Objectives

- Recognize and describe the pathology of common degenerative diseases of the CNS: Alzheimer's disease, Parkinson's disease, Pick disease, Huntington's disease, amyotrophic lateral sclerosis, acquired metabolic disorders, inherited metabolic disorders.
- Chapter 5 Genetic Disorders pages 150-155
- Explain the pathophysiology of common degenerative disorders of the CNS
Ronald Reagan (In case you were unaware).
ALZHEIMER DISEASE

- Most common cause of dementia in the elderly.
- Affects over 5 million Americans with an estimated annual cost of $172 billion.
- 2:1 Female predominance.
- Duration 5 - 20 years.

More likely with late onset

More likely with early onset

Includes lost productivity of affected individuals and family members who care for patient.
UNCOMMON BUT TREATABLE CAUSES OF DEMENTIA

- Thyroid deficiency
- B12 deficiency
- Drug reaction
- Depression
- Central nervous system neoplasm
- Subdural hematoma
- Cardiovascular disease

Rule these out before diagnosing with Alzheimer Disease

Can be evaluated with blood test

Situational Depression is very common. If the depression is identified and treated early on, the patient can recover memory deficits. If depression is left in place for long period of time, treatment will not cause reversal of memory loss.

Elderly- are more likely to fall and also have normal shrinkage of brain, so more at risk. Especially if on anticoagulants.
RISK FACTORS FOR AD

- Family history
- Head trauma
- Hematologic malignancies
- Down’s syndrome
- Apolipoprotein E allele ε4

- Any time during life
- Reason not clear
- Beta amyloid precursor protein is encoded on Chromosome 21. Results in inevitable Alzheimer's Disease development
- Biggest risk factor. Lowers age of onset
GENES LINKED TO AD

Chr 1    PS-2    auto dom    40-70 yrs    2-3%
Chr 14   PS-1    auto dom    30-60 yrs    5-10%
Chr 21   βAPP    auto dom    45-65 yrs    <1%
Chr 19   ApoE4   susceptibility  > 60 yrs    40-50%
Chr 12   two susceptibility genes?  > 50 yrs
Chr 6    HLA-A2  male susceptibility gene?
Chr 10   susceptibility  > 60 yrs

TOMM40 also discovered on Chromosome 19, but contribution is unclear

A few months ago published paper identified 4 new genetic risk factors (not included here).
NORMAL

ALZHEIMER DISEASE

SHRINKAGE of brain!
(Always)
NORMAL

ALZHEIMER DISEASE

Marked ventricular dilation
ALZHEIMER DISEASE NEUROPATHOLOGY

- Cortical atrophy and synapse loss
- Neuritic plaques
- Neurofibrillary tangles
- Amyloid angiopathy
- Granulovacuolar degeneration
- Hirano bodies

- Cross-linked microtubule-associated protein fills up neuronal cell body.
- Protein deposit in blood vessels. Occurs more often in people with APO e4 allele.
- Cytopathological change in Purkinje Neurons in the hippocampus.
- Extracellular deposits of actin also seen in hippocampal formation.
Neuritic Plaques
Neurofibrillary Tangles
Silver stain

Extracellular deposits of amyloid, Tau and other inflammatory mediators

Intraneuronal: cross-linked microtubule-associated proteins (Looks like a cell body)
Hirano Body and Granulovacular degeneration

Eosinophilic extracellular deposits of actin

Granules with "halos" that occur in the cytoplasm of Purkinje neurons in the hippocampus
AMYLOID ANGIOPATHY
Congo Red stain viewed under polarized light

Amyloid: any protein with B-pleated sheet structure.
AUTOPSY FINDINGS

PROBABLE ALZHEIMER DISEASE

AD alone 60%
Dementia with Lewy Bodies 20%
AD + Vascular 10%
Vascular alone 5%
Frontotemporal dementia (Pick’s) 5%
Other <1%

Alzheimer Disease is a diagnosis that can only be confirmed at autopsy

"Alzheimer's + Parkinson's"

Severe cerebrovascular atherosclerosis or strategic infarcts (e.g. PCA territory or dorsal medial nucleus of thalamus)

We'll talk about this in more detail later. Mutations in Microtubule associated protein (Tau)
The most common cause of senile dementia is

A. Adverse drug reaction
B. Normal aging
C. Depression
D. Alzheimer Disease
E. Hardening of the arteries

Question: Of the pathological finding for Alzheimer's, the diagnosis is done on autopsy. What is the criteria for diagnosis?
Low probability: Low amount of plaques and tangles in person with dementia
Med Probability: Med plaques and tangles in person with dementia
High probability: Significant plaques and tangles in person with dementia.
“Involuntary tremulous motion, with lessened muscular power in parts not in action and even when supported; with a propensity to bend the trunk forwards and to pass from a walking to a running pace: the senses and intellect being uninjured.”

