CENTRAL NERVOUS SYSTEM DEGENERATIVE AND METABOLIC DISORDERS

APPROVED

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Objectives

Alzheimer's is THE most common neurological disease.

- 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

This is updated to be correct for this year's edition of Robbins

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.

Includes lost productivity of affected individuals and family members who care for patient.

More likely with late onset

More likely with early onset

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

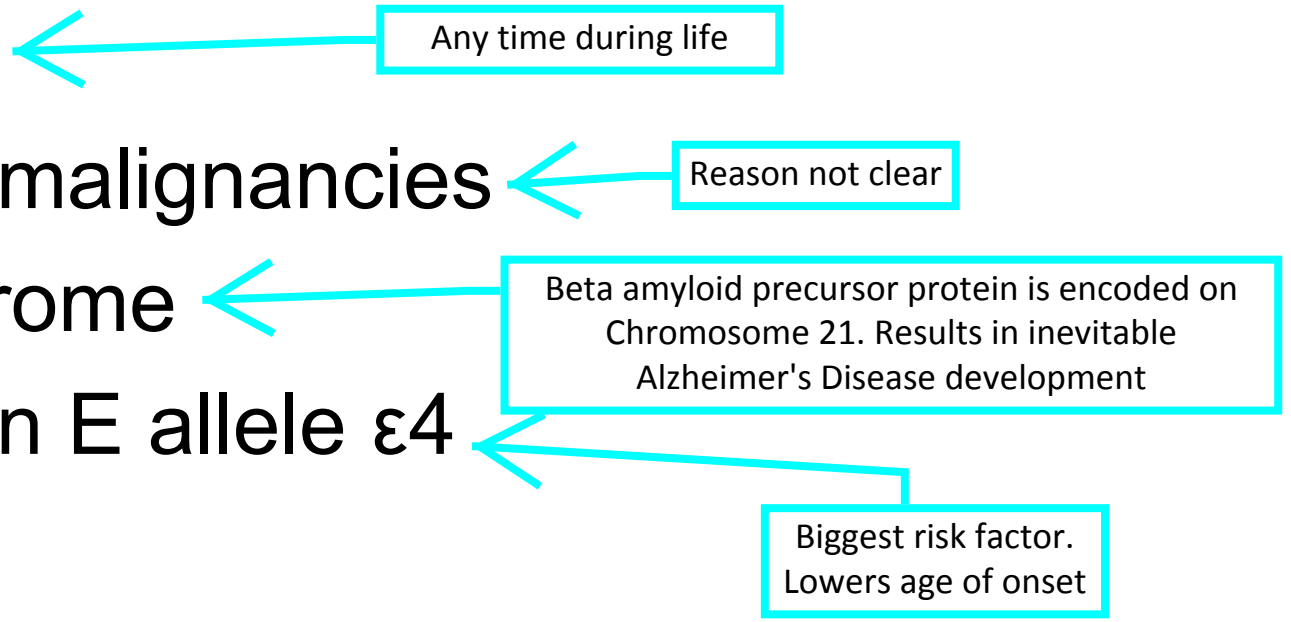
Can be evaluated with blood test

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



She read through this whole slide.

GENES LINKED TO AD

discovered first

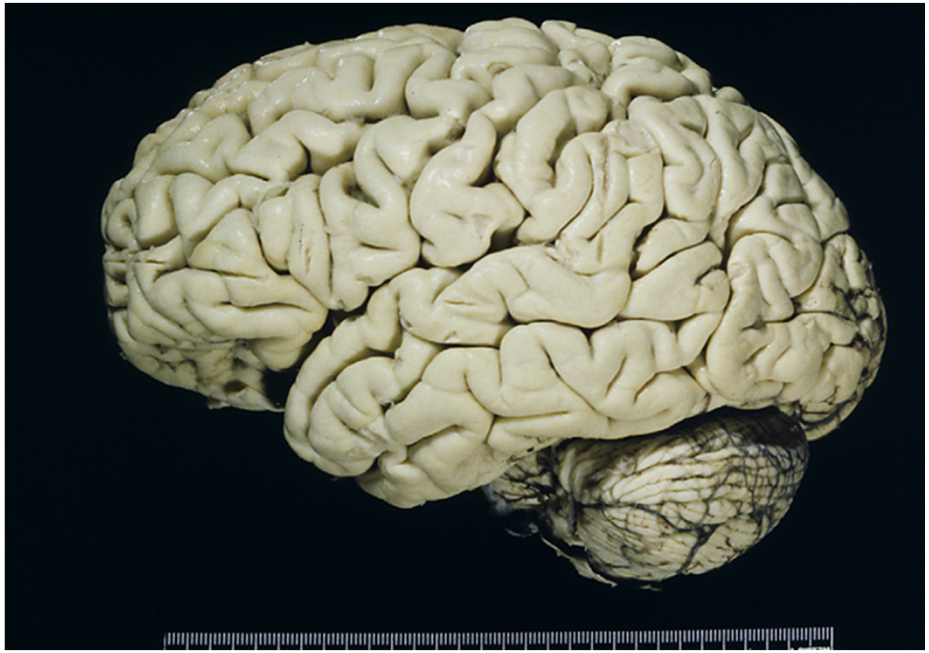
Chr 1	PS-2	auto dom	40-70 yrs	2-3%
Chr 14	PS-1	auto dom	30-60 yrs	5-10%
Chr 21	βAPP	auto dom	45-65 yrs	<1%
Chr 19	ApoE4	susceptibility	> 60 yrs	40-50%
Chr 12	two	susceptibility genes?	> 50 yrs	
Chr 6	HLA-A2	male susceptibility gene?		
Chr 10		susceptibility	> 60 yrs	

early onset

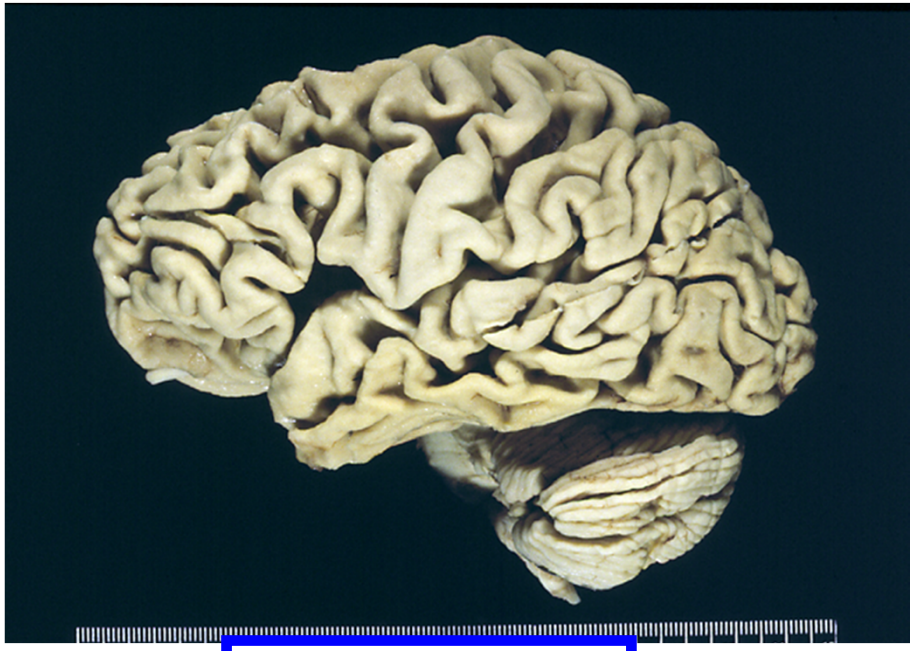
TOMM40 also discovered on Chromosome 19, but contribution is unclear

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

NORMAL

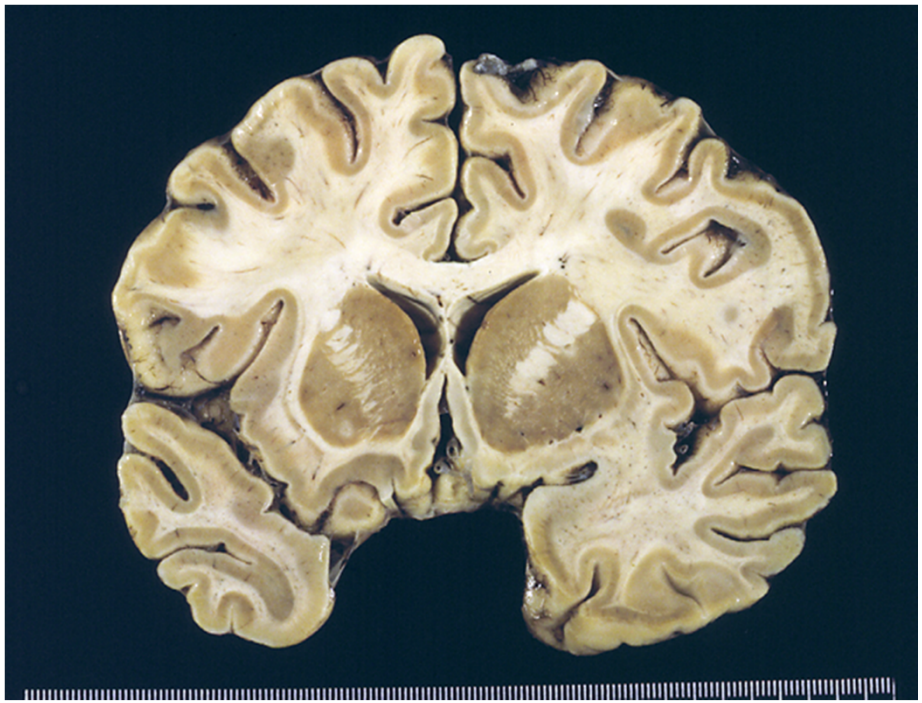


ALZHEIMER DISEASE

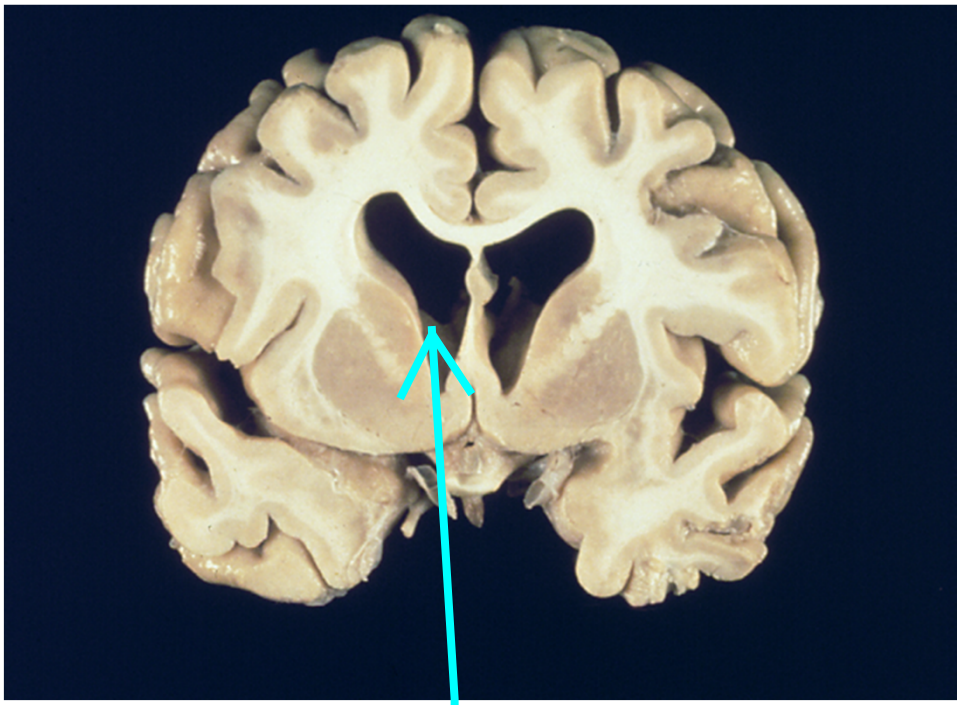


SHRINKAGE of brain!
(Always)

NORMAL



ALZHEIMER DISEASE



ALZHEIMER DISEASE NEUROPATHOLOGY

- Cortical atrophy and synapse loss
- Neuritic plaques
- Neurofibrillary tangles

Cross-linked microtubule-associated protein fills up neuronal cell body.

- Amyloid angiopathy

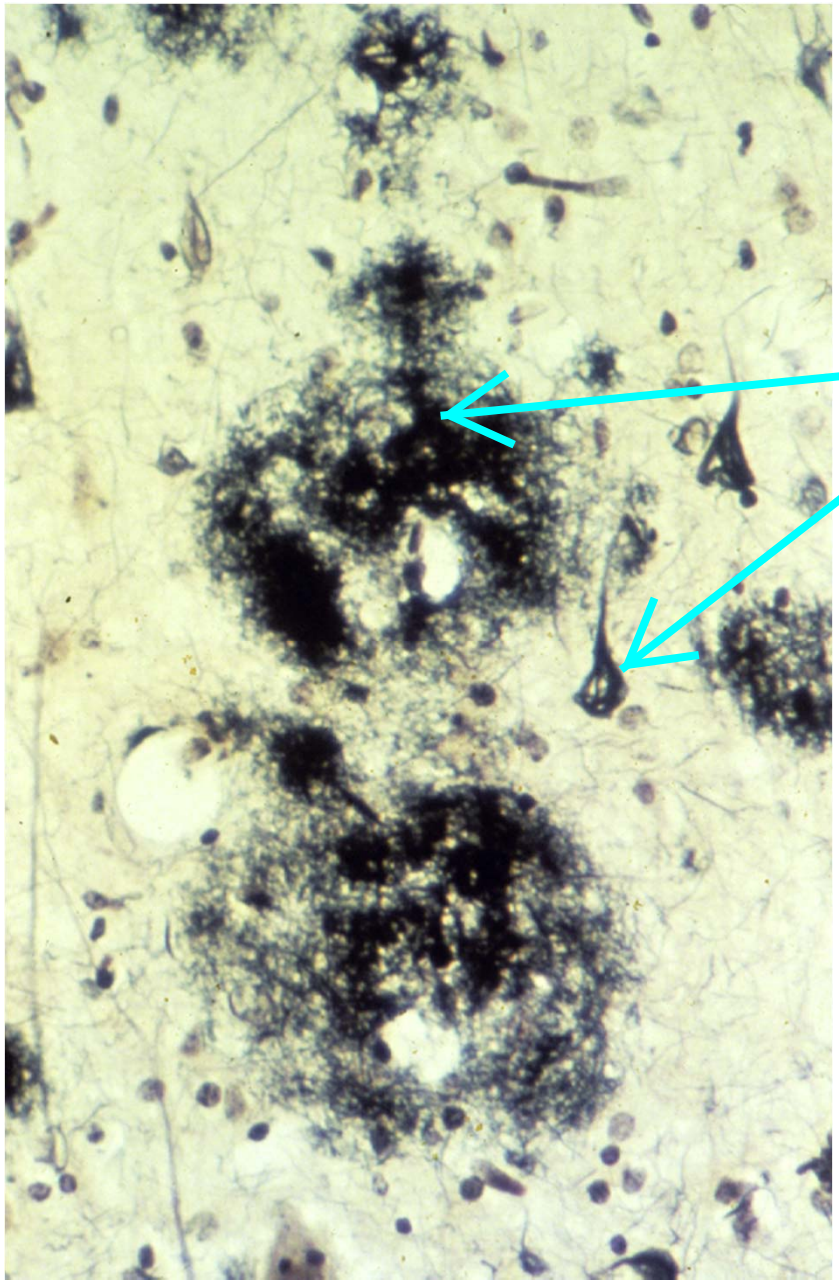
Protein deposit in blood vessels. Occurs more often in people with **APO e4 allele**

- Granulovacuolar degeneration

Cytopathological change in Purkinje Neurons in the hippocampus

- Hirano bodies

Extracellular deposits of actin also seen in hippocampal formation.



