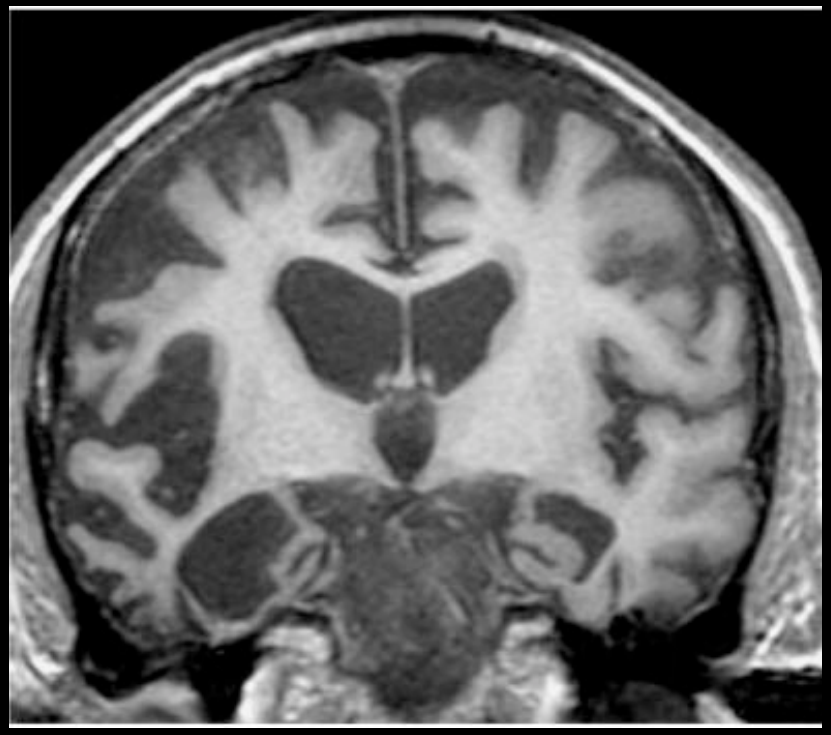
FRACP Lecture
Neurodegenerative and Neurometabolic Disorders



The Five Questions in Neurodegenerative Disorders

1. Is there evidence of regression or lack of progress in any area of development?
2. Could the apparently progressive symptoms be due to a static disorder complicated by other factors?
3. If this is a progressive disorder, what is it's distribution in terms of brain anatomy?
4. Which disorders are known to occur in children of this age, and to produce the other clinical features present in this child?
5. Are there any treatable disorders among the diagnoses being considered in this child?

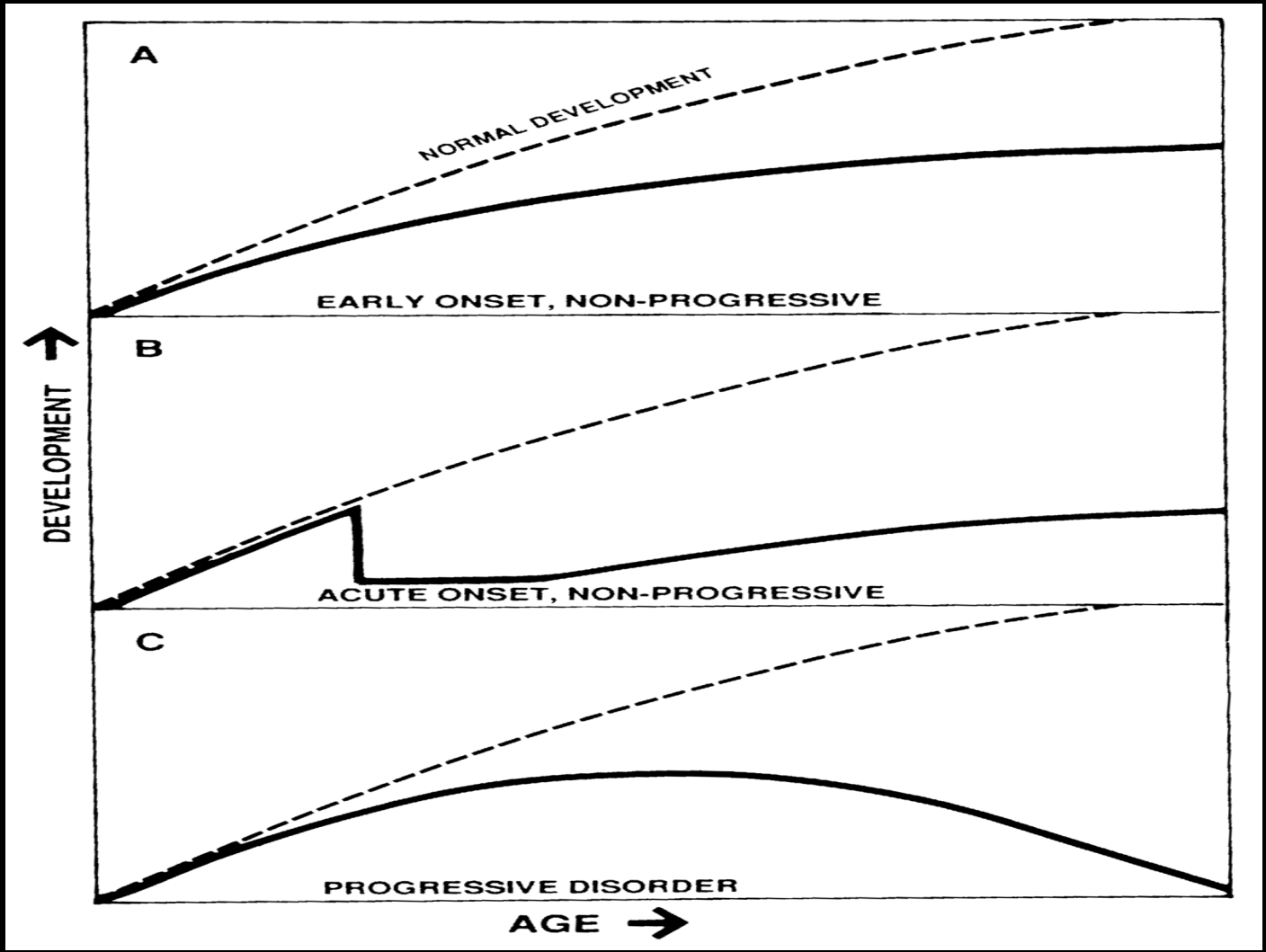
Neurodegenerative Disorders

1. Is there evidence of regression or lack of progress in any area of development?

   - "Is there any area where your child has gone backwards or shown no progress at all?"
   - "How is your child's speech now, compared with this time last year?"

   – a clear permanent loss of former skills raises concern about a progressive disorder, but this may be less certain during the plateau phase

Neurodegenerative Disorders



Neurodegenerative Disorders

2. Could the apparently progressive symptoms be due to a static disorder complicated by other factors?
   - frequent seizures (“epileptic encephalopathy’)
   - drug toxicity
   - infection
   - psychological and emotional
   - autism
   - orthopaedic / joint complications (? contractures)

Neurodegenerative Disorders

3. If this is a progressive disorder, what is it's distribution in terms of brain anatomy?
   - one lesion
   - one system
   - a group of systems
   - a multifocal process
   - a diffuse degenerative disorder of the nervous system
     - disorders of grey matter
     - disorders of white matter

Neurodegenerative Disorders

4. Which disorders are known to occur in children of this age, and to produce the other clinical features present in this child?
   - match age and signs
   - look for specific ocular abnormalities
   - look for organomegaly
   - look for peripheral nerve involvement

Neurodegenerative Disorders

5. Are there any treatable disorders among the diagnoses being considered in this child?
   - very important question as it may alter the priority of further investigations
   - must be rigorously excluded at an early stage
     - Inborn errors: PKU, Wilson's, pyridoxine dependency
     - Neoplasms
     - Infections: TB
     - Intoxications: Lead
     - Deficiency: B12
     - Hydrocephalus