*Essay on the shaking palsy*  Parkinson 1817
Trunk bent forward

Impairment of arm and leg motion.
PARKINSON DISEASE

- Age of onset is generally after 60.
  - Early onset cases occur, especially in families.
- More common in males
- Affects 0.5 million Americans with an estimated annual cost of $5.6 billion.
- Extrapyramidal motor symptoms: Rigidity, Tremor, Bradykinesia
- 20% of patients develop dementia.
- Duration 5 - 15 years.

Because of treatment with L-DOPA, patients live longer, but then they develop dementia.
PARKINSON DISEASE

- Defect is due to loss of dopaminergic neurons in the substantia nigra and brainstem.
- 75% of cases have **Lewy bodies** histopathologically.
- Postencephalitic Parkinsonism is characterized by **neurofibrillary tangles**.
- Rarely PD is caused by the **neurotoxin MPTP** (methyl phenyl tretrahydro pyridine) Synthetic opioid contaminant 1976
- Treatment is with L-Dopa and similar drugs.

We don't see this any more. (Caused by flu pandemic of early 1900s)

Useful in development of animal models
Substantia Nigra is **Brown!** Neuromelanin (precursor of dopamine) normally secreted by these cells is lost.
LEWY BODIES

Lewy Bodies:
Intracytoplasmic, eosinophilic inclusions with a halo

Typically see in cytoplasm of pigmented neurons in substantia nigra
PICK’S DISEASE
FRONTOTEMPORAL DEMENTIA

- Clinical presentation is similar to AD.
- Slightly earlier onset.
- Frontal and temporal lobe signs.
- Behavioral abnormalities.
- Extrapyramidal symptoms.
- Some cases are due to mutations in microtubule associated protein (tau) on Chr 17.
Tau-positive cytoplasmic inclusions that occur in the neurons. "Pencil erasers"

For comparison: Neurofibrillary tangles in AD follow structure of neuron
George Huntington

Neurologist who described Huntington's disease
HUNTINGTON DISEASE

- Age of onset is 35-45 years.
- There are personality changes, chorea and dementia.
- Duration is approximately 15 years.
- Inherited in an autosomal dominant fashion.
- “huntingtin” gene on chr 4

Telomere region!
HUNTINGTON  NORMAL

- Global atrophy
- Caudate nucleus is flattened
- Atrophy of Putamen and Globus Pallidus to lesser degree
NORMAL

- Internal Capsule
- Caudate Nucleus
- Putamen
- Globus Pallidus

HUNTINGTON

- Internal capsule is about the same
- Amygdala is the same
- Can hardly see Caudate Nucleus
AMYOTROPHIC LATERAL SCLEROSIS

- Age of onset is in mid to late life.
- Male predominance.
- Duration 3 - 5 years
- Symptoms are caused by degeneration of corticospinal tract.
- Familial cases may be due to superoxide dismutase gene mutation on chr 21.

Pathology is the same for sporadic vs genetic

Very rapid progression

10% of cases
AMYOTROPHIC LATERAL SCLEROSIS MOTOR CORTEX

Spongy appearance

Loss of pyramidal neurons
NORMAL

ALS

Descending Corticospinal Tract

Pyramid w Descending corticospinal tract

Myelin = blue w stain

Myelin lost. Atrophy of pyramidal tract

Inferior Olivary Nucleus
ALS BUNINA BODY

Lower motor neuron of spinal cord and cranial nerve

Eosinophilic "dumbbell-like" inclusion body
INHERITED METABOLIC DISORDERS

GANGLIOSIDE

GM1 Gangliosidoses
  Variant O  - Galactosidase isoenzymes A, B, C
  Variant A  - β-Galactosidase isoenzymes B, C

GM2 Gangliosidoses
  Variant B  - Hexosaminidase A (Tay Sachs)
  Variant O  - Hexosaminidases A and B

Deficiencies:

Most common of the Ganglioside disorders!

More severe
6 mo old Baby with Tay Sachs

Enlarged head.
"Frontal Bossing"
TAY SACHS DISEASE

- GM2 gangliosidosis
- Hexosaminidase A
- Motor and mental deterioration beginning at 6 months
- "Amaurotic familial idiocy"

Inherited
Blind
Failed development

Born normal
Old literature
Side Note: If you want to see this, you'll have to go into pediatric neuro.

TAY SACHS

CHERRY RED SPOT

Fovea

Ganglioside accumulates in Retinal neurons: Retina becomes pale. Fovea then appears as red spot because no retinal ganglia cells are present there.
TAY SACHS STORAGE PRODUCT

Multilamellar profiles in the cytoplasm of neurons (electron micrograph)
INHERITED METABOLIC DISORDERS

SPHINGOMYELIN

Sphingomyelinase <--Loss of this

Niemann-Pick disease Type A, B, C
Bunina Bodies are found in the neurons of patients with which disease?