Extracellular deposits of amyloid, Tau and other inflammatory mediators

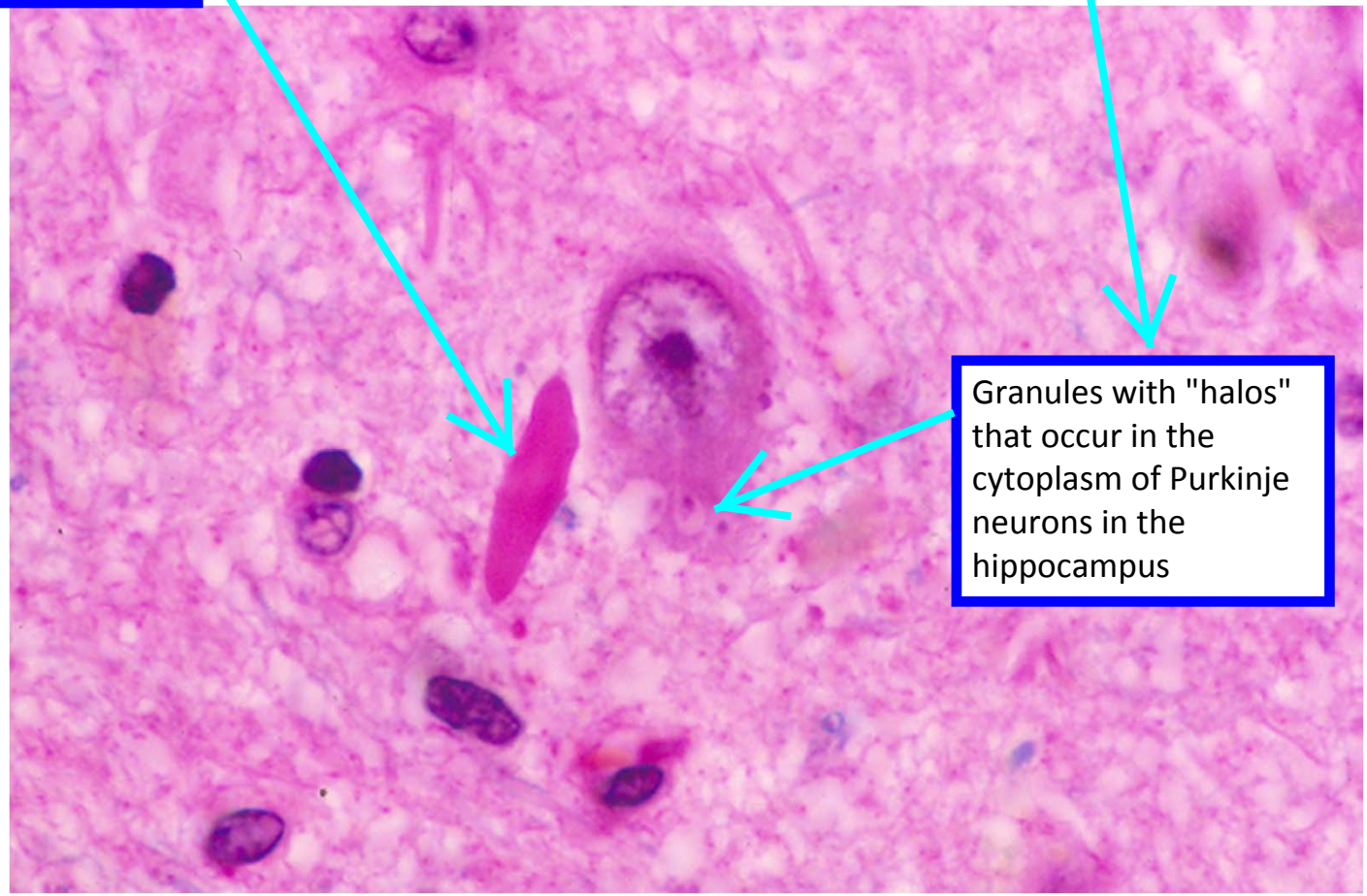
Neuritic Plaques

Neurofibrillary Tangles

Silver stain

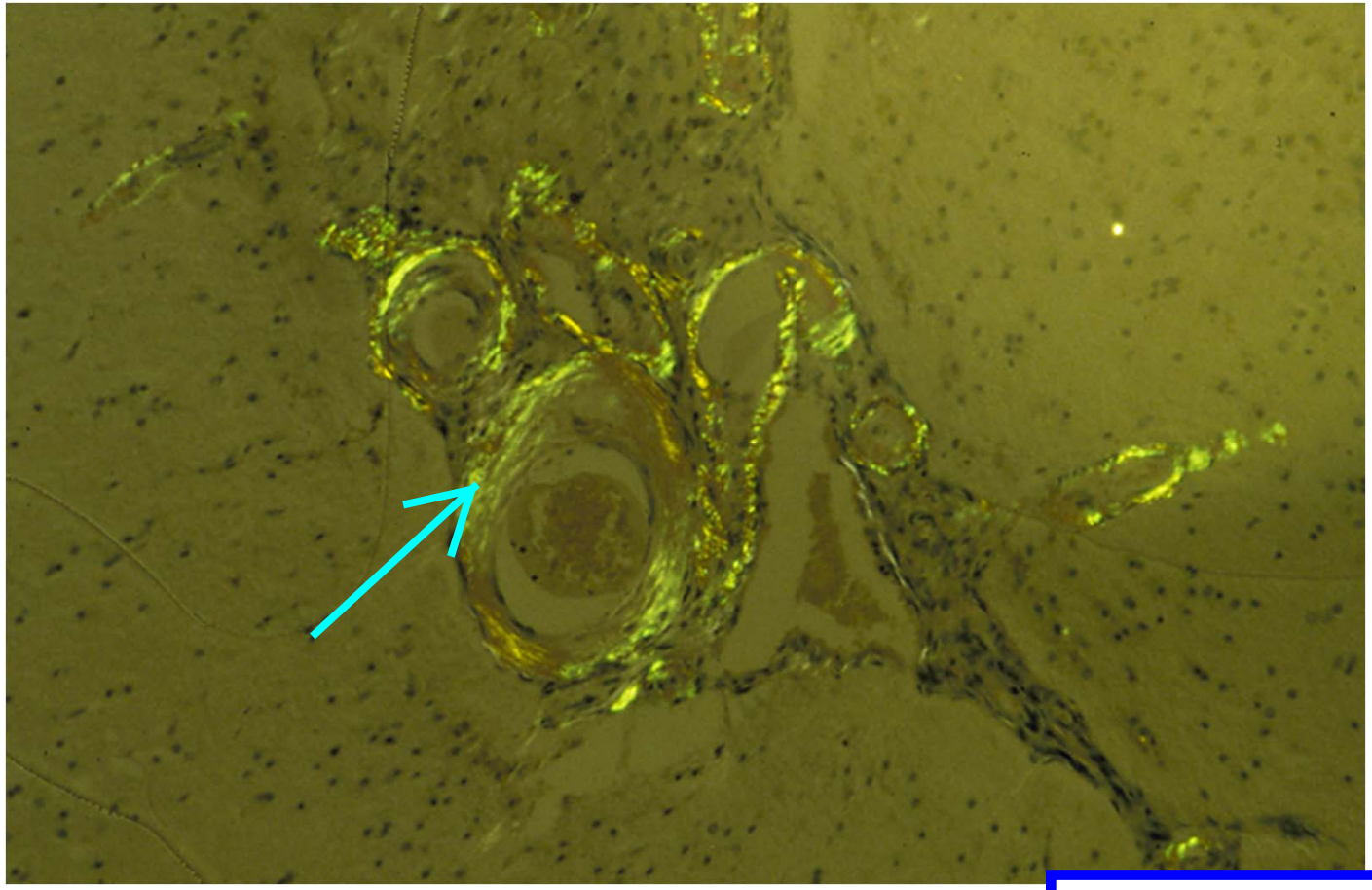
Intraneuronal: cross-linked microtubule-associated proteins (Looks like a cell body)

Hirano Body and Granulovacular degeneration



AMYLOID ANGIOPATHY

Congo Red stain viewed under polarized light



Amyloid: any protein with B-pleated sheet structure.

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

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'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

Answer on next page

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.

Answer: D
Alzheimer Disease

All are contributing factors!

"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.

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

- Rarely PD is caused by the neurotoxin MPTP

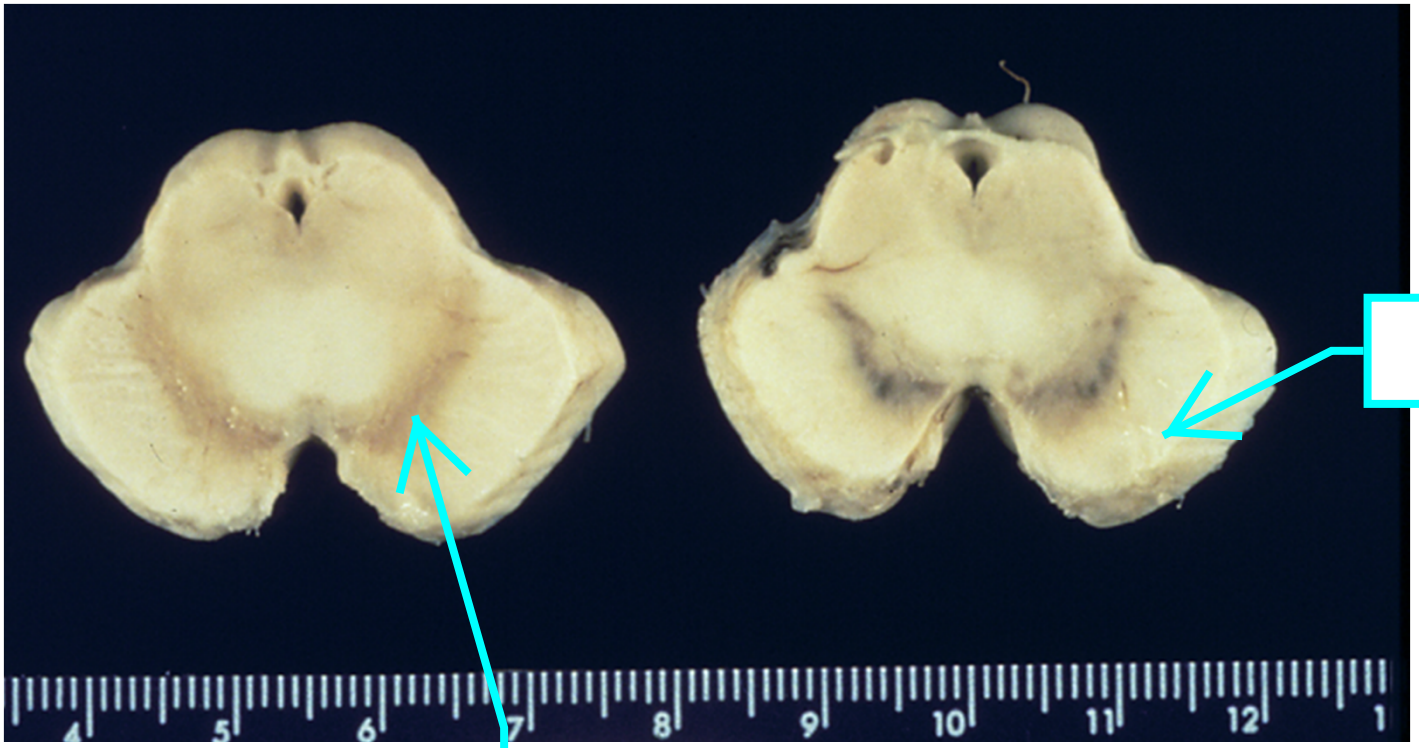
  (methyl phenyl tretrahydro pyridine) Synthetic opioid contaminant 1976

- Treatment is with L-Dopa and similar drugs.

Useful in development of animal models

PARKINSON NORMAL

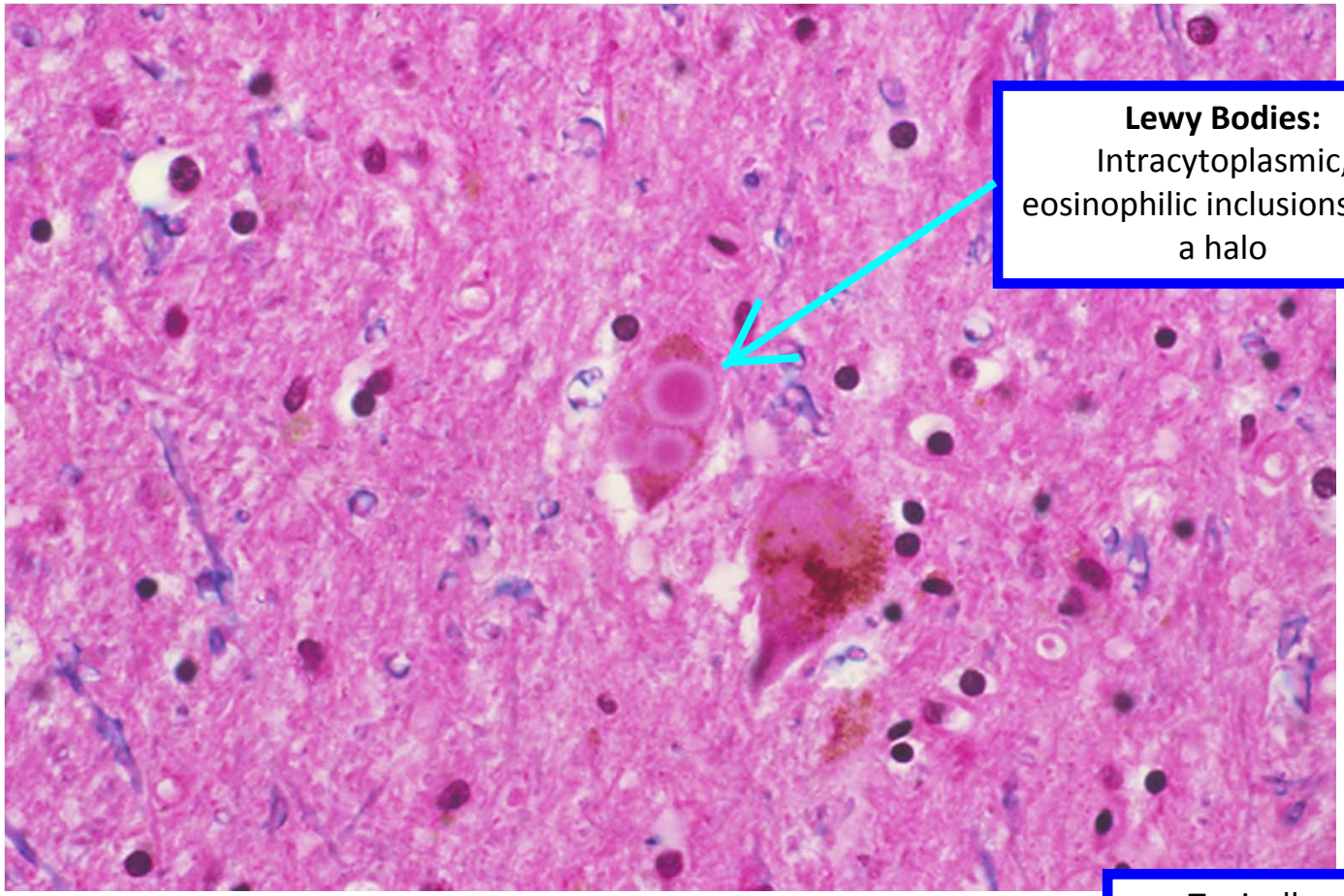
Midbrain



Cerebral Peduncle

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 pigemented neurons in **substantia nigra**

