IX. NEURODEGENERATIVE DISEASES

X. TOXIC AND ACQUIRED METABOLIC DISEASES

GOALS AND OBJECTIVES:

At the end of this learning activity participants should be able to:

- Provide examples of neurodegenerative diseases that primarily affect neurons in the cerebral cortex, basal ganglia, substantia nigra and basal ganglia, cerebellum and connected systems, or motor neurons and compare the typical clinical presentation of these diseases
- Discuss the gross and microscopic pathology of Alzheimer disease and Parkinson disease
- Discuss the gross and microscopic pathology associated with thiamin and vitamin B₁₂ deficiency (Wernicke-Korsakoff syndrome and subacute combined degeneration of the spinal cord)
- Discuss common neuropathologic consequences of chronic alcoholism

ABSTRACT

Neurodegenerative diseases are characterized by progressive dysfunction and death of neurons. In these diseases neuronal loss is selective, affecting one or more groups of neurons while leaving others intact. Diseases of known vascular, toxic, metabolic, infective, or autoimmune cause are excluded by convention. As the most common neurodegenerative diseases primarily affect the elderly, this group of diseases is becoming increasingly significant with the progressive aging of the population in industrialized societies. Toxic and acquired metabolic diseases are relatively common causes of neurologic illness and will also be reviewed here.

KEYWORDS: dementia, Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, Wernicke-Korsakoff syndrome, alcoholic cerebellar degeneration

IX. NEURODEGENERATIVE DISEASES

- Characterized by progressive dysfunction and death of neurons
- Diseases of known vascular, toxic, metabolic, infective, or autoimmune cause are excluded by convention
- Degeneration often affects specific systems implying some form of selective vulnerability
- Pathogenesis not well understood; interaction of genetic susceptibility factors, environmental factors and aging is thought to be important in most cases
- Abnormal protein accumulation in neurons is also a typical feature

DIFFERENT TYPES OF NEURODEGENERATIVE DISEASE

Cognitive disturbance (dementia)
A. Degeneration involving cerebral cortex. Dementia. (e.g. Alzheimer disease, Pick disease)

Movement disorders
A. Degeneration of motor neurons. Motor weakness. (e.g. amyotrophic lateral sclerosis, spinal muscular atrophy)
B. Degeneration involving the cerebellum and its connecting tracts (spinocerebellar degeneration). Cerebellar ataxia. (e.g. Friedreich ataxia, ataxia-telangiectasia)
C. Degeneration involving substantia nigra and basal ganglia. Extrapyramidal defects: akinetic and rigid. (e.g. Parkinson disease, progressive supranuclear palsy,)
D. Degeneration involving basal ganglia. Dysregulation of movement: hyperkinetic. (e.g. Huntington disease)
E. Multiple system atrophy. May manifest as C. (striatonigral degeneration), as B. (olivopontocerebellar atrophy), or as autonomic system dysfunction (Shy-Drager syndrome) or with overlapping symptoms of the above
IX/1. ALZHEIMER DISEASE

• Most common cause of dementia accounting for more than half of the cases (second most common cause: vascular disease)

• Dementia: Impairment of previously attained occupational or social functioning due to persistent impairment of memory associated with an impaired intellectual function in one or more of the following domains: language, visuospatial skills, emotion, personality, cognition in the presence of normal consciousness.

• Alzheimer disease: Progressive course over 5-10 years; patients become immobile and mute

• Three main groups, with different molecular genetic associations:
  - sporadic (commonest, ~90%): increased risk for Apo E4 carriers
  - familial: mutations of amyloid precursor protein (APP, chr. 21), presenilin-2 (APP processing protein on chr.1), presenilin-1 (APP processing protein on chr.14)
  - associated with Down syndrome: trisomy 21

• Risk factors: aging, head trauma, menopause, low educational level

• Protective factors: anti-inflammatory and antioxidant drugs, estrogen, high educational level

GROSS AND MICROSCOPIC PATHOLOGY OF ALZHEIMER DISEASE

• Gross: Cortical atrophy involving primarily the frontal, temporal, parietal lobes and the hippocampus; dilatation of the lateral ventricles

• Key microscopic findings:
  - neuronal loss and gliosis
  - neuritic plaques
  - neurofibrillary tangles