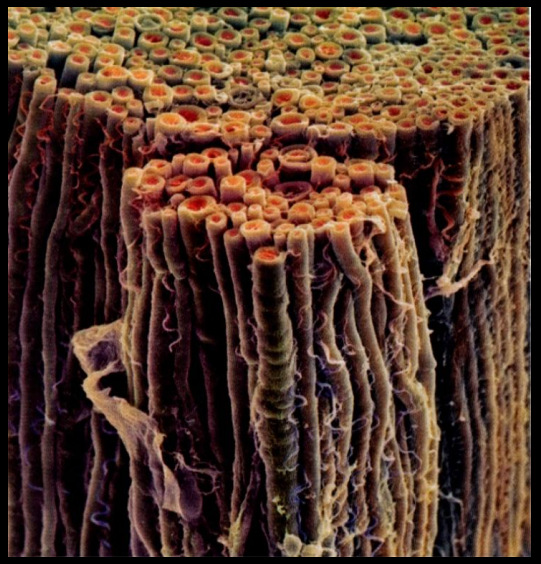
Approach to classification

- Small molecule vs. large molecule
- Predominantly grey vs. white matter disorders
  - grey matter
    - Encephalopathy, seizures
  - white matter
    - Spasticity, cerebellar signs
- Mixed grey and white / multiorgan / multisystem

The Leucoencephalopathies

MRI has expanded the concept of disorders affecting myelin

The Leucoencephalopathies



- Pathological classification – MYELIN!
  - Demyelinating (broken down)
    - ALD
  - Dysmyelinating (abnormally formed)
    - Krabbe, MLD
  - Hypomyelinating (never formed)
    - Pelizaeus Merzbacher, Alexander's disease, VWD
  - Spongioform (cystic degeneration)
    - Canavan's disease

The Leucoencephalopathies

- Biochemical classification
  - Lipid disorders
    - ALD, Krabbe, MLD
  - Myelin protein disorders
    - Pelizaeus Merzbacher, Myelin basic protein deficiency
  - Organic acid disorders
    - Canavan's
  - Defects of energy metabolism
    - MELAS, LEber, Complex I, III, COX
  - Other
    - CADASIL, Merosin deficiency, Alexanders

Disorders of Lysosomal Enzymes

- Lysosomes are cytoplasmic vesicles containing enzymes that degrade the products of cellular catabolism
- When lysosomal enzymes are deficient, abnormal storage of materials occur with multiple organ systems may be involved
- The disorders include:
  - Mucopolysaccharidoses
  - Krabbe disease
  - Metachromatic leukodystrophy (MLD)
  - Niemann-Pick disease
  - Tay-Sachs disease
  - Sandhoff disease

The Classical Leucodystrophies

Krabbe Disease

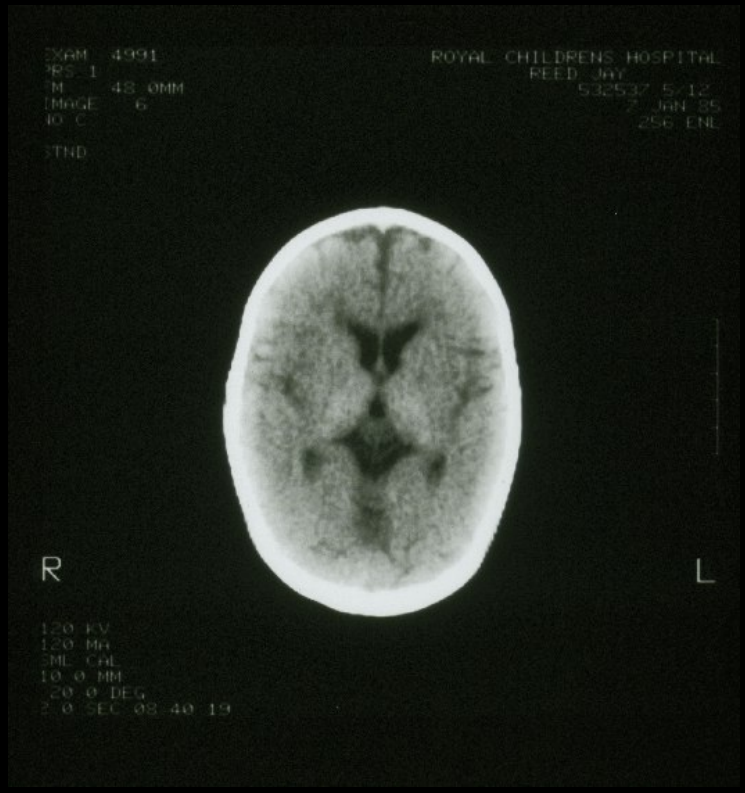
- Clinical
  - Rapidly progressive disorder caused by a deficiency of galactocerebrosidase with autosomal recessive inheritance
  - Infantile form presents 3-4 months with irritability, psychomotor deterioration, seizures, spasticity with, opisthotonos, myoclonus, visual loss: death in 2-5 years
  - Older variant has a more benign course
- Diagnosis
  - Clinical, imaging and lysosomal studies
  - Caused by mutations in the glycosylceramidase gene (*GALC*)

Krabbe Disease
Clinical

Regression with irritability, spasticity and opisthotonos.

Absent deep tendon reflexes.

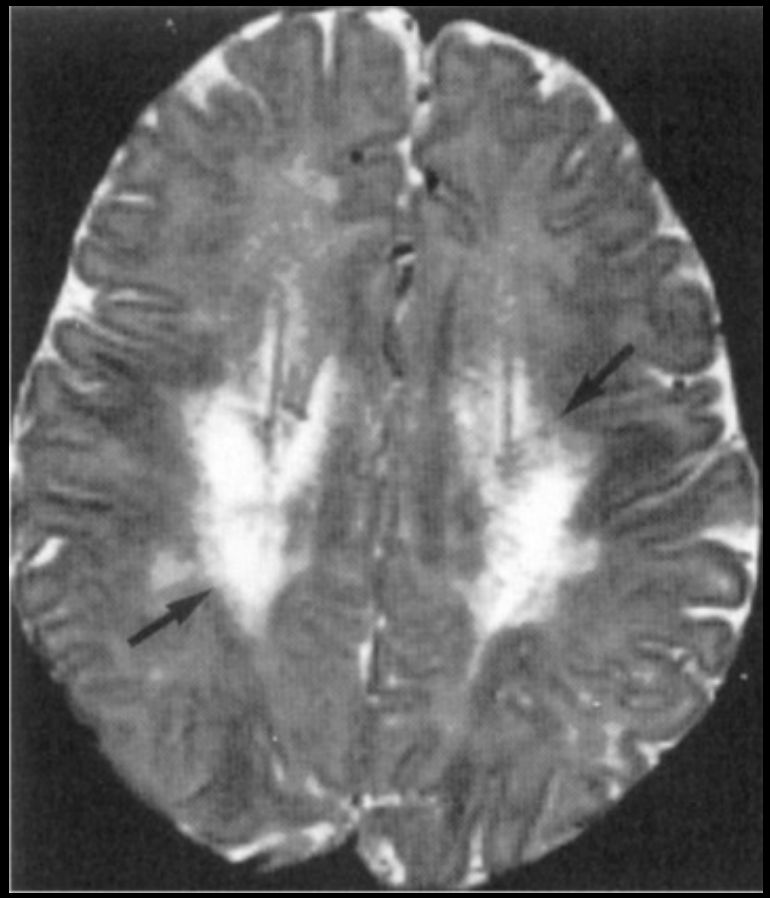
Krabbe Disease
CT Findings



Typical increased density of the basal ganglia on CT scan.