PICK'S DISEASE
FRONTOTEMPORAL DEMENTIA

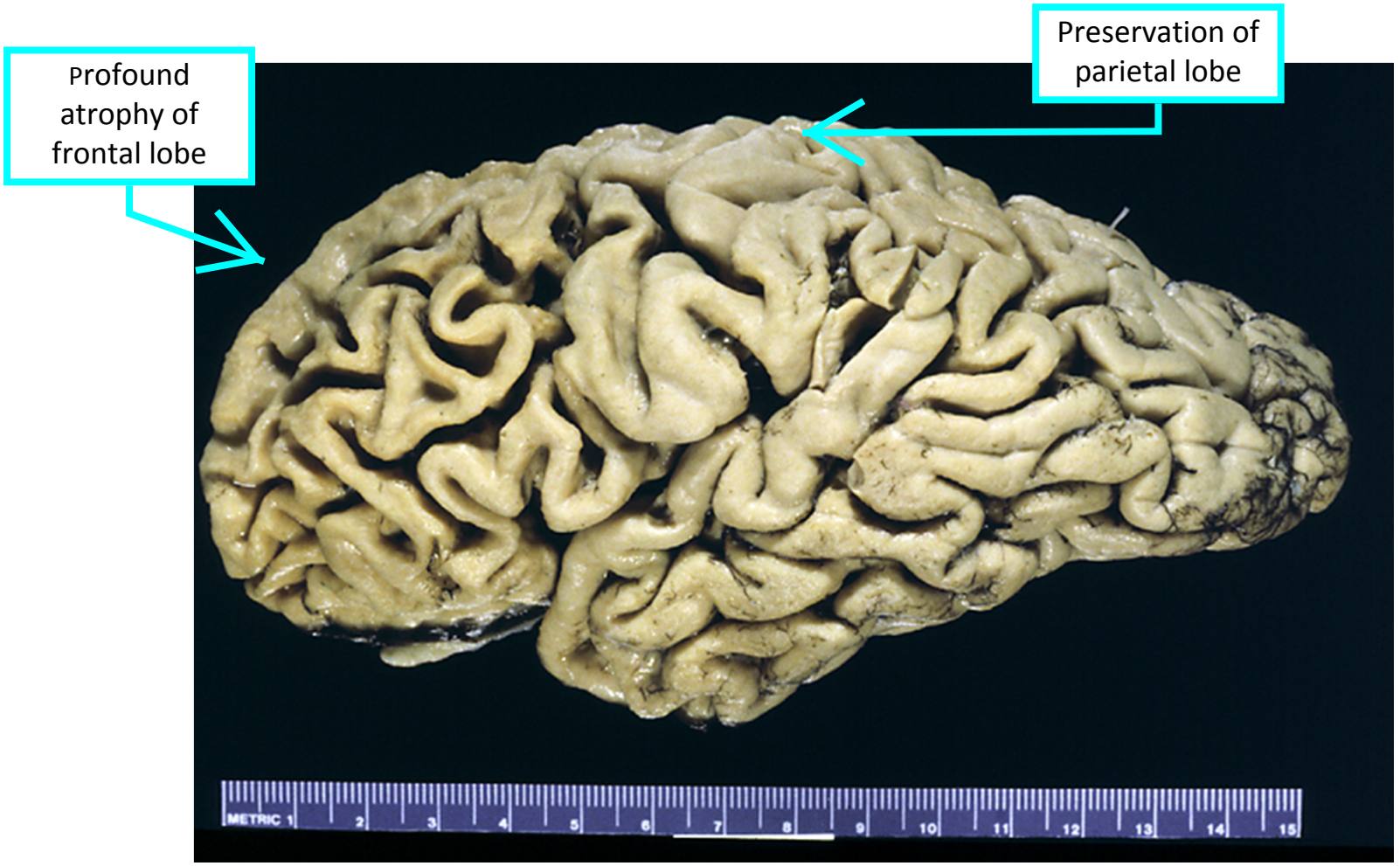
- Clinical presentation is similar to AD.
- Slightly earlier onset.
- Frontal and temporal lobe signs.
- Behavioral abnormalities.
- Extrapyramidal symptoms.
- Some cases are due to mutations in microtubule associated protein (tau) on Chr 17.

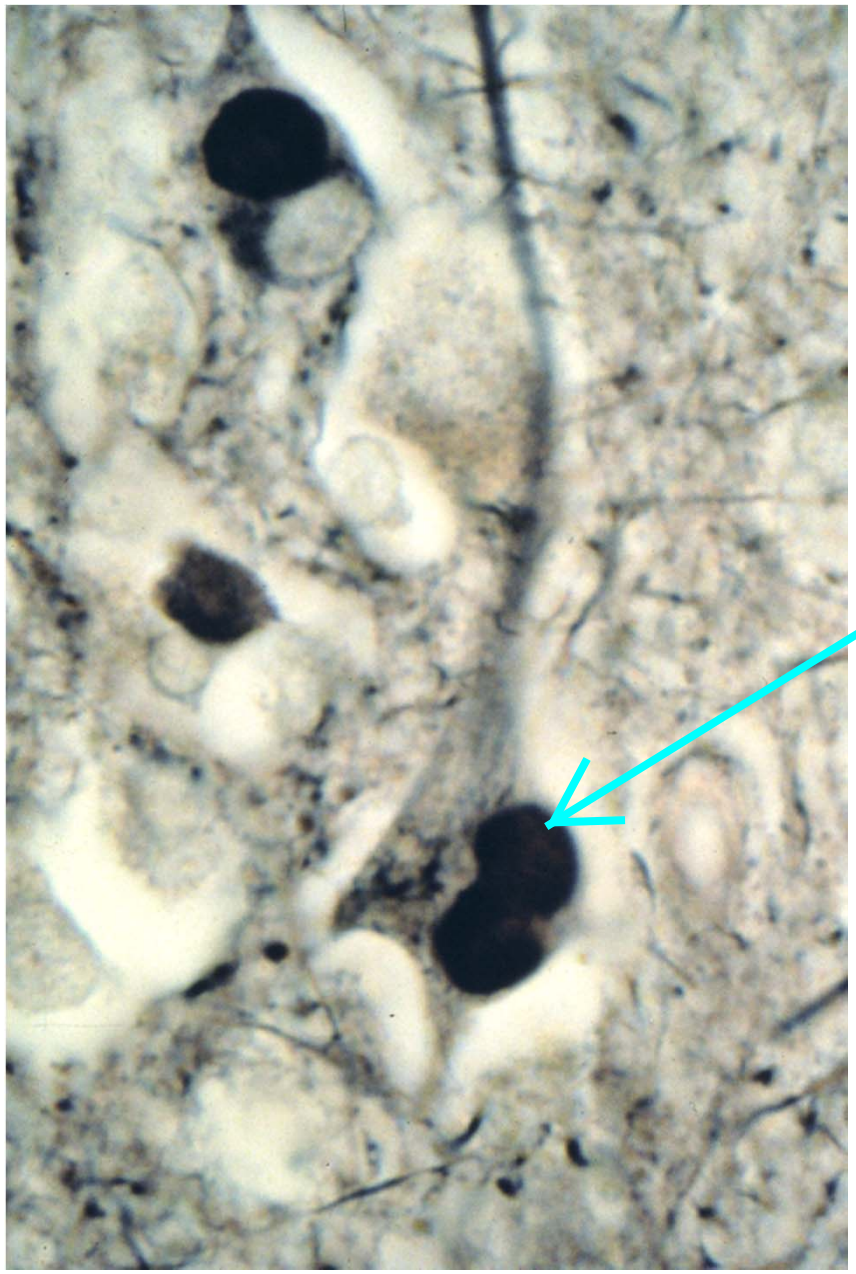
Sparing of Parietal and Occipital lobes

Many different mutations have been identified

Difficult to manage these patients!

PICK'S DISEASE





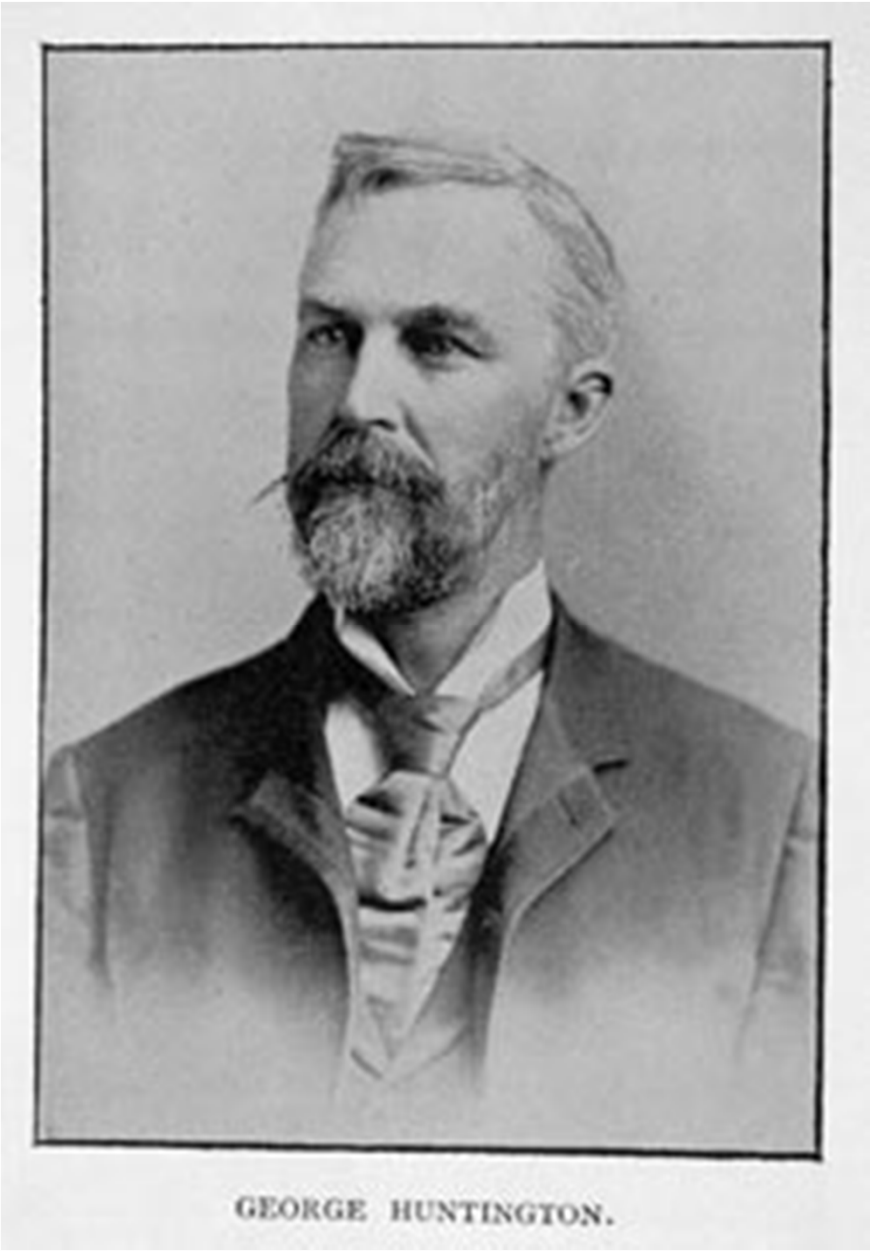
PICK BODIES

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

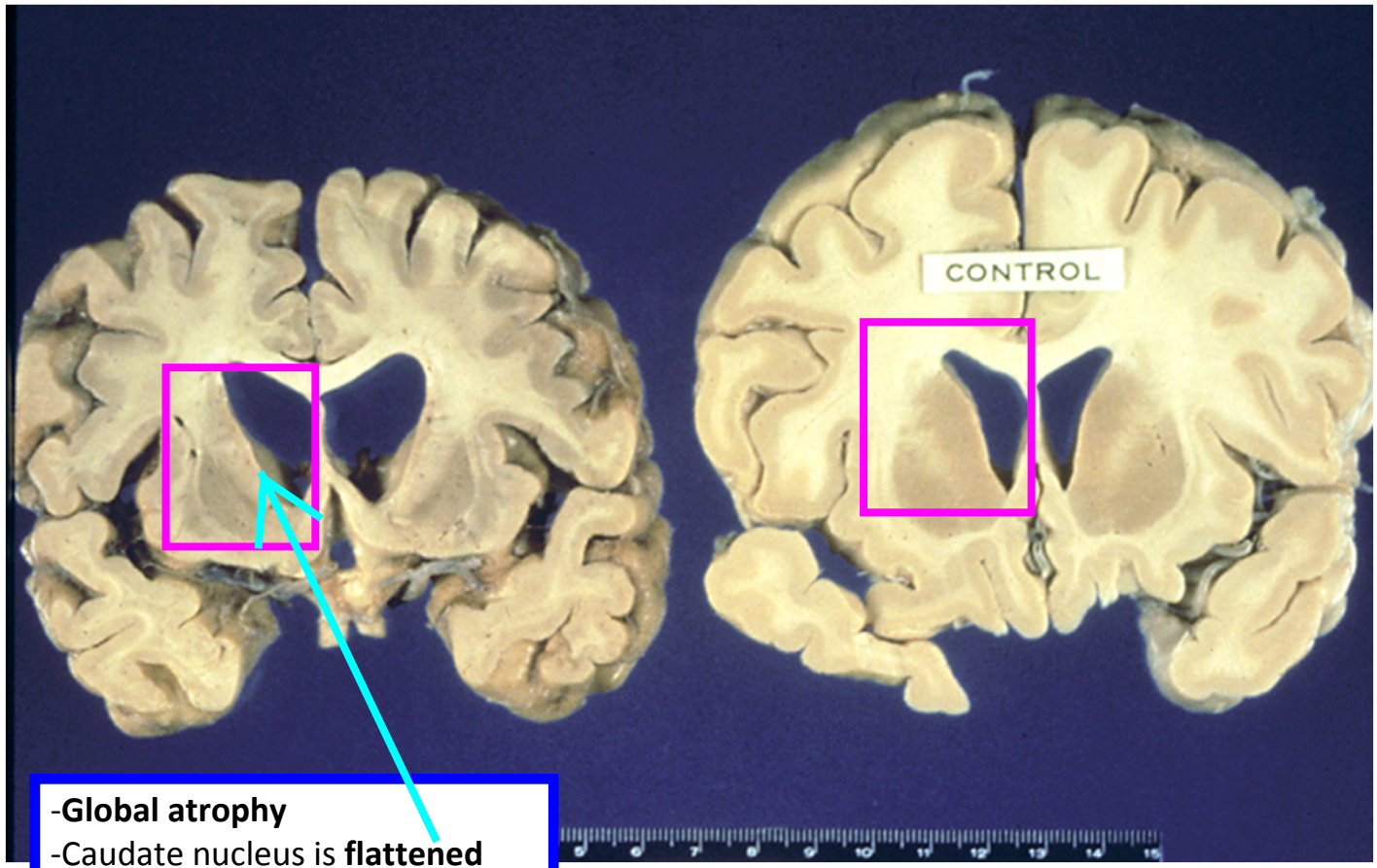


GEORGE HUNTINGTON.

