caudate nucleus in severe cases
Right: normal
Micro: marked astrocytic gliosis and loss of neurons in caudate and putamen

III. Diseases of cerebellum and spinal cord

III/A. Multiple system atrophy
- Neuronal degeneration in: substantia nigra, striatum, cerebellum, inferior olive
- Symptoms consist of variable combination of:
  - Motor symptoms (parkinsonism)
  - Autonomic dysfunction (orthostatic hypotension, urinary incontinence, erectile dysfunction)
  - Cerebellar ataxia
- MSA-P – parkinsonian symptoms predominate
- MSA-C – cerebellar symptoms predominate
- Pathology: glial cytoplasmic inclusions containing \( \alpha \)-synuclein (\( \alpha \)-synucleinopathy)
Coronal brain sections:
Atrophy of putamen which is flattened with dark discoloration
Also atrophy of: substantia nigra, cerebellum, pons and olivary nuclei

III/B. Amyotrophic Lateral Sclerosis (ALS)

- Affects both upper and lower motor neurons
- Motor neuron loss and cytoplasmic inclusions
  - Upper motor neuron symptoms:
    - Spasticity and increased tendon reflexes
  - Lower motor neuron symptoms:
    - Muscle weakness, atrophy and fasciculation
  - +/- bulbar signs such as slurred speech, difficulty swallowing
  - Symptoms are highly variable and can be subtle (e.g. loss of dexterity, changes in vocal clarity)
- 5-10% are familial with subset having mutations in the superoxide dismutase gene (SOD1) on chromosome 21
- Male:female - 2:1
- Onset in the middle to late age
- Death within 3-5 years in most cases (respiratory failure, dysphagia)

Ventral cord:
atrophy of the ventral roots of the spinal cord
Degeneration of corticospinal tracts
Atrophy of anterior nerve roots
(Luxol fast blue myelin stain)

Loss of anterior horn cells

Normal anterior horn cells

III/C. Friedreich’s Ataxia

Friedreich’s Ataxia

• Trinucleotide repeat GAA in frataxin gene on chromosome 9
  – Frataxin is essential for mitochondrial iron regulation
• Most common form of hereditary ataxia
• Autosomal recessive
• Degeneration of cerebellum \(\rightarrow\) ataxia
• Degeneration of spinal cord tracts \(\rightarrow\) loss of sense of vibration and proprioception, muscle weakness, loss of deep tendon reflexes
• + electrical conduction and structural anomalies of heart \(\rightarrow\) \(~50\%\) of deaths due to cardiac cause
Degeneration of posterior columns, spinocerebellar and corticospinal tracts; atrophy of dorsal roots. Spinal cord, Luxol fast blue myelin stain.

Neurodegenerative protein misfolding diseases - summary

- Tauopathies
  - AD
  - Pick’s disease
  - Some other FTLDs

- Synucleinopathies
  - Parkinson’s disease
  - Lewy body disease
  - Multiple systems atrophy

- TDP43-pathies
  - FTLD

- Poly-Q disorders
  - Huntington disease
  - Spinocerebellar ataxia
  - Friedreich ataxia

- Toxic and Metabolic Disorders
Ethanol toxicity

- Wernicke's encephalopathy (thiamine deficiency)
- Central pontine myelinolysis
- Cortical atrophy
- Atrophy of cerebellar vermis

Wernicke's encephalopathy

- Thiamine pyrophosphate is the active form of Thiamine (B1)
- B1 is involved in:
  - brain glucose metabolism
  - nerve conduction
  - membrane transport
- Chronic alcoholism causes:
  - increased thiamine utilization
  - reduced GI uptake (reduced expression of thiamine transporter-1)
  - impaired phosphorylation of thiamine into its active form
- Impaired brain glucose metabolism is a major effect

Wernicke's encephalopathy

- Triad of (almost never see all three):
  - oculomotor abnormalities (ophthalmoplegia, nystagmus) in ~60%
  - cerebellar dysfunction in ~50%
  - confusion in ~40%
- Treatment: high dose IV thiamine
- +/- Korsakoff psychosis (chronic phase):
  - Targets limbic system:
    - Anterograde amnesia
    - Retrograde amnesia
  - Loss of memory compensated by confabulation
Wernicke’s encephalopathy