Krabbe Disease
MRI Findings

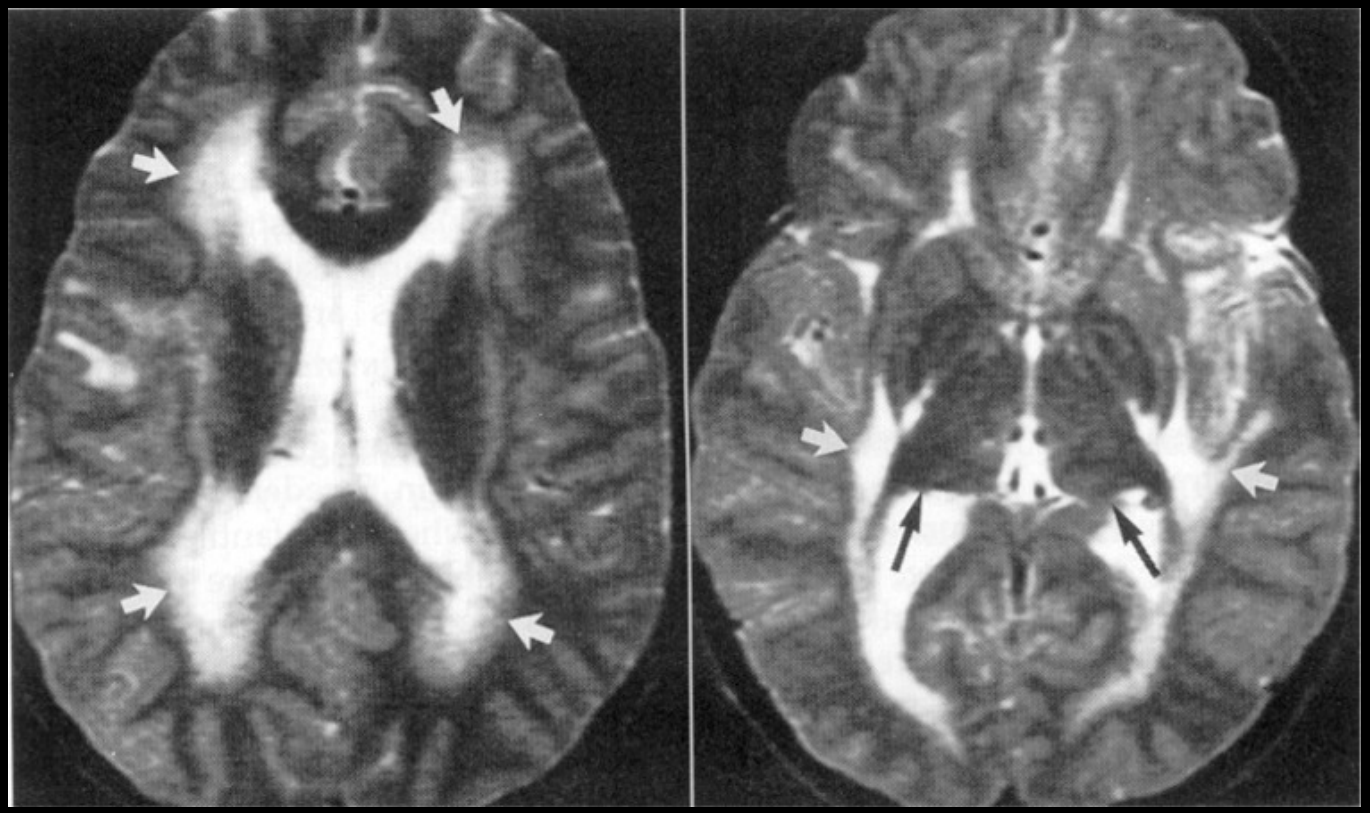
Periventricular abnormalities of white matter

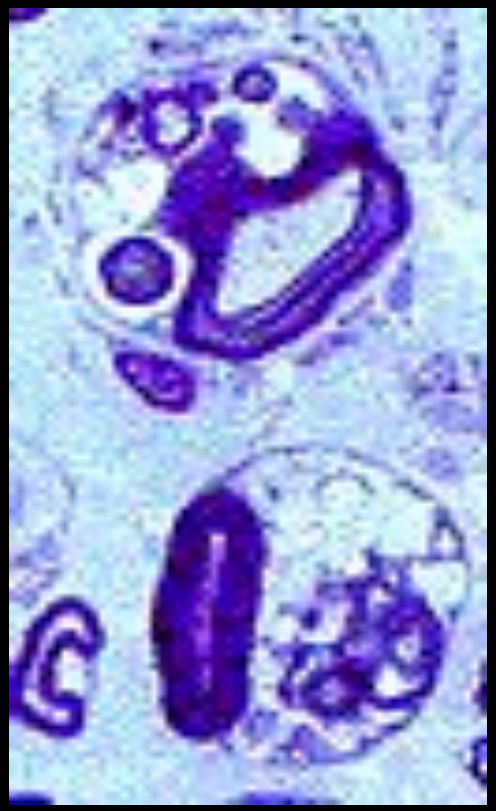


Metachromatic Leukodystrophy (MLD)

- Clinical
  - A disorder of central and peripheral myelin metabolism due to a defect in arylsulfatase A with autosomal recessive inheritance
  - Infantile type (80% cases)
    - Onset of cerebral symptoms in 2nd year of life, although "peripheral findings" present 3-12 months prior
    - Regression, ataxia and optic atrophy common symptoms
    - Death within months to years
  - Late-infantile type
    - Early development is normal, onset by 30 months of demyelinating disease with neuropathy, dementia, late optic atrophy, death by 5-10 years
- Diagnosis is based on the clinical, radiological, CSF, electrophysiological findings with deficient arylsulfatase A
- Caused by mutation in the arylsulfatase A gene (*ARSA*)

Metachromatic Leukodystrophy (MLD)
Diagnostic Findings





Red flags for a white matter disorder

- Motor stagnation or regression
- Episodic deterioration with an intercurrent illness or head injury
- Mixed UMN and cerebellar signs
- Mixed central and peripheral motor signs
- Acquired macrocephaly
- Deterioration in school performance, change in personality or new onset hyperactivity in an adolescent male

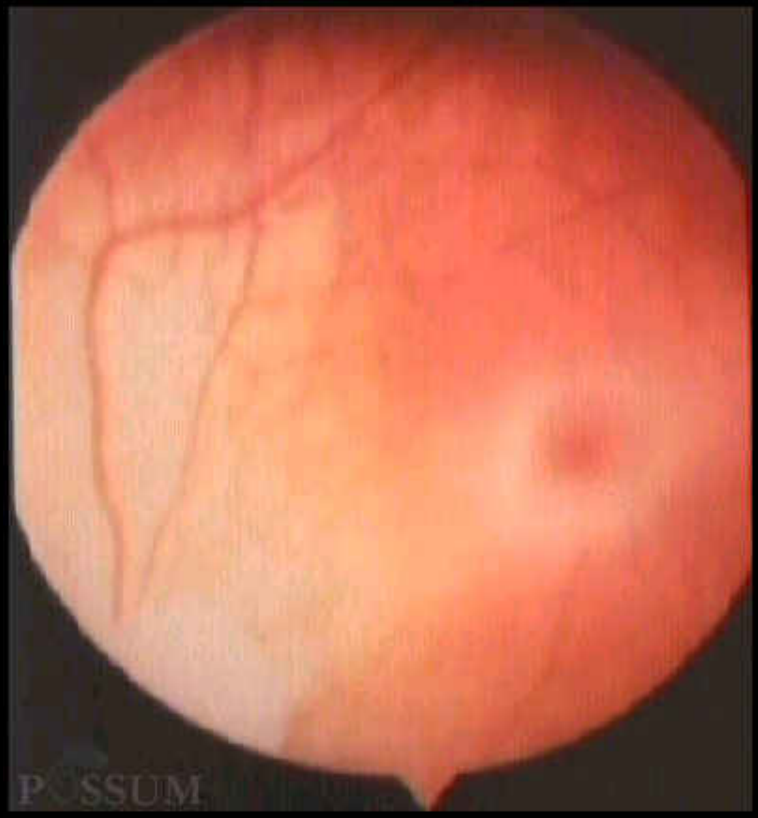
Niemann-Pick Disease

- Clinical
  - Acute forms (types IA and IIA) with rapid progression of hepatosplenomegaly and neurological deterioration with death by 6 years
  - Subacute forms (types IS and IIS) are more slowly progressive and if neurological deterioration follows death occurs in 2nd or 3rd decade
    - Autosomal recessive
    - Sphingomyelinase deficiency
    - Cherry red spot macular may be seen
  - Type (C) is a chronic form and usually of adult onset although they may present with neonatal hepatitis and oculomotor apraxia
- Diagnosis is based on the clinical findings, vacuolated histiocytes and demonstration of sphingomyelinase deficiency
- Genetic testing available