HUNTINGTON DISEASE

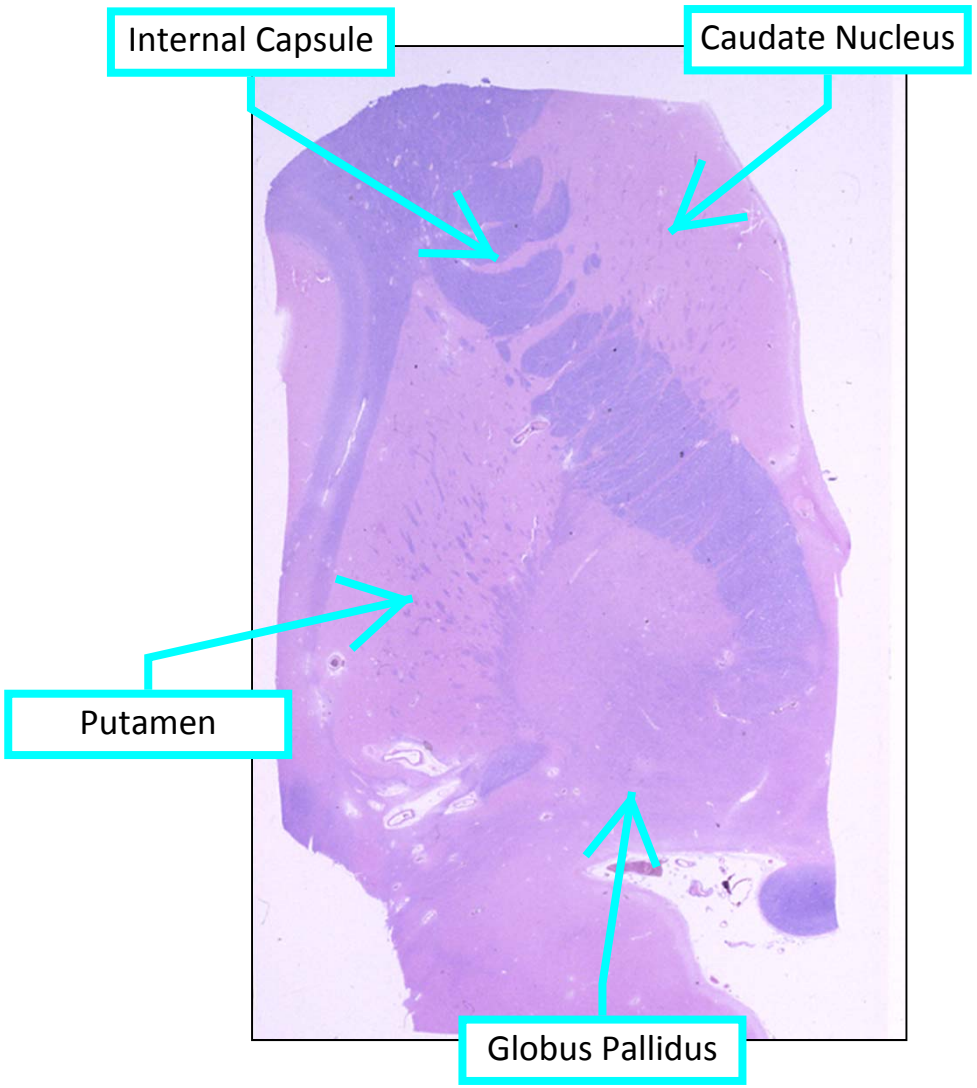
- Age of onset is 35-45 years.
- There are personality changes, chorea and dementia.
- Duration is approximately 15 years.
- Inherited in an autosomal dominant fashion.
  - **"huntingtin" gene on chr 4**

HUNTINGTON NORMAL

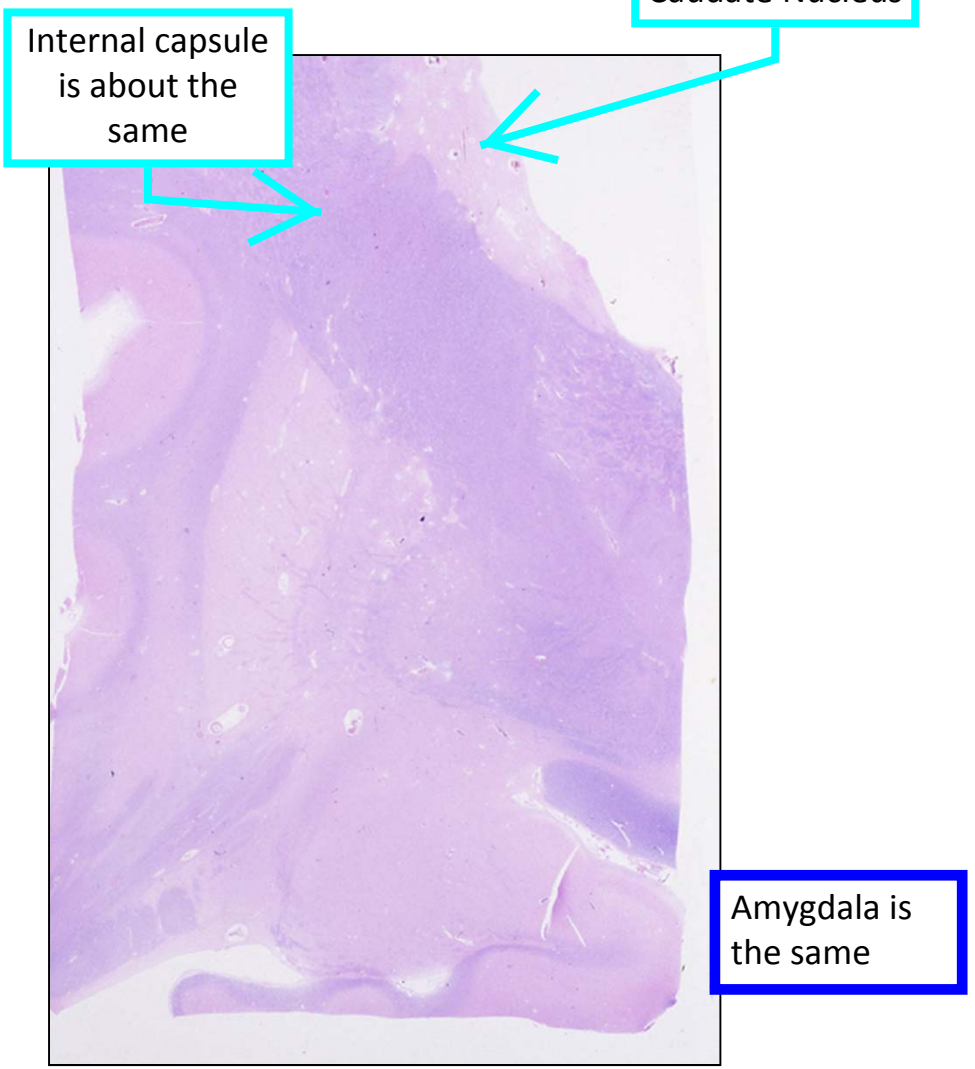


-**Global atrophy**
-Caudate nucleus is **flattened**
-Atrophy of Putamen and Globus Pallidus to lesser degree

NORMAL



HUNTINGTON




Lou Gehrig
YANKEES AL

AMYTROPHIC LATERAL SCLEROSIS

- Age of onset is in mid to late life.
- Male predominance.
- Duration 3 - 5 years

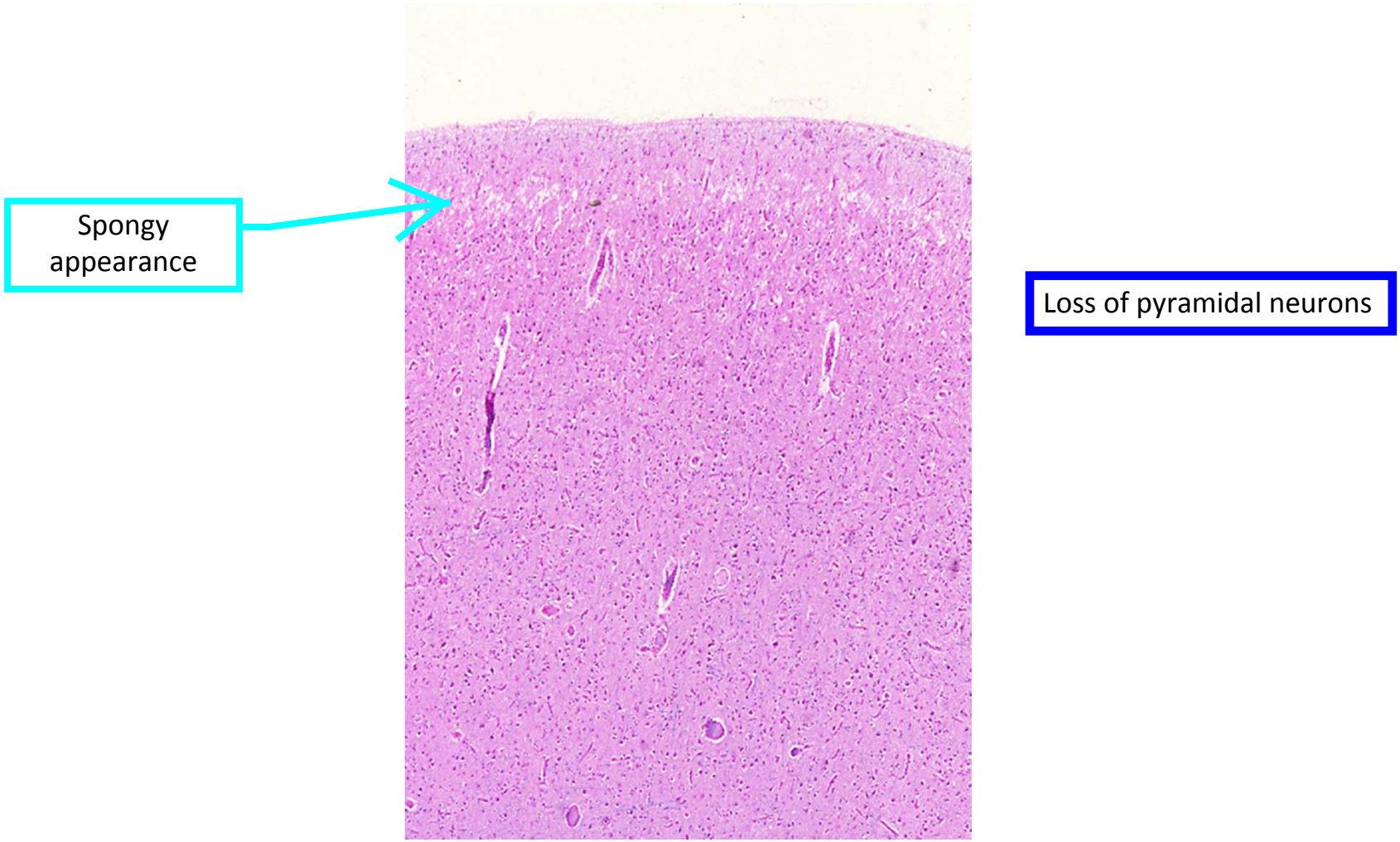
Very rapid progression

- Symptoms are caused by degeneration of corticospinal tract.
- Familial cases may be due to superoxide dismutase gene mutation on chr 21.

10% of cases

Pathology is the same for sporadic vs genetic

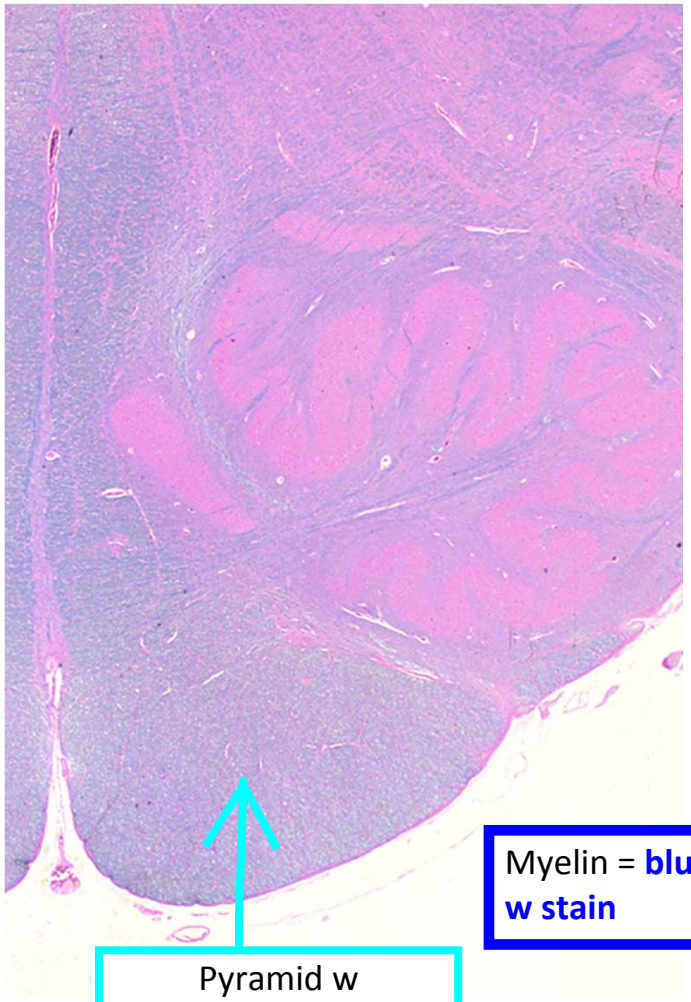
AMYOTROPHIC LATERAL SCLEROSIS MOTOR CORTEX



Descending Corticospinal Tract

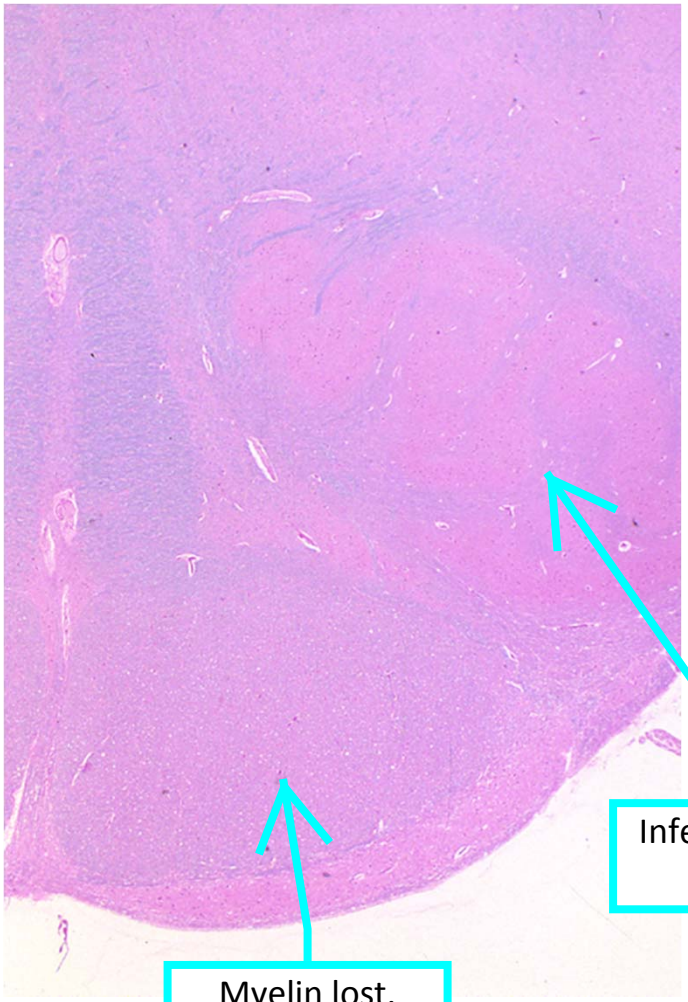
NORMAL

ALS



Myelin = **blue w stain**

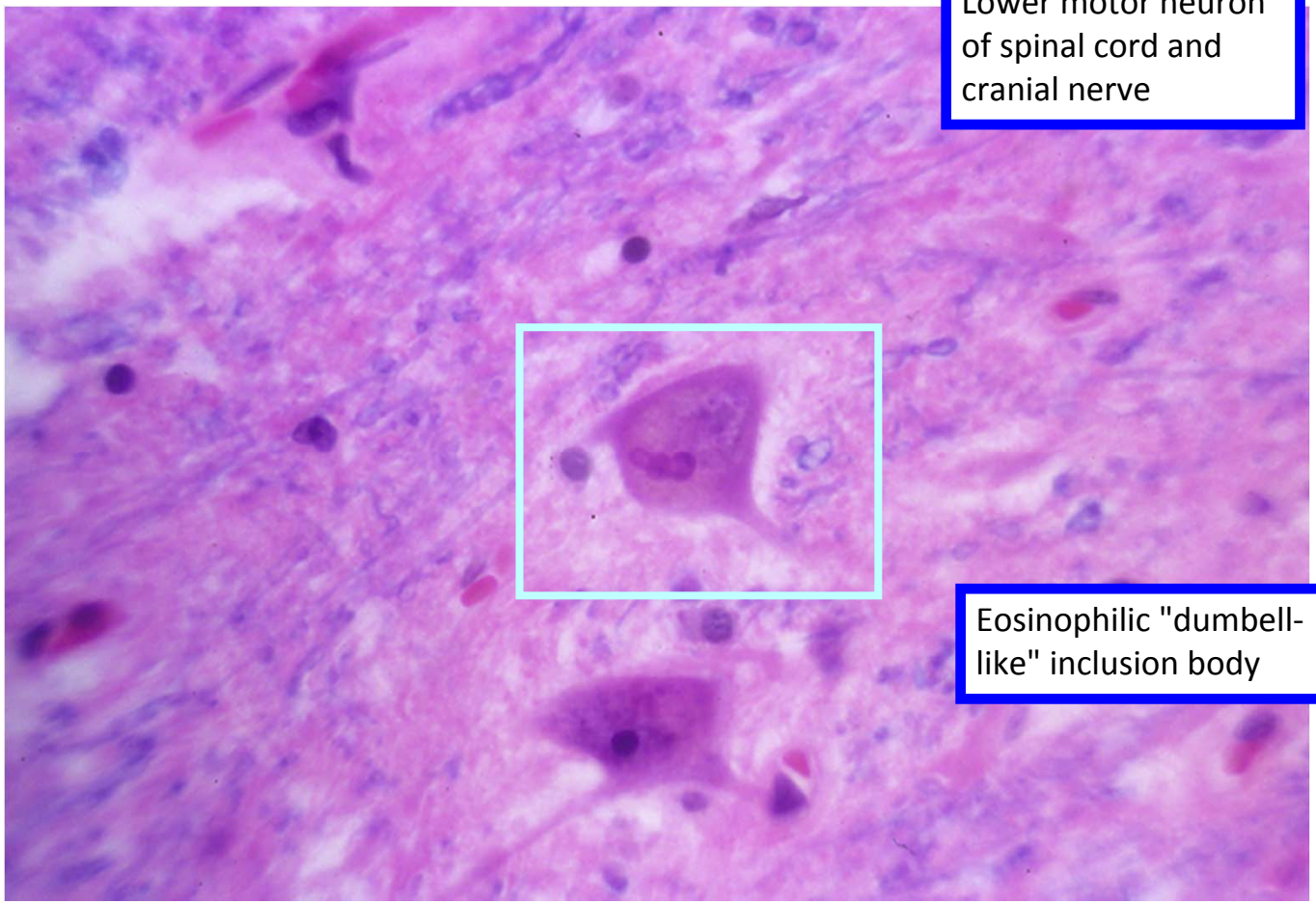
Pyramid w Descending corticospinal tract