• Plaques and tangles can also be seen in the absence of dementia. The diagnosis of Alzheimer disease is based on neuritic plaque numbers significantly increased for age and clinical history of dementia
IX/2. IDIOPATHIC PARKINSON DISEASE

- Parkinsonism: rigidity, bradykinesia, resting tremor (think of the Pope)
- Most common cause: Idiopathic Parkinson’s disease (IPD)
- Other causes include vascular disease damaging the substantia nigra, drug-induced parkinsonism, progressive supranuclear palsy, others
- Typical onset of IPD: 5\textsuperscript{th}-7\textsuperscript{th} decades
- Sporadic worldwide incidence of 1/100 people over age 50 years
- IPD is inherited in some families as an autosomal dominant trait
- Environmental agents: there is similarity between IPD and the disorder produced by MTPT (a byproduct of illicit production of meperidine analogues)

PATHOLOGY OF PARKINSON DISEASE

Gross: pallor (depigmentation) of the substantia nigra and the locus ceruleus

Microscopic changes in the substantia nigra and locus ceruleus:
- Neuron loss
- Pigment (neuromelanin)-laden macrophages
- Gliosis
- Lewy bodies in neurons

Lewy bodies: appear to be involved in the removal of damaged cytoskeletal proteins; contain cytoskeletal proteins and proteins involved in their metabolism: alpha synuclein, ubiquitin, etc.

IX/3. HUNTINGTON DISEASE

- Neurodegenerative disease involving primarily the basal ganglia: the caudate and usually to a lesser extent the putamen are involved
- Presents around 40 years of age with dysregulation of movement. Chorea: non-rhythmic rapid involuntary movements
- Inherited with autosomal dominant pattern; complete penetrance
- Molecular genetics: increased number of trinucleotide CAG repeats in huntingtin gene on chr.4.
- Pathology: striking atrophy of the caudate, neuronal loss
IX/4. AMYOTROPHIC LATERAL SCLEROSIS

- Degenerative disease of motor neurons (in anterior horn of spinal cord, brainstem, and upper motor neurons in cerebral cortex)
- Progressive weakness and wasting of extremities; eventually impairment of the respiratory muscles
- Frequency of the disease peaks during the 5th decade
- 5% familial, autosomal dominant pattern; gene: e.g. superoxide dismutase
- Pathology: loss of large motor neurons, loss of myelinated fibers in the lateral corticospinal tracts, atrophic anterior nerve roots, shrunken atrophic muscles

IX/5. FRIEDREICH ATAXIA

- Example for degenerative disease involving the cerebellum and its connecting tracts (spinocerebellar degenerations)
- Ataxia: shaky movements and unsteady gait due to the brain’s failure to regulate posture, and strength and direction of limb movement
- Autosomal recessive progressive illness, generally beginning in the first decade of life
- Neuronal degeneration: dentate nucleus, Purkinje cells in cerebellum, dorsal root ganglion cells, spinal cord (Clarke column), brain stem, motor cortex
- Loss of axons and gliosis in the spinal cord (posterior columns, spinocerebellar and corticospinal tracts
- Symptoms: gait ataxia, hand clumsiness, dysarthria, also cardiac arrhythmias, congestive heart failure, death within about 5 years
- Trinucleotide repeat expansion on chr. 9 (frataxin gene)

IX/6. MULTIPLE SYSTEM ATROPHY

- Group of disorders characterized by glial cytoplasmic inclusions, typically in oligodendrocytes
- Inclusions can be demonstrated by silver stains and by immunostaining for tau, ubiquitin or alphaB-crystallin

Manifest between the fourth and sixth decades as:
- striatonigral degeneration – symptoms of parkinsonism
- olivopontocerebellar atrophy – cerebellar ataxia
- Shy-Drager syndrome - autonomic system dysfunction
- or with overlapping symptoms of the above
MULTISYSTEM ATROPHY – CONT.