Tay-Sachs Disease

- Clinical
  - Onset of symptoms is between 3-6 months with a higher incidence in the Jewish population
  - An abnormal startle response to noise and light is characteristically the first symptom
  - Regression occurs between 4-6 months
  - A "cherry red spot" macula is universal
  - Macrocephaly and seizures in second year of life
  - Death in early years
- Diagnosis is made by demonstrating hexosaminadase A deficiency
- Caused by mutations in the hexosaminidase A, alpha polypeptide gene (*HEXA*)

Cherry Red Spot Macula



Cherry Red Spot Macula
Causes

- Tay-Sachs disease
- Sandhoff disease
- Cherry-red-spot myoclonus
- Farber lipogranulomatosis
- Niemann-Pick disease
- Metachromatic leukodystrophy
- Sialidosis III

Peroxisomal disorders - disorders of lipid metabolism

- adrenoleukodystrophy
- adrenomyeloneuropathy
- Zellweger syndrome
- Refsums disease
- rhizomelic chondrodysplasia punctata
- pipecolic acidaemia
- actalasia

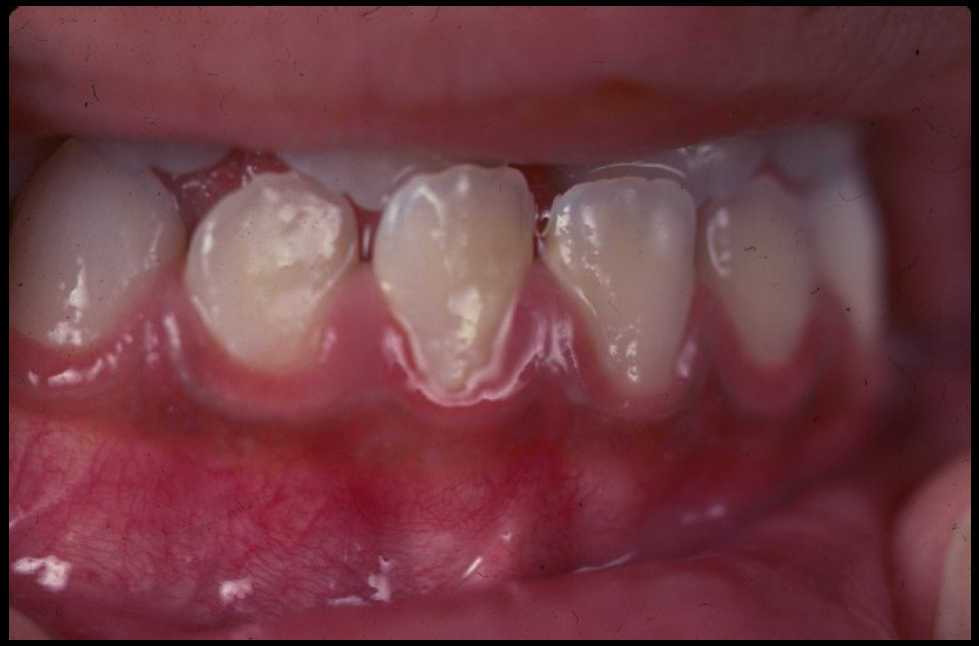
Adrenoleukodystrophy
Clinical

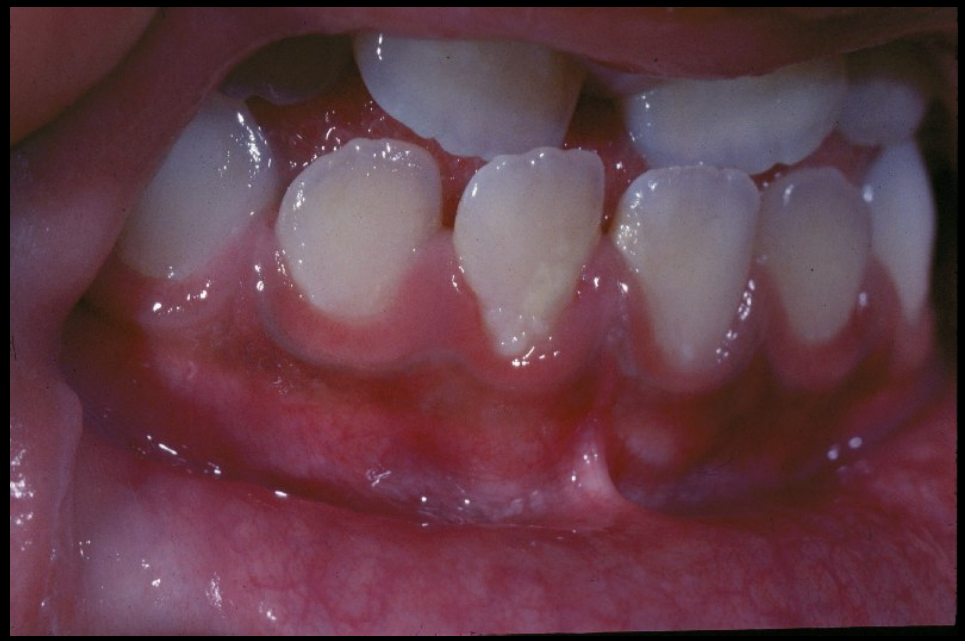
- X-linked progressive peroxisomal disorder of the central nervous system associated with adrenal cortical failure
- Clinical features are considerably variable
  - Neurological deterioration precedes adrenal insufficiency in 85%
    - Onset between 5-10 years
    - Behavior change is the most common initial complaint
    - Poor school performance follows invarialbly
    - Disturbance of gait and coordination, loss of vision and hearing and progression to a persistent vegetative state is the typical clinical pattern

Adrenoleukodystrophy

- Childhood cerebral 48%
- Adolescent cerebral 5%
- Adult cerebral 3%
- Adrenomyeloneuropathy 25%
- Addisons only 8%
- Symptomatic heterozygote female carriers 10-15%
- MRI posterior predominant parieto-occipital lesions