Inferior Olivary Nucleus

Myelin lost. **Atrophy of pyramidal tract**

ALS BUNINA BODY



INHERITED METABOLIC DISORDERS

GANGLIOSIDE

GM1 Gangliosidoses

Deficiencies:

Variant **O** - Galactosidase isoenzymes A, B, C

Variant **A** - β-Galactosidase isoenzymes B, C

GM2 Gangliosidoses

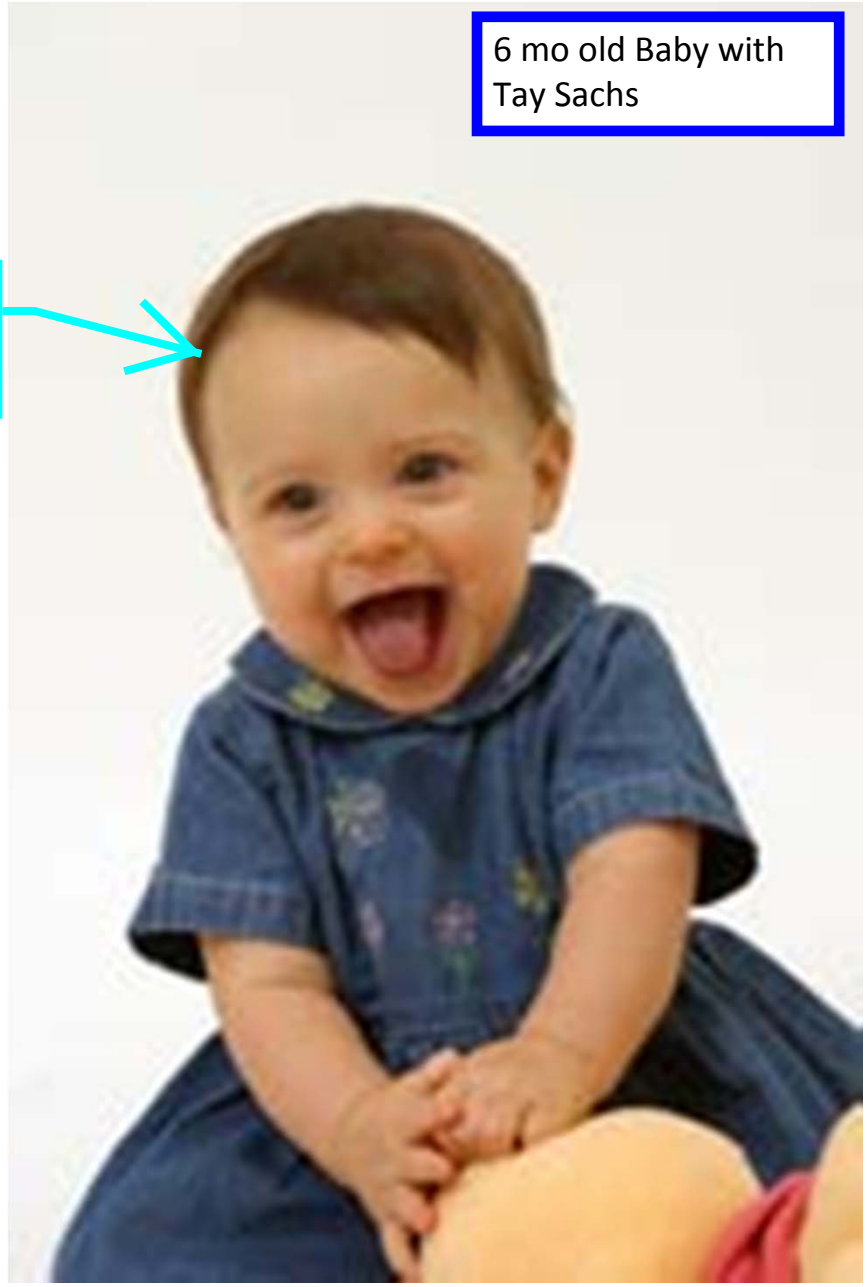
Deficiencies:

Variant **B** - Hexosaminidase A (Tay Sachs)

Variant **O** - Hexosaminidases A and B

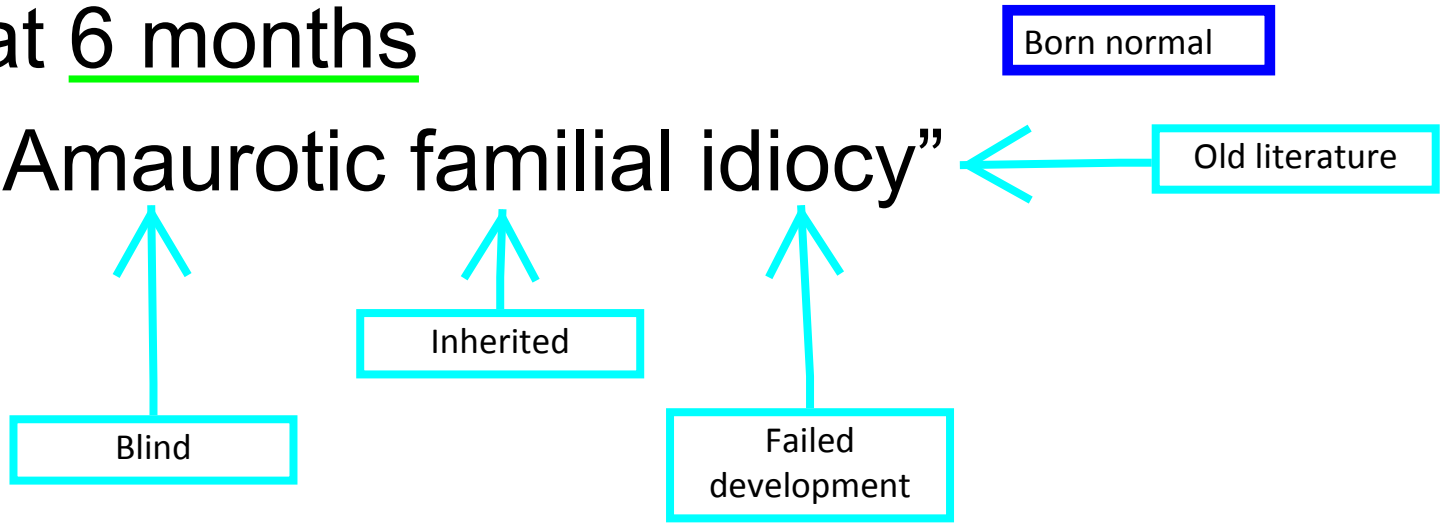
More severe

Most common of the Ganglioside disorders!


6 mo old Baby with Tay Sachs
Enlarged head. "Frontal Bossing"

TAY SACHS DISEASE

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

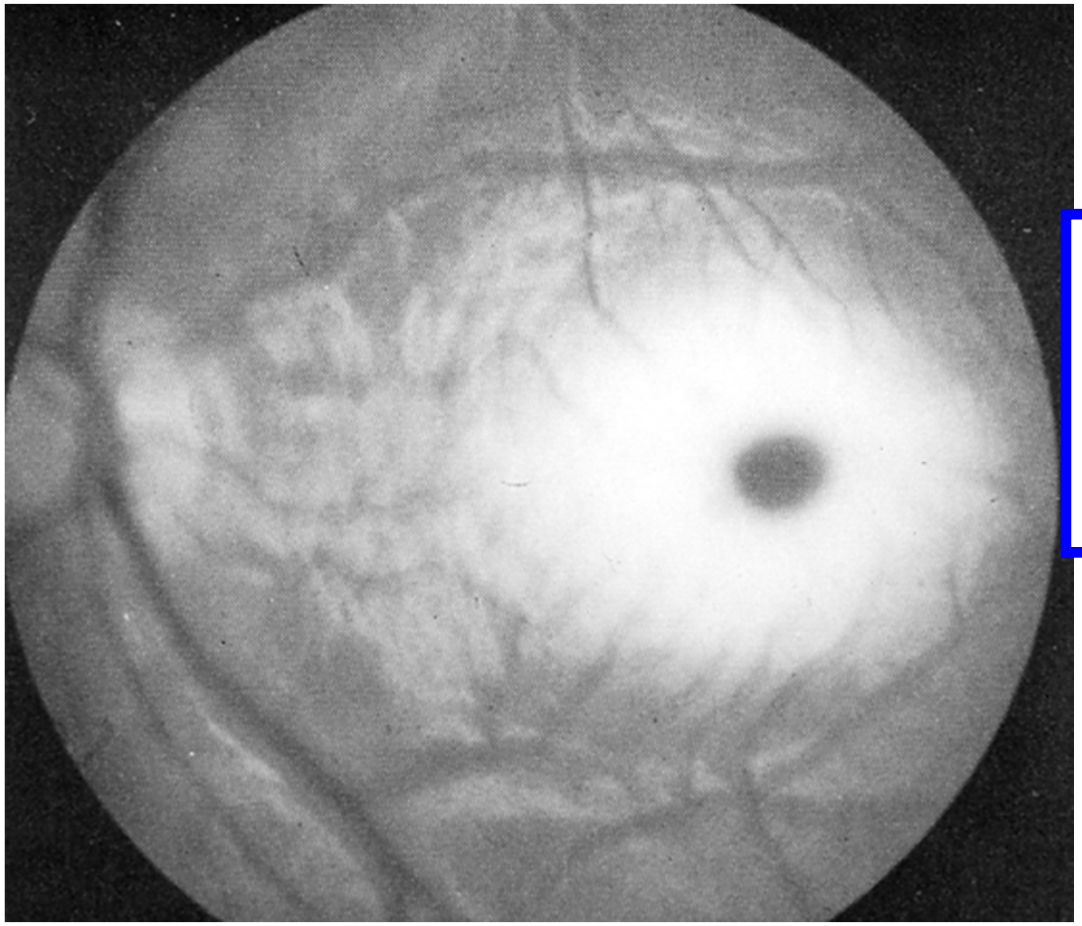


Side Note: If you want to see this, you'll have to go into pediatric neuro.