- Striatonigral degeneration: degeneration of the caudate and putamen with neuronal loss and gliosis, loss of pigmented neurons in the substantia nigra – symptoms of parkinsonism

- Olivopontocerebellar atrophy: atrophy of the cerebellum and basis pontis, inferior olives in the medulla – cerebellar ataxia

- Shy–Drager syndrome: degeneration of the intermediolateral column of the spinal cord – orthostatic hypotension, impotence, disturbances in sweat gland secretion, pupillary abnormalities

X. TOXIC AND ACQUIRED METABOLIC DISEASES

- Relatively common causes of neurologic illness.
  - Vitamin deficiencies: thiamine, B₁₂
  - Metabolic disturbances: hypoglycemia, hepatic encephalopathy
  - Toxic disorders: carbon monoxide, ethanol

THIAMINE (VITAMINE B₁) DEFICIENCY

- Common in the setting of chronic alcoholism
- May also affect patients with gastric disorders including carcinoma, chronic gastritis, persistent vomiting

May cause cardiovascular syndrome (wet beriberi) and neurological consequences:

A. Peripheral neuropathy (polyneuropathy) first affecting legs extending to arms with footdrop, wristdrop, areflexia

B. Wernicke-Korsakoff syndrome
  - Wernicke encephalopathy: ophthalmoplegia, nystagmus, ataxia, confusion
  - Korsakoff syndrome: memory disturbances, confabulation (invention of fictitious detail about events supposed to have occurred in the past)
Neuropathology IV
Neurodegenerative Diseases; Toxic and Acquired Metabolic Diseases

VITAMINE B\textsubscript{12} DEFICIENCY

- May occur in the setting of chronic atrophic gastritis, after gastrectomy and ileal resection, tapeworm infestation, strict vegetarianism
- Neurologic symptoms (may occur in association with pernicious anemia or in the absence of hematologic abnormalities): slight ataxia, numbness and tingling of lower extremities, may rapidly progress to spastic weakness of lower extremities, complete paraplegia
- Vitamin replacement leads to clinical improvement but with complete paraplegia recovery is poor
- Pathology: swelling of myelin layers producing vacuoles that begin segmentally at the midthoracic level of the cord. Later, axons of the ascending posterior columns and descending pyramidal tracts degenerate = subacute combined degeneration of the spinal cord

METABOLIC DISTURBANCES: HYPOGLYCEMIA

- Causes of hypoglycemia: excess of exogenous insulin, islet cell adenoma, severe liver disease, adrenal insufficiency
- Patients present with headache, confusion, irritability, and lethargy, leading to stupor, and coma
- The brain requires glucose and oxygen for energy production – effects of hypoglycemia are similar, but not identical to oxygen deprivation
- Typically, there is selective injury to large pyramidal neurons in layers III and V of the cerebral cortex, CA1 field of the hippocampus. Cerebellar Purkinje cells are also vulnerable but are relatively less sensitive to hypoglycemia
- Severe, persistent hypoglycemia: widespread CNS injury

METABOLIC DISTURBANCES: HEPATIC ENCEPHALOPATHY

- Hepatic encephalopathy can be a complication of severe liver disease or chronic portocaval shunting
- Symptoms: confusion, asterixis (flapping tremor of the outstretched hands), musty breath odor, stupor, coma
- Pathology: Alzheimer type II astrocytes in the deep layers of the cerebral cortex, basal ganglia and other subcortical gray matter regions
- These have enlarged vesicular nucleus with marginated chromatin and scanty cytoplasm
- Pathogenesis: hyperammonemia
TOXIC DISORDERS: CARBON MONOXIDE

- Many of the pathologic findings that follow acute carbon monoxide exposure are those of hypoxia.
- Selective injury to large pyramidal neurons in layers III and V of the cerebral cortex, CA1 field of the hippocampus, cerebellar Purkinje cells.
- Bilateral necrosis of the globus pallidus may also occur and is more common in carbon monoxide-induced hypoxia than in hypoxia from other causes.

TOXIC DISORDERS: ETHANOL

- The “toxic” CNS effects of chronic alcoholism may be either direct effects of ethanol or secondary nutritional effects (e.g. thiamine deficiency).
- Direct CNS effects: cerebral atrophy and cerebellar degeneration.
- Cerebellar degeneration: atrophy and loss of granule cells predominantly in the anterior superior part of the vermis.
- Cerebellar dysfunction occurs in about 1% of chronic alcoholics: truncal ataxia, unsteady gait, nystagmus.