Adrenoleukodystrophy
Clinical





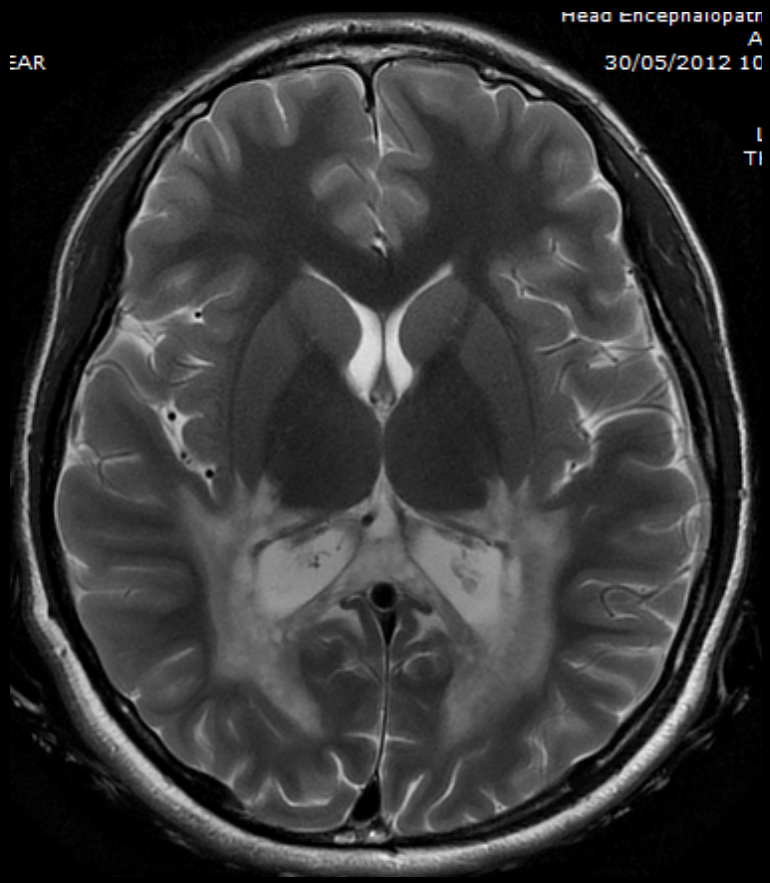
Gum Pigmentation

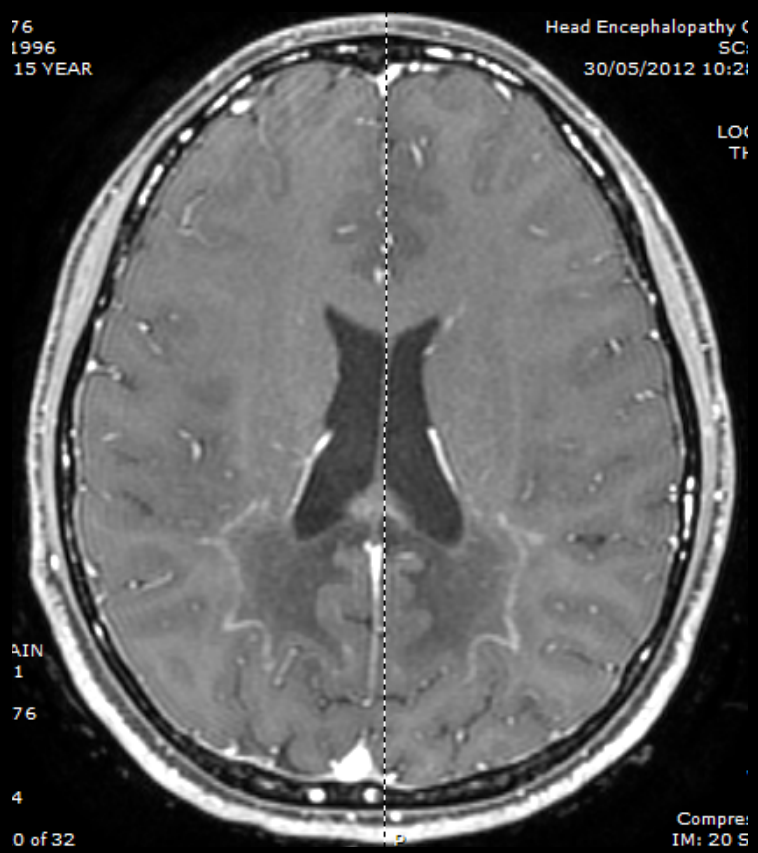
Adrenoleukodystrophy
Diagnosis

- The diagnosis is based on:
  - Clinical history
  - Presence of adrenal insufficiency
  - Laboratory evidence of demyelination
    - CSF protein elevated
    - CT or MRI evidence of white matter abnormalities
  - Elevated serum levels of very-long-chain fatty acids (C26:C22 ratio)
  - caused by mutations in the ATP-binding cassette, subfamily D, member 1 (*ABCD1*) that is located in the peroxisomal membrane (ALDP protein)

Adrenoleukodystrophy

MRI Imaging





Adrenoleukodystrophy
Treatment

- Treat adrenal insufficiency with steroids
- Lower very-long-chain fatty acids
  - Dietary restriction
  - Erucic Acid (Lorenzo's oil)
  - Other
- Immune modulation
- Gene therapy
  - Bone marrow transplantation
  - Other

Zellweger syndrome

- autosomal recessive due to mutations in multiple *PEX* genes associated with peroxisome biogensis
- unable to import proteins into peroxisomes efficiently
- wide clinical spectrum
  - dysmorphic
  - failure to thrive
  - liver problems (prolonged jaundice)
  - renal / genital malformations
  - stippled epiphyses

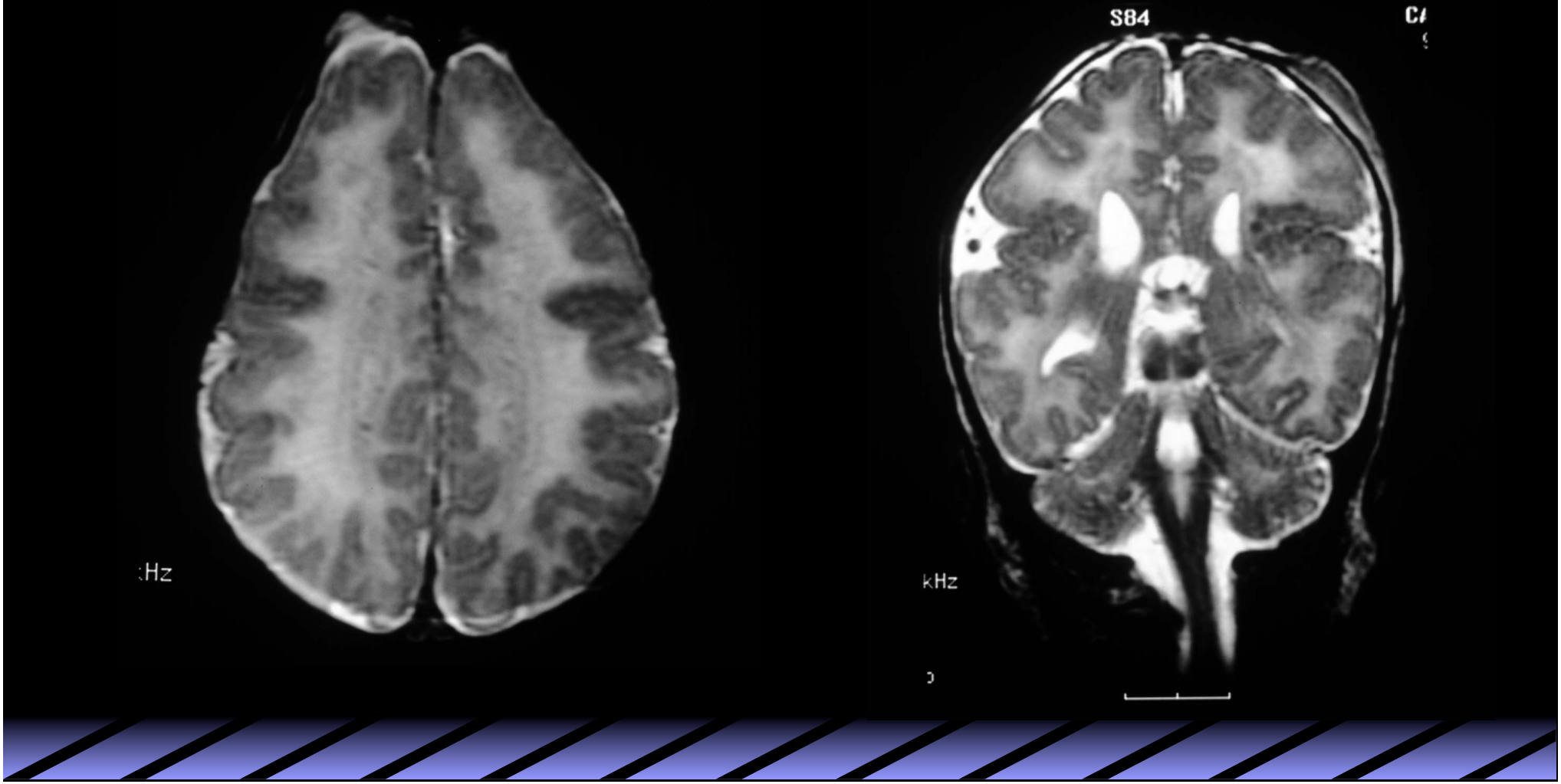
Zellweger syndrome

- neurological manifestations
  - severe mental retardation / GDD then regression
  - hypotonia
  - seizures
  - sensorineural deafness
  - brain malformations
    - polymicrogyria
    - abnormal white matter
    - callosal dysgenesis

Zellweger syndrome

- macrocephaly
- flat / round face
- high forehead
- micrognathia
- low, posterior ears
- anteverted nares
- hypertelorism
- cataracts
- high arched palate