Pathology:
- Small hemorrhages in mammillary bodies, thalamus and periaqueductal grey
- Mammillary bodies atrophy

Acute Wernicke’s encephalopathy: mammillary body of normal dimensions but with recent petechial hemorrhages

Chronic state: pale and rarefied mammillary body
Methanol toxicity

- Ingestion of improperly distilled alcohols or fuels
- Liver metabolism:
  - Methanol → formaldehyde → formic acid
  - Formate is a cytochrome oxidase inhibitor
- Symptoms:
  - Severe acidosis
  - Optic neuropathy (may lead to blindness)
  - Altered mental status
- Pathology:
  - Global hypoxic injury with white matter necrosis and hemorrhages
  - Hemorrhagic infarction of putamen

Carbon monoxide poisoning

- Binds to hemoglobin with more than 200 x affinity of oxygen → carboxyhemoglobin
  - Decreased O2 carrying capacity of Hb
  - Decreased release of O2 in tissues
  - CO binding to myoglobin causing cardiac ischemia
- Pathology:
  - Cerebral edema
  - White matter petechial hemorrhages
  - Hemorrhagic necrosis of globus pallidus
Acute CO poisoning

Bilateral necrosis of globus pallidus

Subacute Combined Degeneration

- Vitamin B12 (cobalamin) deficiency
- Physiologic function:
  - Red blood cell formation
  - Fatty acid metabolism (effects CNS myelination)
- Causes:
  - Pernicious anemia (autoantibodies against intrinsic factor)
  - Chronic gastritis
  - Gastrectomy
  - Malnutrition
- Symptoms:
  - Megaloblastic anemia
  - Neurologic symptoms: weakness, paresthesias of hands and feet → loss of sense of vibration → ataxia
  - Dementia, depression etc.

Subacute Combined Degeneration

Myelin loss in posterior and lateral columns
Spinal cord, LFB/PAS stain
Osmotic demyelination syndrome
(Central pontine myelinolysis and Extrapontine myelinolysis)

- Causes: **Rapid correction of chronic hyponatremia**
- CPM affects central region of the pons
- Extrapontine myelinolysis: cerebellum, basal ganglia, lateral geniculate body, grey/white junction
- Symptoms: rapid onset of extremity weakness, confusion, gaze palsy, hypotension
  - Locked-in syndrome

Central pontine myelinolysis

- Pons with central triangular region of myelin loss (Luxol fast blue myelin stain)

Metabolic encephalopathy

- Fluctuations in mental status in severe liver disease
  - Less often seen in renal failure
- Due to high blood ammonia levels
Hepatic encephalopathy

Alzheimer type II astrocytes: nuclear swelling and chromatin clearing

Wilson’s Disease

- “Hepatolenticular degeneration”: liver cirrhosis and cerebral degeneration
- Mutation in ATP7B gene – failure of copper secretion and elimination – copper deposition in extrahepatic tissues
- Clinical symptoms:
  - Keiser-Fleischer ring – Cu deposition in the limbus of the cornea
  - Neurological: Parkinsonian features (tremor, bradykinesia, rigidity)
  - Neuropsychological: abnormal behavior, personality changes, schizophrenia-like symptoms

Wilson’s Disease
<table>
<thead>
<tr>
<th>Disease</th>
<th>Lesions</th>
<th>Components</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Plaques</td>
<td>B-amyloid</td>
<td>Extracellular</td>
</tr>
<tr>
<td></td>
<td>Tangles</td>
<td>Tau</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Pick's disease</td>
<td>Pick bodies</td>
<td>Tau</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Lewy bodies</td>
<td>α-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Lewy bodies</td>
<td>α-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Neuronal and glial inclusions</td>
<td>TDP-43</td>
<td>Intracytoplasmic</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Glial inclusions</td>
<td>α-synuclein</td>
<td>Intracytoplasmic</td>
</tr>
</tbody>
</table>