A. Alzheimer Disease  
B. Huntington Disease  
C. Tay Sachs Disease  
D. Amyotrophic Lateral Sclerosis  
E. Parkinson Disease
NIEMANN-PICK DISEASE

- Sphingomyelinase deficiency
- Genetically and biochemically heterogeneous
- Type A - infantile
- Type B - juvenile, no CNS involvement
- Type C - juvenile, CNS involvement, may present in adulthood
NIEMANN-PICK DISEASE

Oligolamellar profile rather than multilamellar seen in Tay Sachs
INHERITED METABOLIC DISORDERS

CEREBROSIDE

Glucosylceramide lipidosis (Gaucher’s disease)
Glucocerebroside $\beta$-glucosidase

Galactosylceramide lipidosis (Krabbe’s Disease)
Galactocerebroside $\beta$-galactosidase

deficiency in
KRABBE’S LEUCODYSTROPHY

- Galactosylceramide lipidoses
- Onset 6 months with rigidity, diminished alertness, blindness, deafness
- Fatal within one year

Stem Cell transplant is being attempted at Duke with reasonable success
KRABBE’S LEUCODYSTROPHY

"Leuco" = "White" so pathology is in white matter

Question: Why is white matter affected, not gray matter? Genetic defect in enzyme important in metabolizing myelin as opposed to an intraneuronal lipid.
KRABBE’S LEUCODYSTROPHY

Perivascular Giant Cells: Engulfing the abnormal lipid, recycling into blood stream
INHERITED METABOLIC DISORDERS

SULFATIDE

Metachromatic leucodystrophy
  Arylsulfatase A
Multiple sulfatase deficiency
  Arylsulfatases A,B,C
METACHROMATIC LEUCODYSTROPHY

- Onset 1 - 4 years
- Rare adult forms
- Motor and mental deterioration
- Peripheral neuropathy
METACHROMATIC LEUCODYSTROPHY

Cerebral cortex is normal

Corpus Callosum (mostly white matter) is very atrophic

This is an adult who developed dementia at age 35. No family history. Example of rare adult-onset
METACHROMATIC LEUCODYSTROPHY

Characteristic inclusions in astrocytes and oligodendroglia in white matter.
Which of the following diseases is a leucodystrophy?

A. Tay Sachs Disease  
B. Amyotrophic Lateral Sclerosis  
C. Krabbe’s disease  
D. Huntington’s disease  
D. Leukemia
INHERITED METABOLIC DISEASES AFFECTING THE CNS

- Hepatolenticular Degeneration
  - Wilson disease
  - Abnormal copper transport
  - Decreased ceruloplasmin
  - Autosomal recessive

- Phenylketonuria

Answer: C Krabbe's Disease

Liver → Globus pallidus (lenticular nuclei)

Protein carrying Copper around in blood

Largely eliminated because infants are tested and given a special diet.
HEPATOLENTICULAR DEGENERATION (Wilson’s Disease)

- Copper deposit
- Discoloration of the Caudate and Putamen, Globus Pallidus
VITAMIN DEFICIENCIES AFFECTING THE CNS

- Thiamine deficiency caused by alcohol abuse or chemotherapy.
  - Wernicke encephalopathy – psychotic symptoms and ophthalmoplegia
  - Korsakoff syndrome – memory disturbance and confabulation
    - Hemorrhage and necrosis in the mamillary bodies and periventricular regions
WERNICKE’S ENCEPHALOPATHY

Hemorrhages in mamillary bodies
VITAMIN DEFICIENCIES AFFECTING THE CNS

- Vitamin $B_{12}$ deficiency - gastric resection, pernicious anemia.
  - Ataxia, numbness and tingling in the lower extremities
    - Subacute combined degeneration of the spinal cord

After this happens, it is not reversible.
SUBACUTE COMBINED DEGENERATION

Pallor in the ascending sensory columns
ACQUIRED METABOLIC DISEASES AFFECTING THE CNS

- Cretinism
- Thyroid deficiency
- Kernicterus
  - Hyperbilirubinemia in the neonatal period

Common in some areas of China. Access to sea have enough iodine, but in internal regions they don’t.
This diagram shows where bilirubin accumulates and how it causes damage: Substantia nigra, Globus Pallidus, Hippocampus
KERNICTERUS

Billirubin deposit and destruction of substantia nigra

Patient had ABO incompatibility and jaundice at birth.
ETHANOL

Profound cortical atrophy and dementia with alcohol abuse
SUPERIOR CEREBELLAR ATROPHY

Atrophy causes Ataxic gait

Inferior is fine

Dilantin can also do this. Anti-seizure drug
All the conditions we covered in this lecture!

ALZHEIMER DISEASE
PARKINSON DISEASE
PICK DISEASE
HUNTINGTON DISEASE
AMYOTROPHIC LATERAL SCLEROSIS
INHERITED METABOLIC DISORDERS
TAY SACHS
NEIMANN-PICK
KRABBE’S LECUODYSTROPHY
METACHROMATIC LECUODYSTROPHY
HEPATOLENTICULAR DEGENERATION
ACQUIRED METABOLIC DISORDERS
KERNICTERUS
SUBACUTE COMBINED DEGENERATION
ALCOHOL