Zellweger syndrome

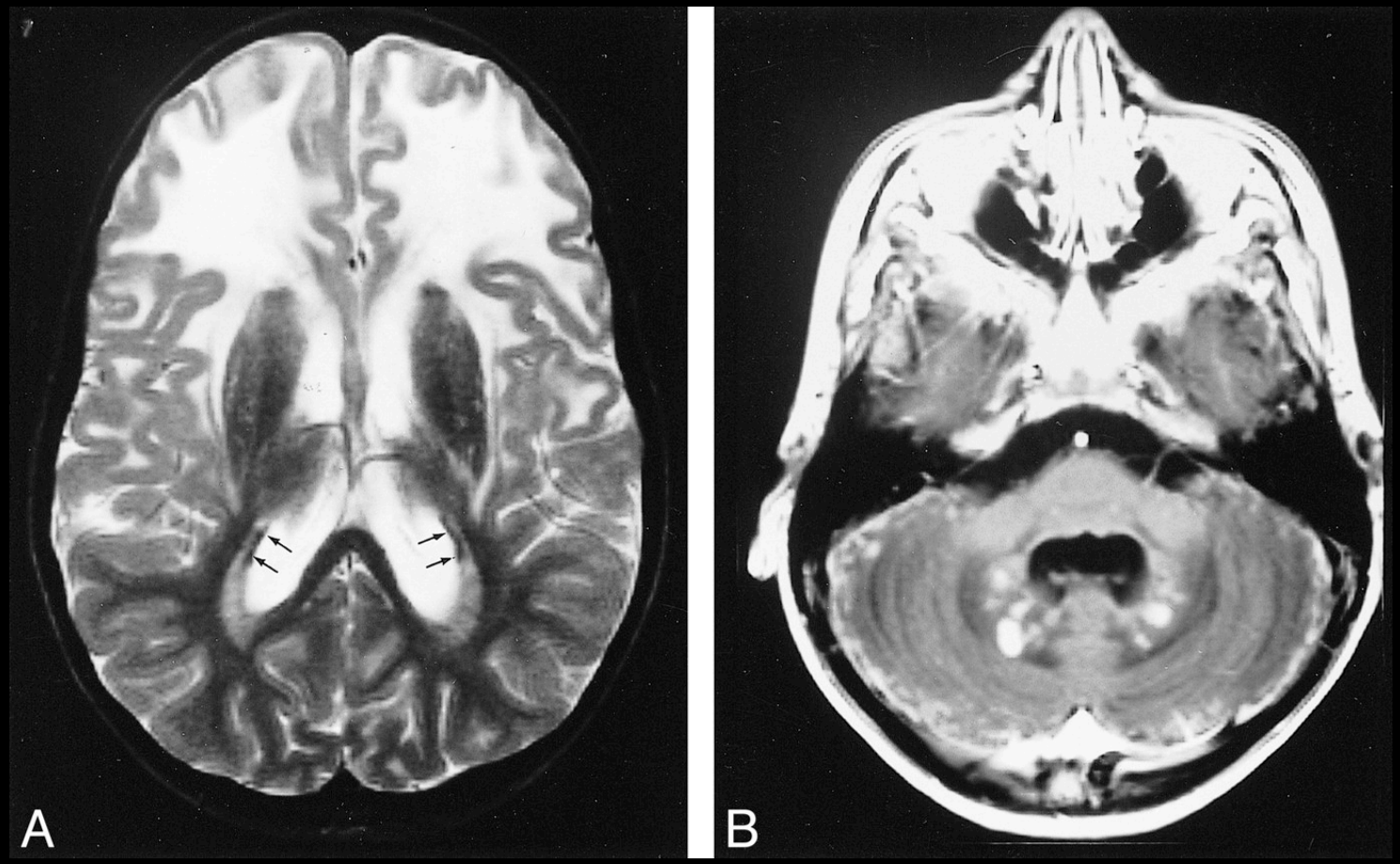


Other types of leucoencephalopathies

Alexander Disease

- Clinical
  - Progressive neurodegenerative disorder with early onset megalencephaly, psychomotor retardation, spasticity and seizures
  - Death usually by 6 yrs
- Diagnosis is based on:
  - Clinical history and findings
  - Brain biopsy showing Rosenthal fibres in a predominantly perivascular position
  - Caused by mutations in the glial fibrillary acidic protein gene (*GFAP*)

Alexander Disease



Canavan Disease

- Clinical
  - Developmental regression in infancy, visual loss, progressive head enlargement, seizures, spasticity, optic atrophy and death in childhood
- Diagnosis is based on:
  - Clinical history with evidence of macrocephaly
  - Imaging with macrocephaly and diffuse subcortical and periventricular white matter abnormalities
  - Increased NAA peak on MRS
  - Aspartoacylase deficiency with N-acetylaspartic aciduria
  - Caused by mutations in the aspartoacylase gene (*ASPA*)

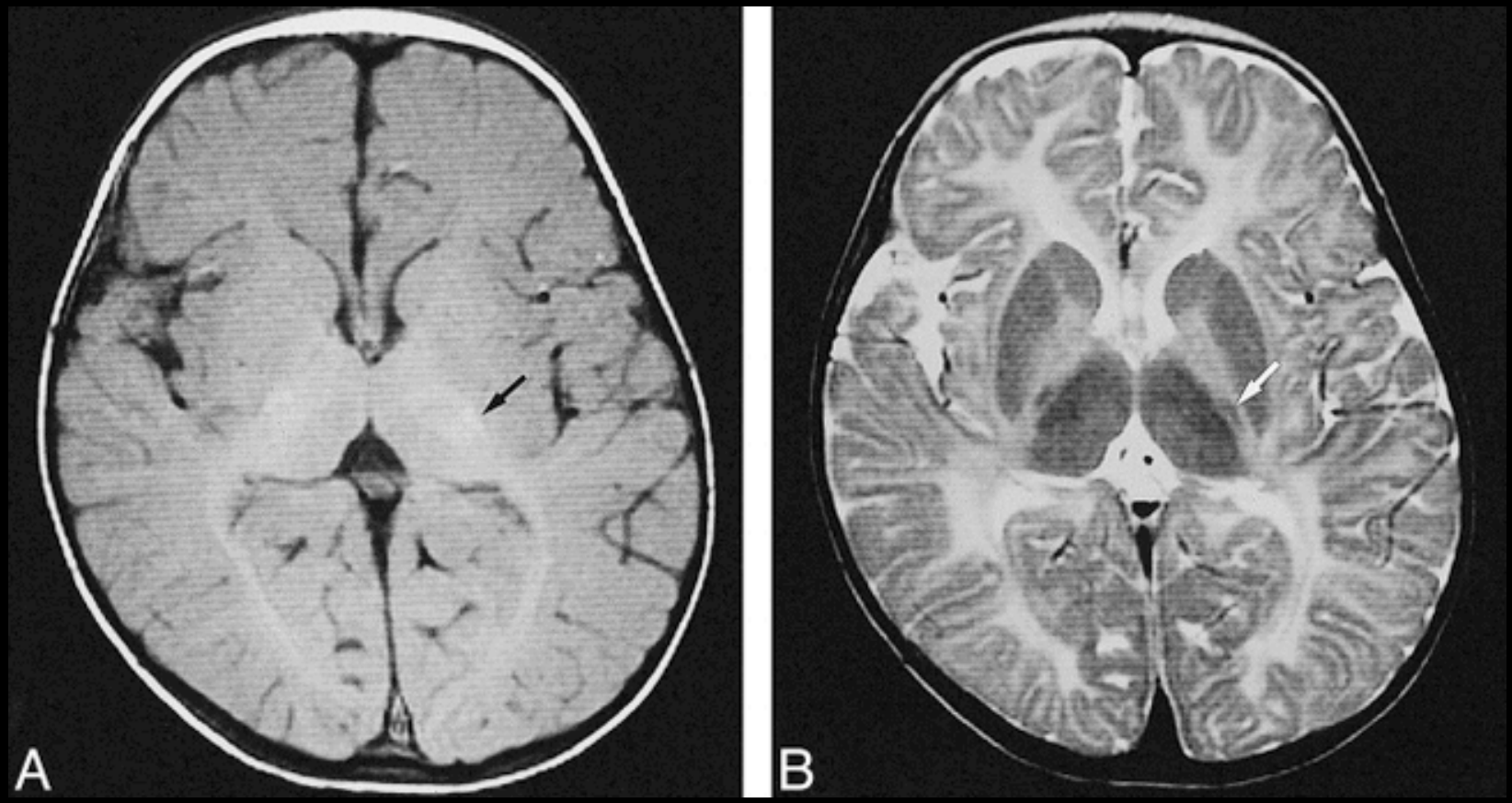
Pelizaeus-Merzbacher Disease

- Myelin Protein Disorder
- Hypomyelinating leucoencephalopathy
- Clinical
  - Progressive psychomotor retardation, nystagmus, choreoathetosis and ataxia with death in the second decade
  - The connatal form presents shortly after birth with aggressive course including severe hypotonia and feeding difficulties