TAY SACHS

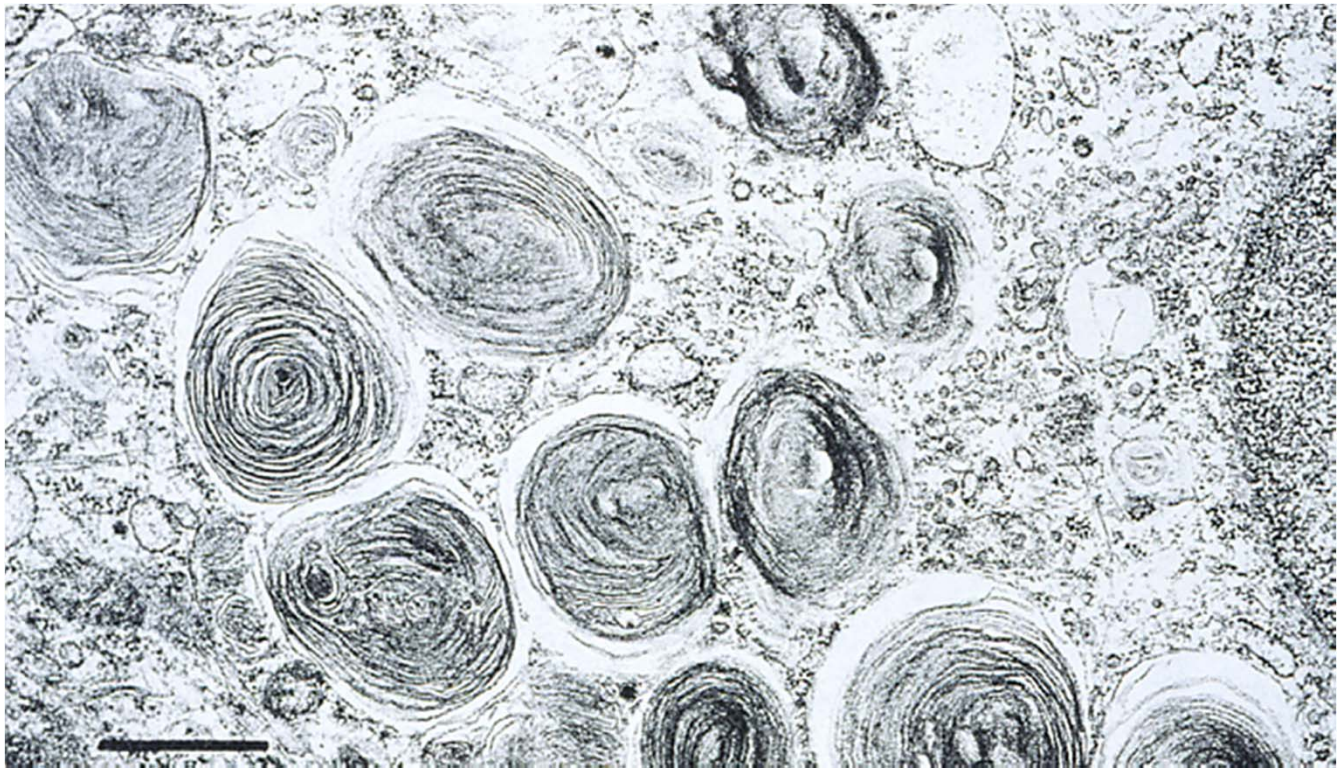
CHERRY RED SPOT

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. Parknison Disease

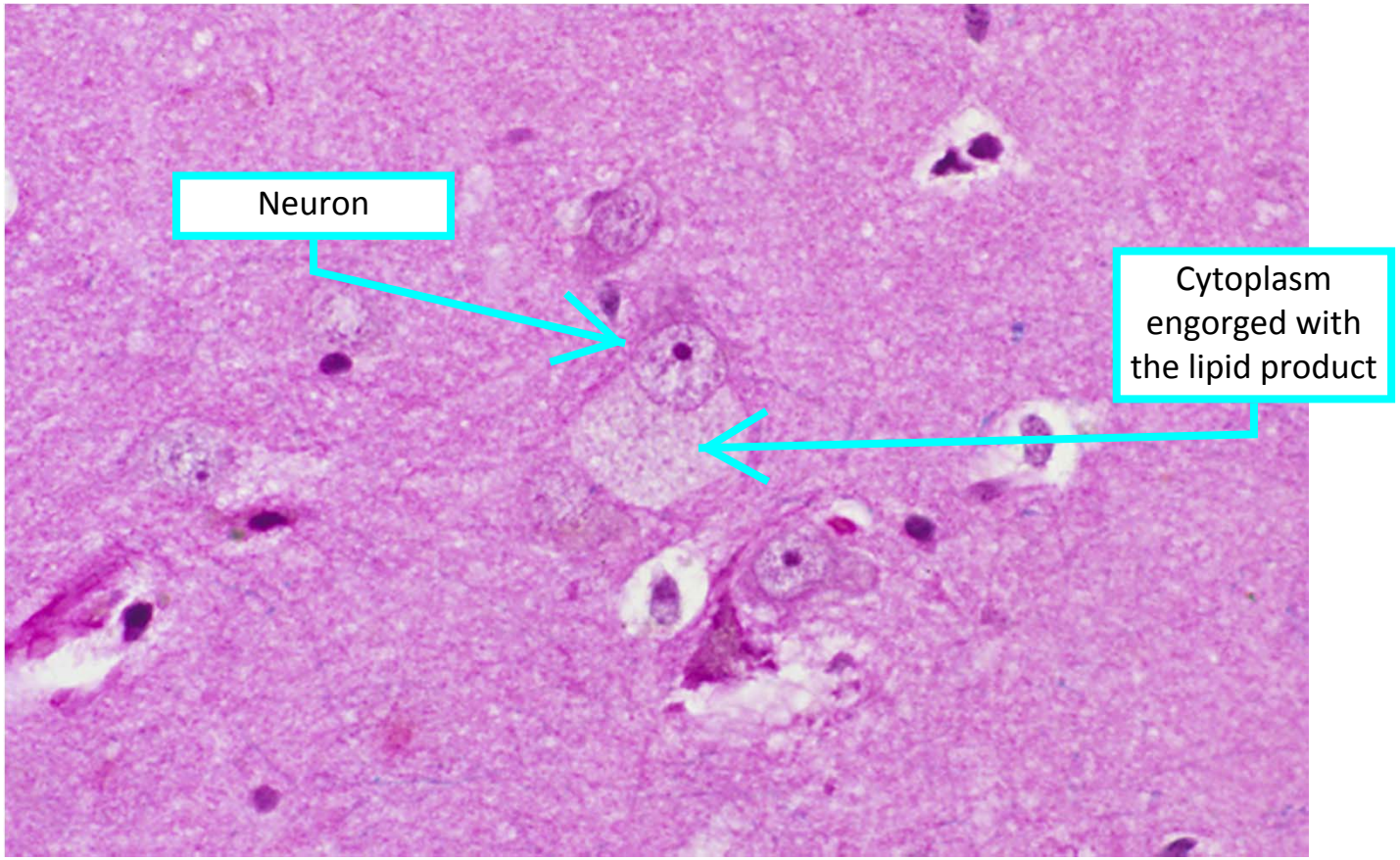
Answer on next page

Answer: D
Amyotrophic Lateral Sclerosis

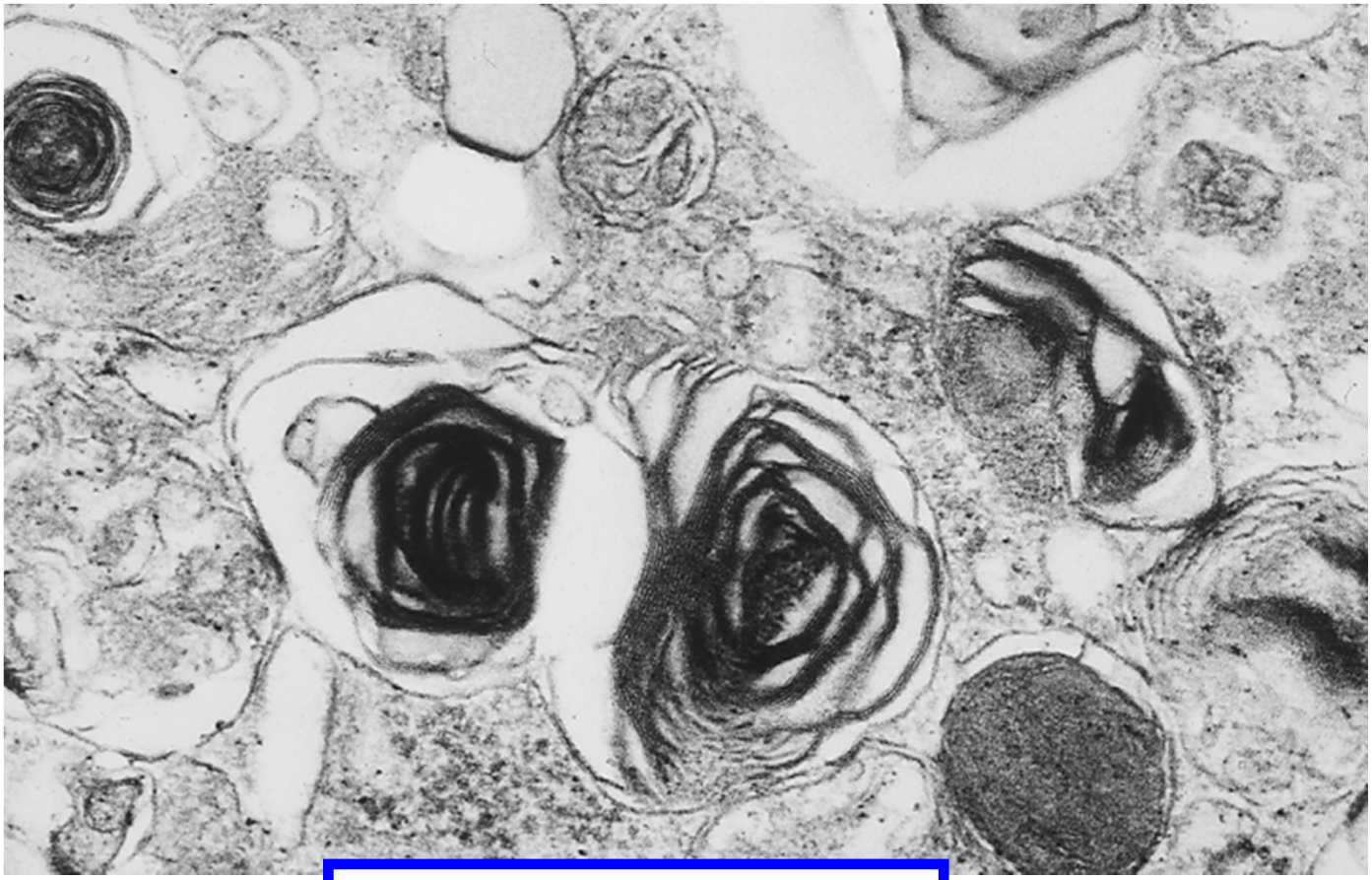
NIEMANN-PICK DISEASE

- 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



NIEMANN-PICK DISEASE



Oligolamellar profile rather than multilamellar seen in Tay Sachs

INHERITED METABOLIC DISORDERS

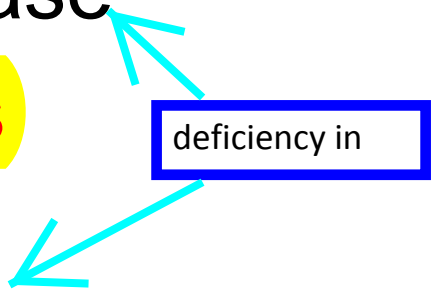
CEREBROSIDE

Glucosylceramide lipidosis (Gaucher's disease)

Glucocerebroside β-glucosidase

Galactosylceramide lipidosis (Krabbe's Disease)

Galactocerebroside β-galactosidase



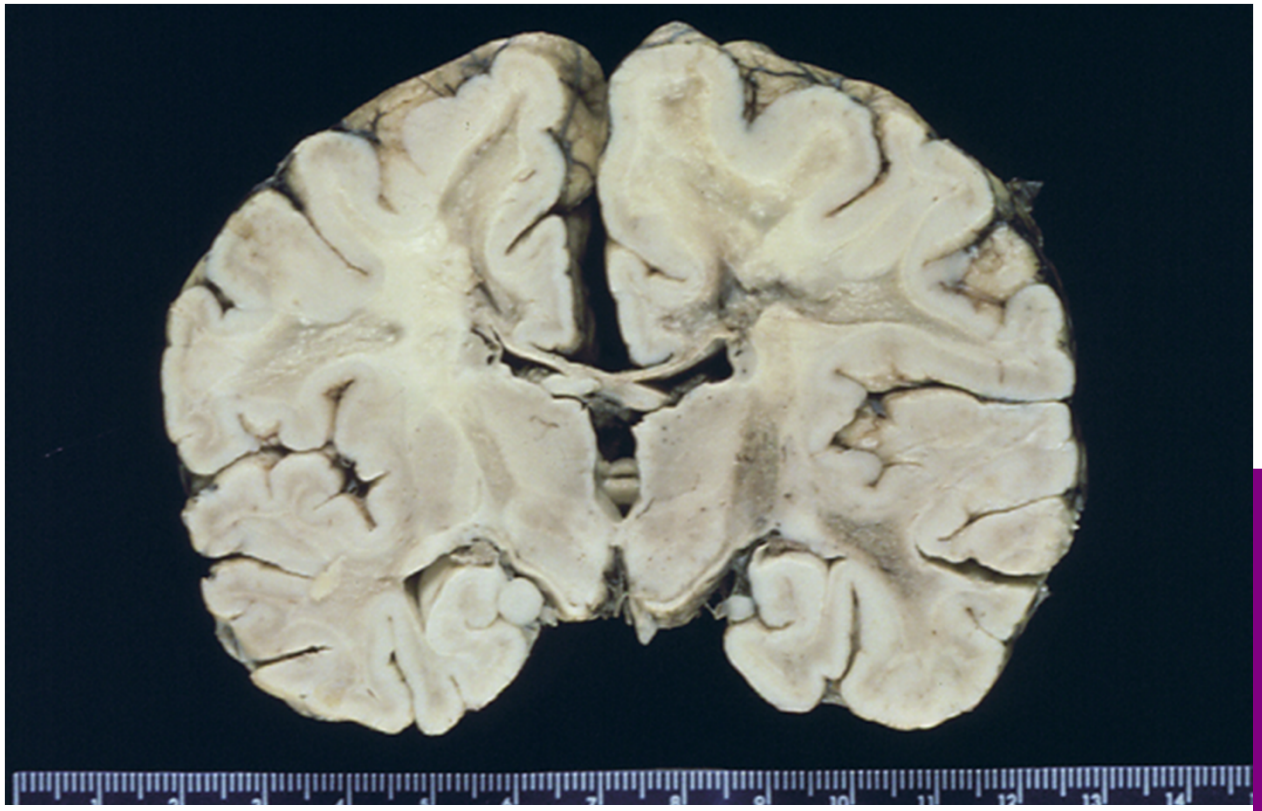
KRABBE'S LEUCODYSTROPHY

- 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

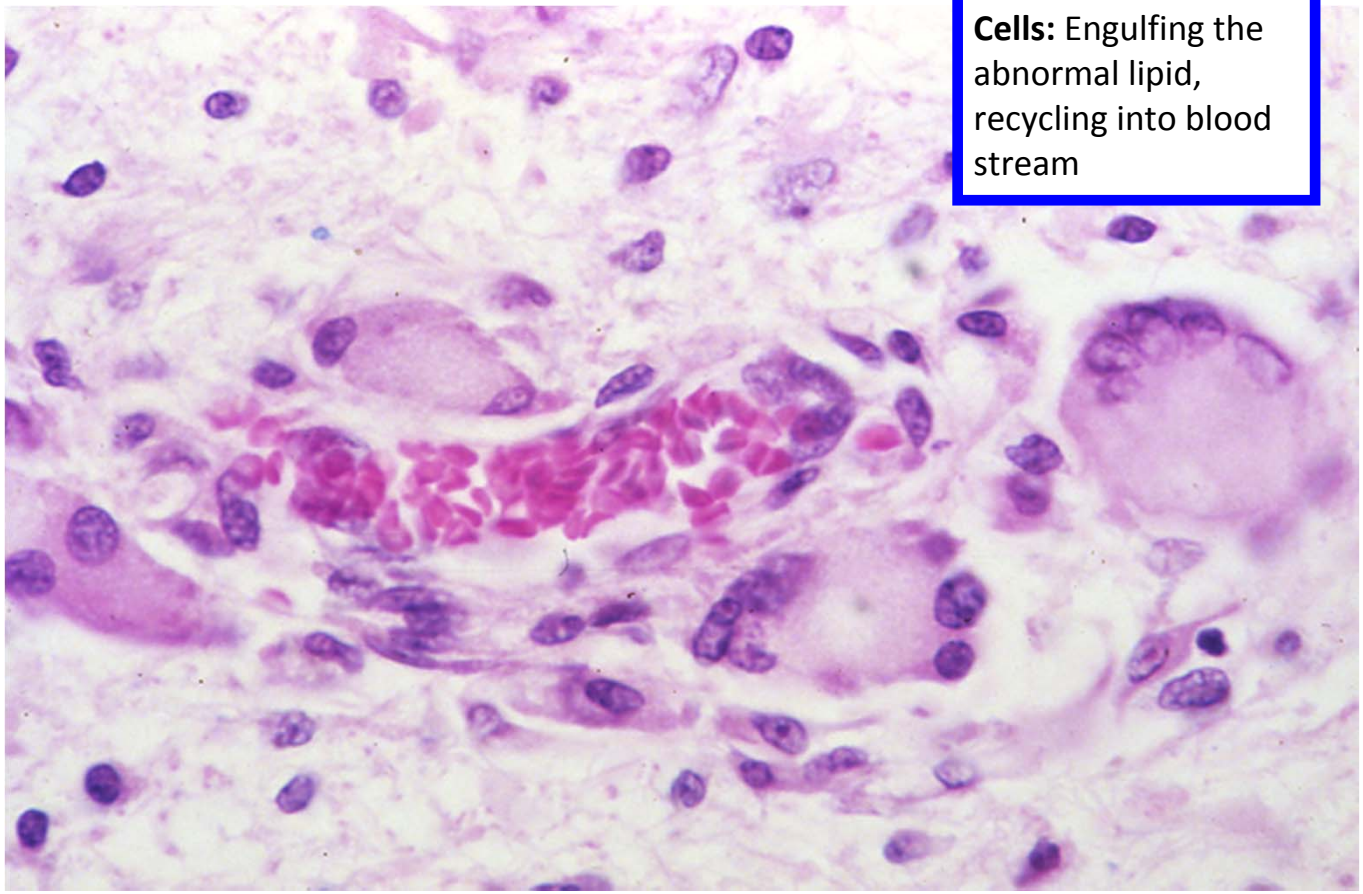
"Leuco" = "White" so pathology is in white matter

KRABBE'S LEUCODYSTROPHY



Question: Why is white matter effected, not gray matter?
Genetic defect in enzyme important in metabolizing myelin as opposed to an intra-neuronal 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