Pelizaeus-Merzbacher Disease

- Radiology
  - MRI: "tigroid" appearance in white matter.
  - Diffuse increase in WM signal on T2 weighted images
- Genetics
  - X-linked and caused by mutations in the proteolipid protein 1 gene (*PLP1*)
  - a related disease known as Peliaeus-Merzbacher-like disease caused by mutation in the gap junction alpha-12 gene (*GJA12*)

Pelizaeus-Merzbacher Disease



Other degenerative disorders

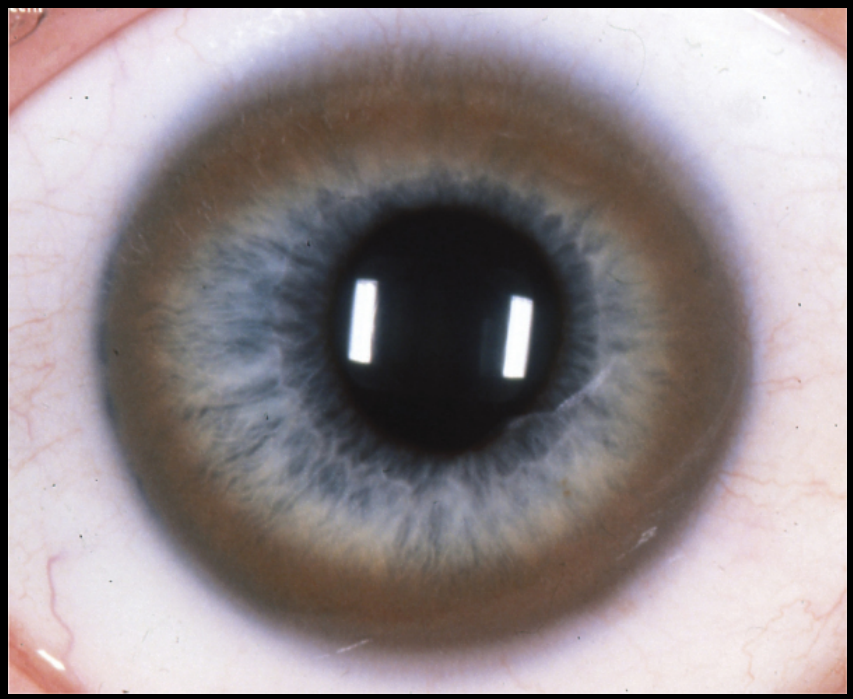
Wilson Disease
General

- Inherited autosomal recessive disorder of copper metabolism resulting in copper accumulation and toxicity in liver, brain, cornea, kidney and other organs
- Prevalence 30 per million
- 1 in every 90 is a carrier
- Caused by mutation in the ATPase, Cu++ transporting, beta polypeptide gene (*ATP7B*) which transports copper across cell membranes

Wilson Disease
Clinical

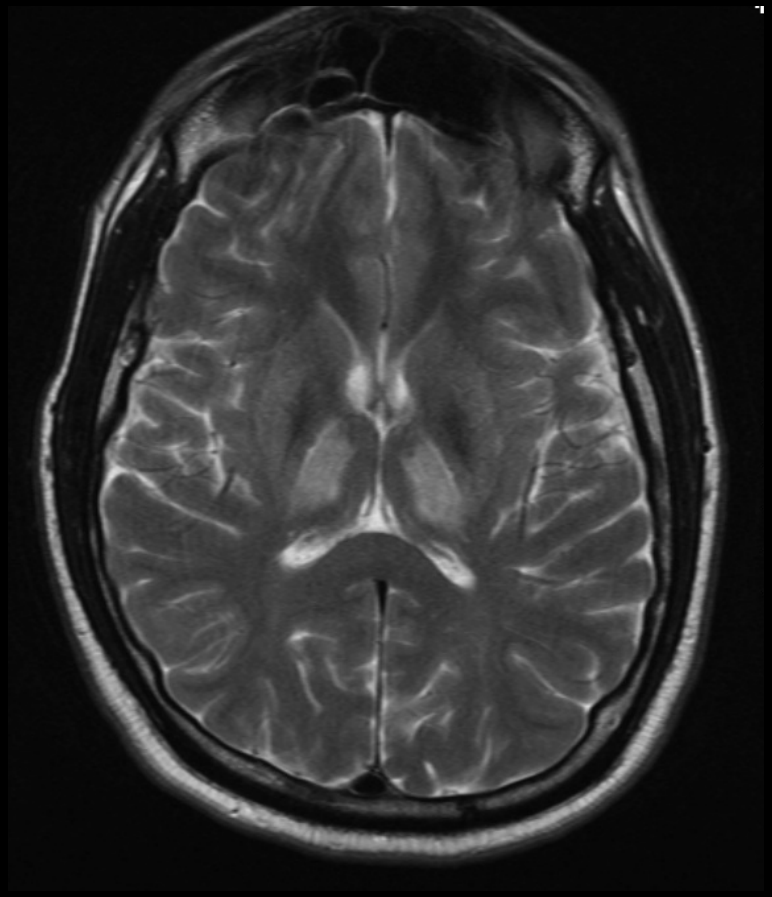
- Heterogeneous clinical manifestations
  - Hepatic
    - May present in acute liver failure with haemolysis
  - +/- neurological and psychiatric symptoms
- Neurological presentation
  - Parkinsonism
  - Pseudosclerotic
  - Dystonia
  - Chorea
- Kaiser-Fleischer rings usually present when there is neurological involvement

Wilson Disease
Ophthalmological findings



Kayser-Fleischer Rings

Wilson Disease
MRI Findings

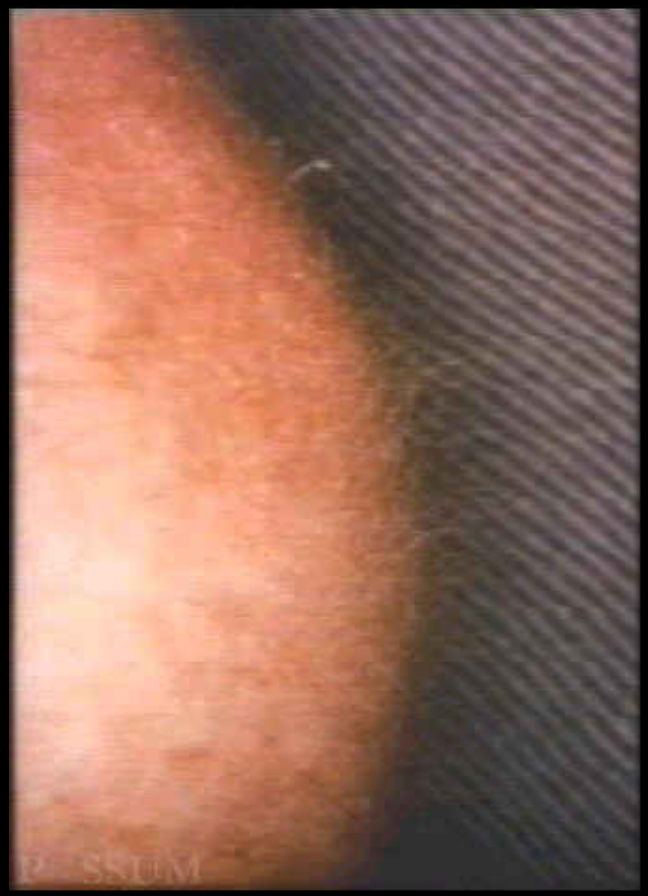


Wilson Disease
Treatment

DECOPPERING

- **REDUCE INGESTION**
  - Nuts, seeds, liver, shellfish
  - Water (copper pipes?)
- **CHELATORS**
  - D-Penicillamine
  - Trientine
  - Tetrathiomolybdate
- **UPTAKE INHIBITION**
  - Zinc