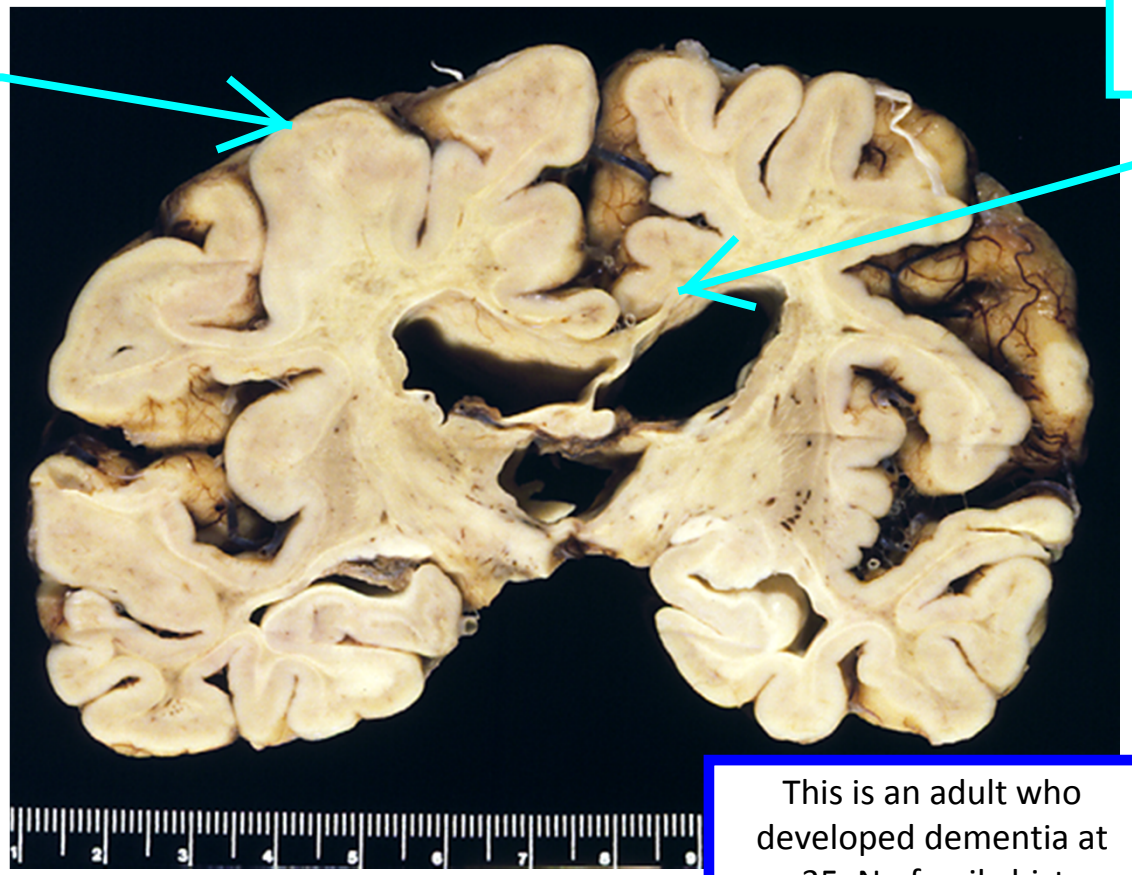
METACHROMATIC LEUCODYSTRPHY

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

METACHROMATIC LEUCODYSTROPHY

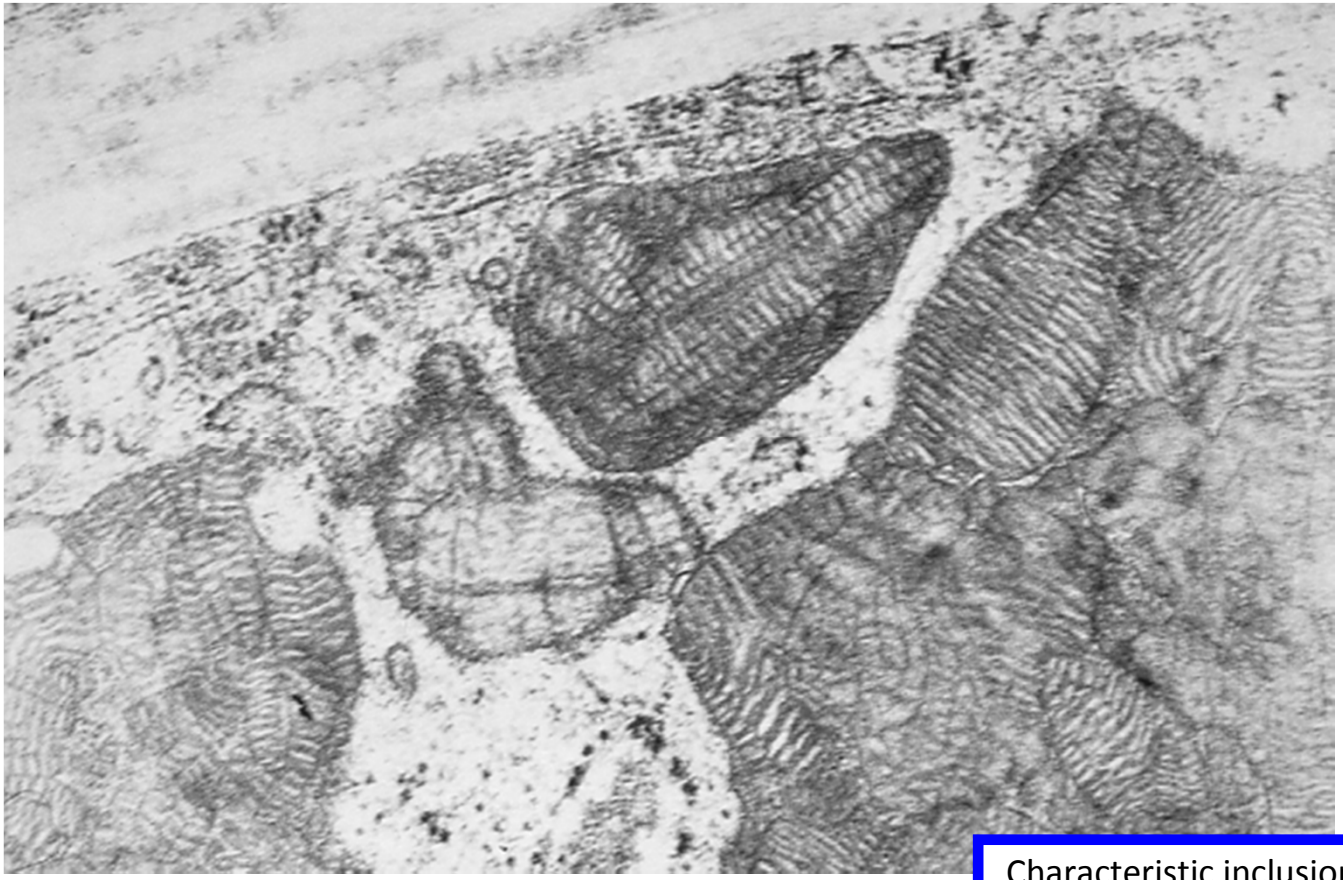
Cerebral cortex is normal

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

Answer on next page

Answer: C Krabbe's Disease

INHERITED METABOLIC DISEASES AFFECTING THE CNS

Favorite test topics!!

Liver

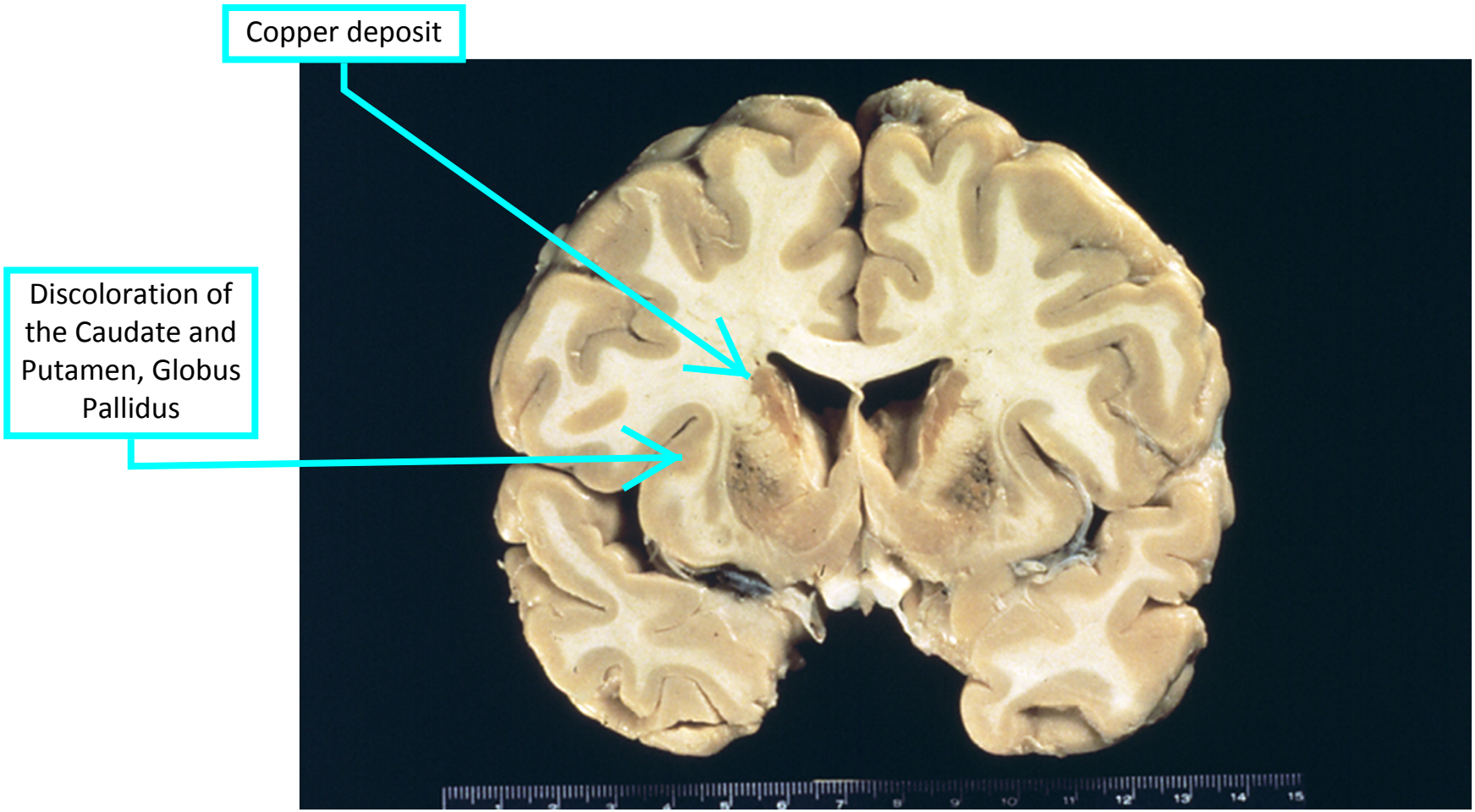
Globus pallidus (lenticular nuclei)

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

Protein carrying Copper around in blood

Largely eliminated because infants are tested and given a special diet.

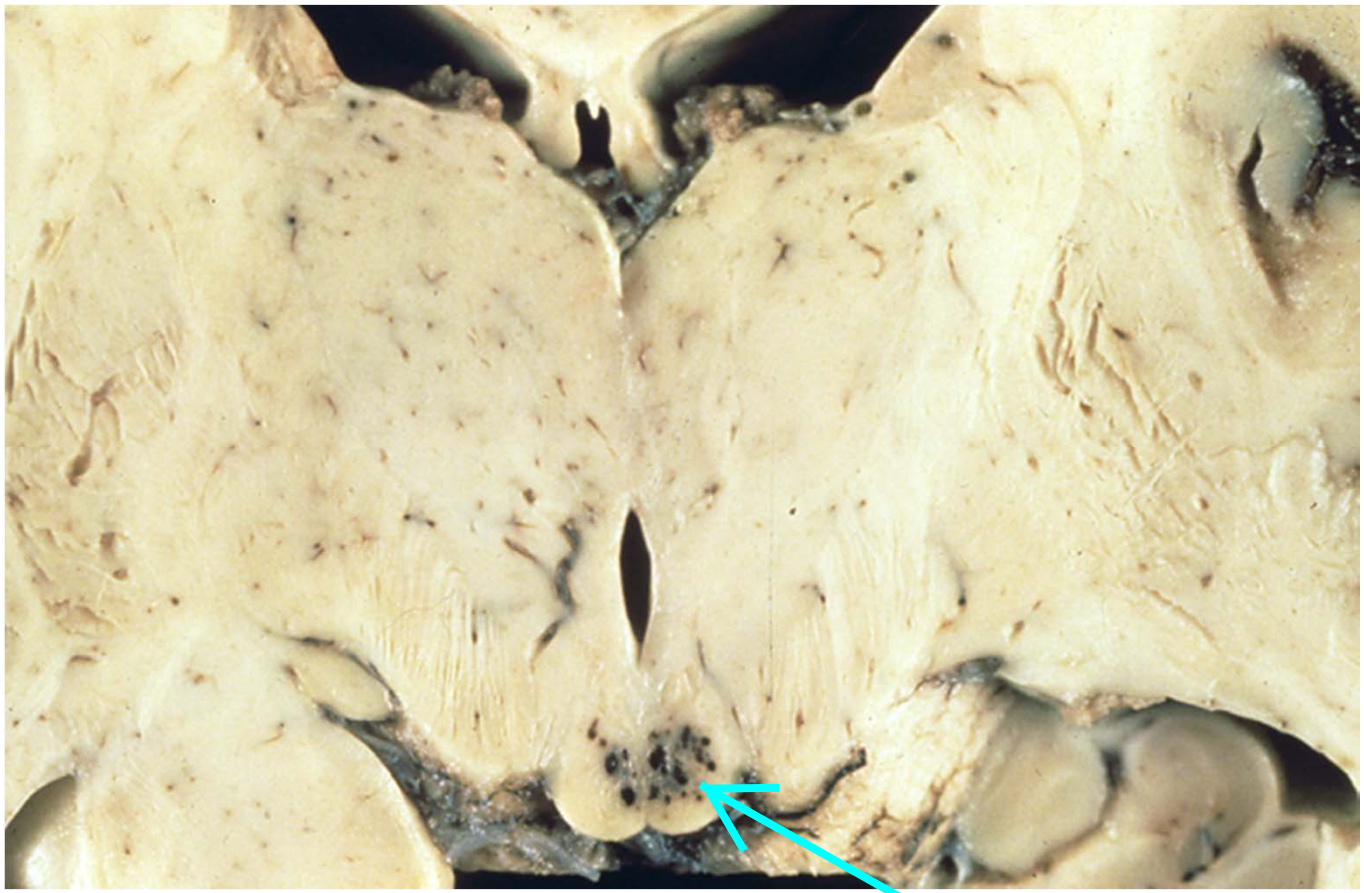
HEPATOLENTICULAR DEGENERATION (Wilson's Disease)



VITAMIN DEFICIENCIES AFFECTING THE CNS

- Thiamine deficiency caused by alcohol abuse or chemotherapy.
  - Wernicke encephalopathy – psychotic symptoms and opthalmoplegia
  - Korsakoff syndrome – memory disturbance and confabulation
    - Hemorrhage and necrosis in the mamilary bodies and periventricular regions

WERNICKE'S ENCEPHALOPATHY

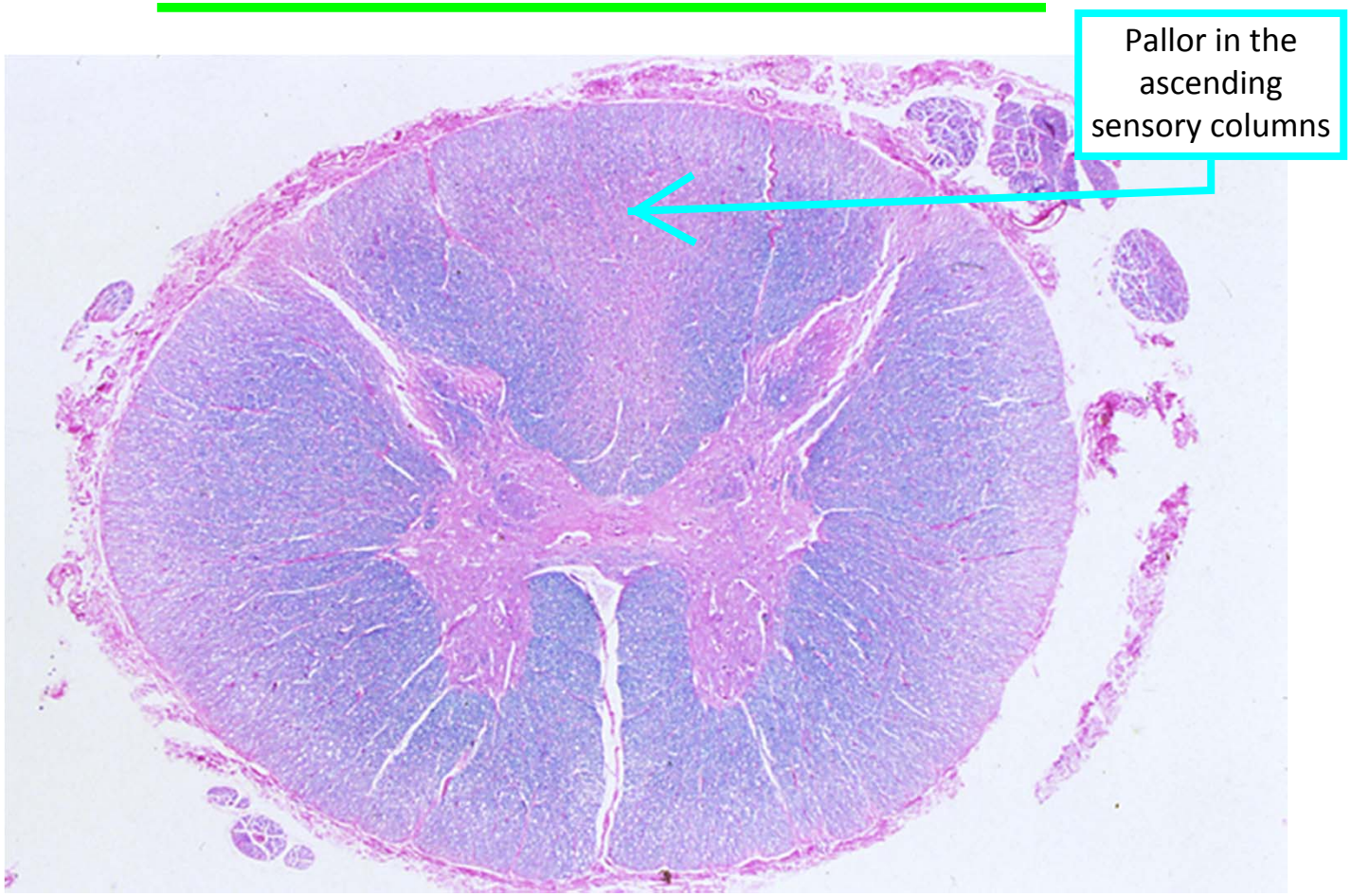


VITAMIN DEFICIENCIES AFFECTING THE CNS

- 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



ACQIRED METABOLIC DISEASES AFFECTING THE CNS

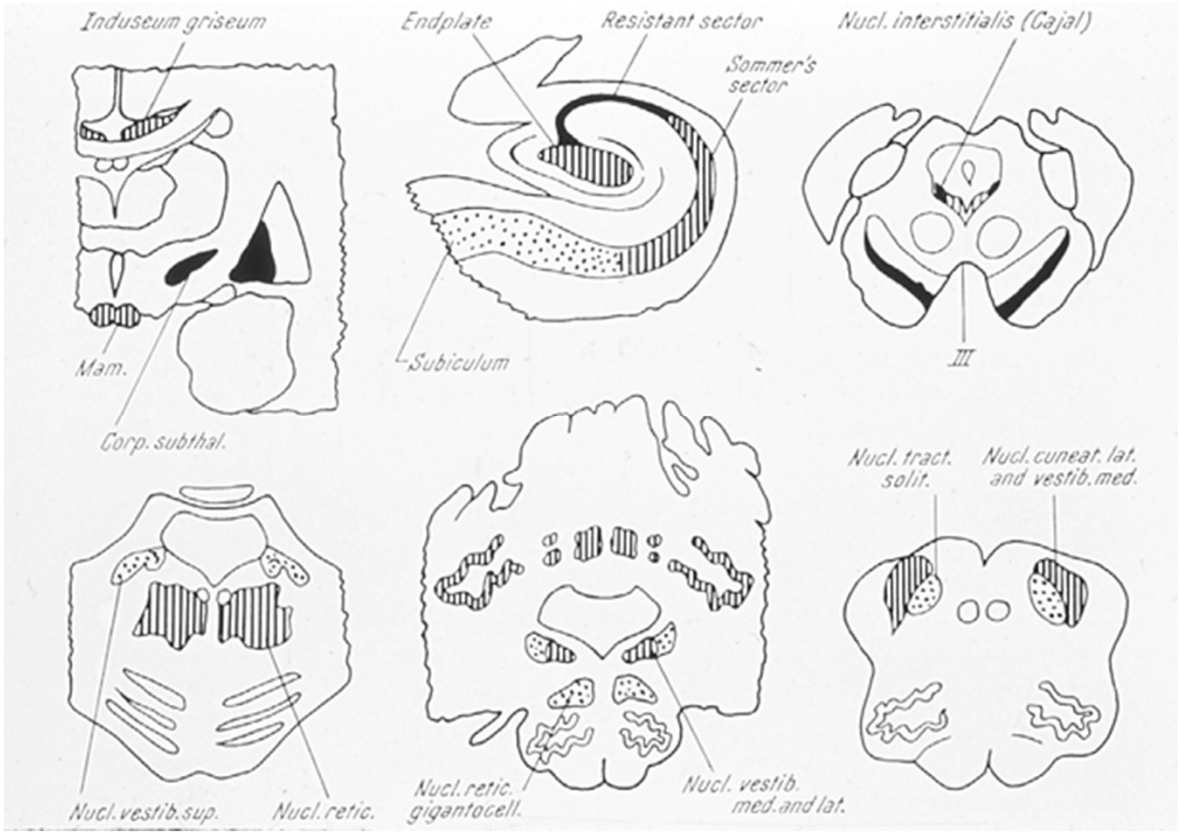
- **Cretinism**
  - Thyroid deficiency

Common in some areas of China. Access to Sea have enough iodine, but in internal regions they don't.

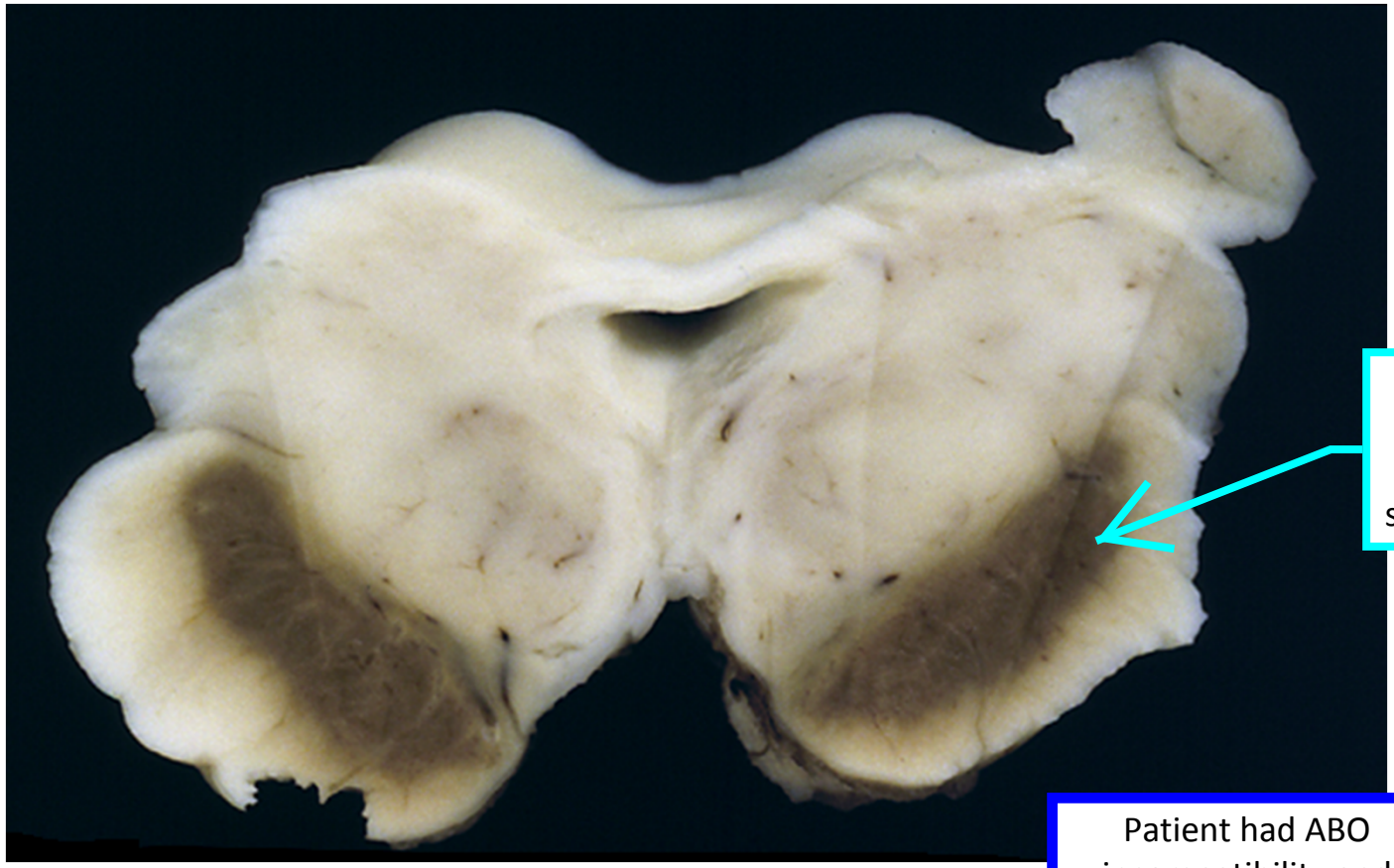
- **Kernicterus**
  - Hyperbilirubinemia in the neonatal period

This diagram shows where billirubin accumulates and how it causes damage: Substantia nigra, Globus Pallidus, Hippocampus

KERNICTERUS



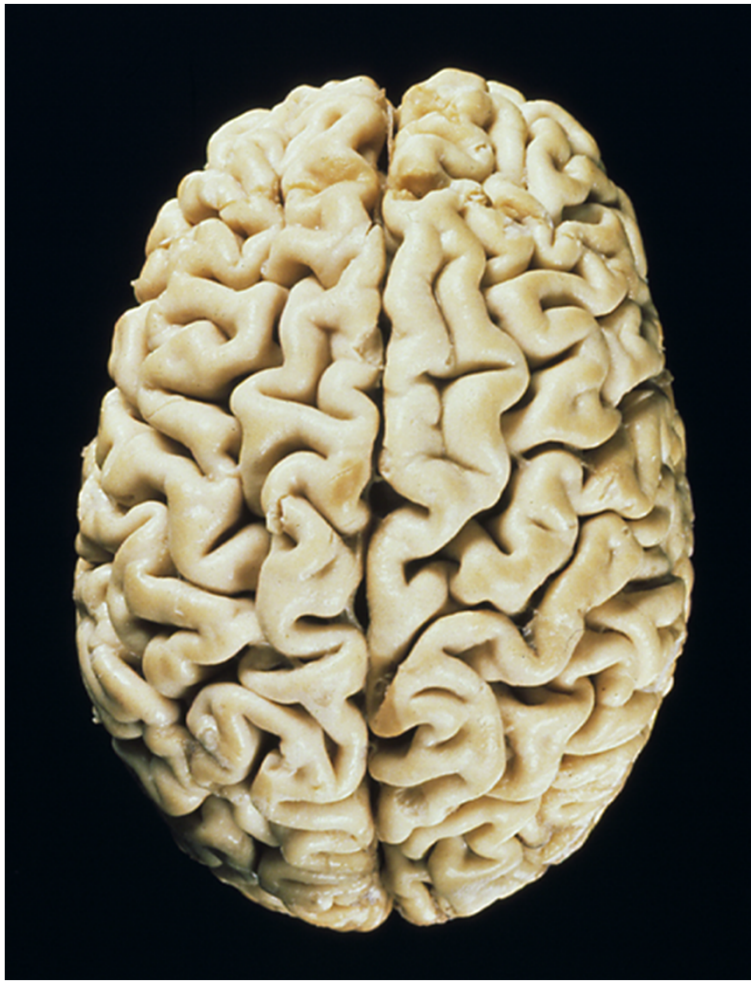
KERNICTERUS



Billirubin deposit and destruction of substantia nigra

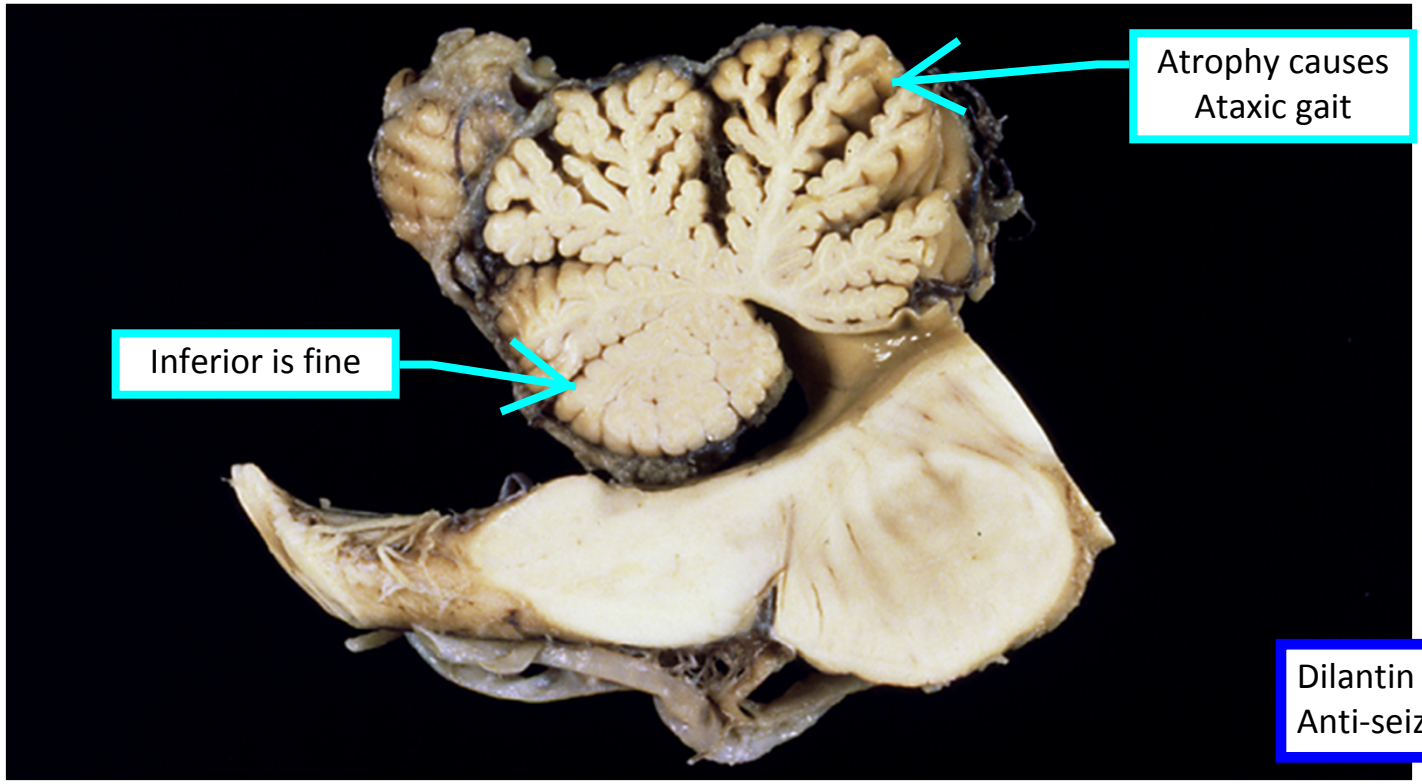
Patient had ABO incompatibility and jaundice at birth.

ETHANOL



Profound cortical atrophy and dementia with alcohol abuse

SUPERIOR CEREBELLAR ATROPHY



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