The other side of the coin



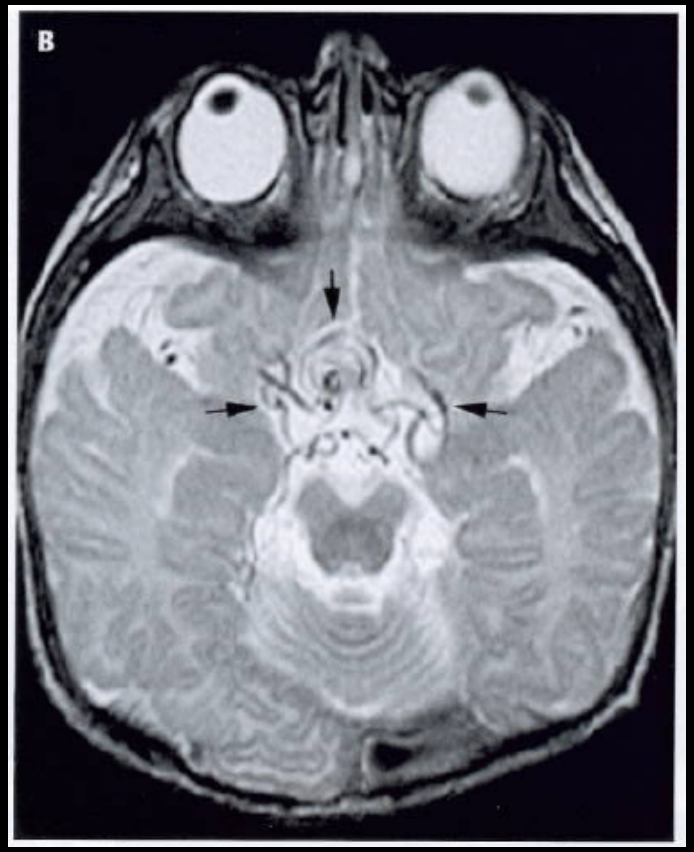
Menkes Disease
Clinical

- X-linked defect of copper transport and metabolism, with abnormal intracellular copper utilisation
- Symptoms are attributed to secondary deficiency of copper-dependent enzymes
  - Temperature instability and feeding difficulties during the neonatal period
    - Prematurity common
  - Developmental regression, seizures, ataxia, growth retardation are seen during the first three months
  - Hypopigmented, sparse, stubby and twisted hair with hypopigmented and hyperextensible skin and hypermobile joints
  - Cerebral neuronal and arterial degeneration
  - Survival rare beyond 3 years although there are reports of milder variants with survival to second decade

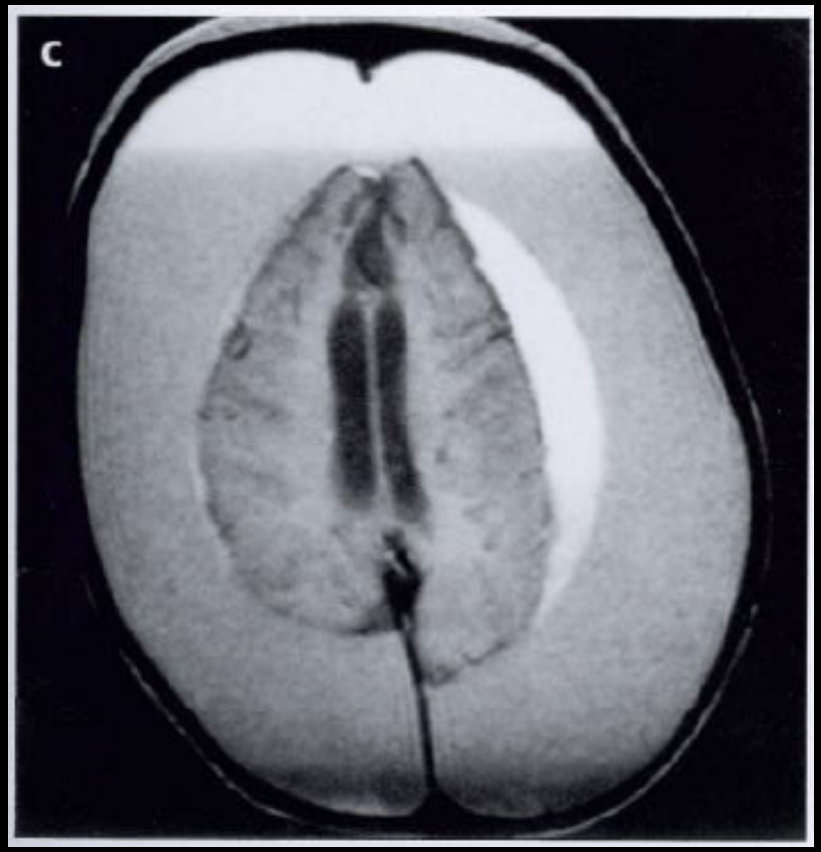
Menkes Disease
Diagnosis and Therapy

- Diagnosis is based on:
  - Clinical history
  - Sex of the child
  - Decreased serum copper and caeruloplasmin levels
- The gene maps to Xq13.2-q13.3
  - Caused by mutation in the ATPase, Cu++ transporting, alpha polypeptide gene (ATP7A)
- Treatment is supportive although intramuscular copper can be used

MRI



Early



Late

Barkovich 2012

Menkes Disease
Treated Child

Child was delivered prematurely and has been on intramuscular copper since birth

Rett Syndrome

- Clinical
  - Females with apparently normal early development and head size, with loss of speech and hand skills and mental regression occurring at around 2 years of age
  - Develop microcephaly, seizures, movement disorder, loss of hand function (hand wringing), hyperventilation/apnoea
  - Neurodevelopmental arrest
  - May be non-ambulant with severe handicap for many years
- Diagnosis is based:
  - on the characteristic history in females
  - caused by mutations in the methyl-CpG-binding protein-2 gene (*MECP2*)

Rett Syndrome

Neuronal Ceroid Lipofuscinosis
General

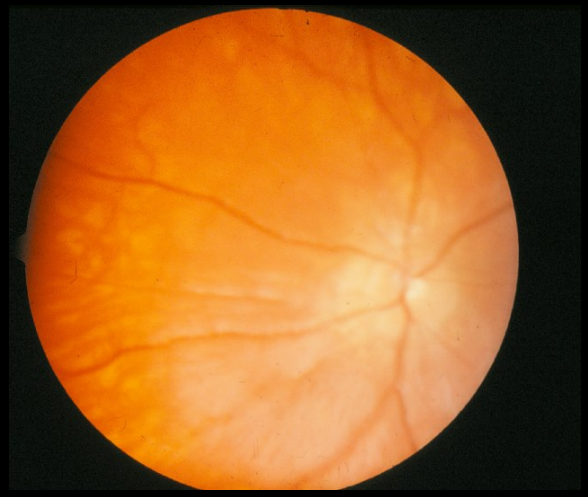
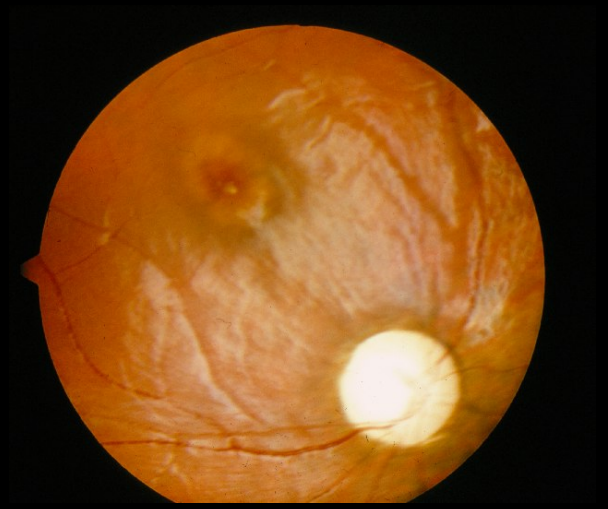
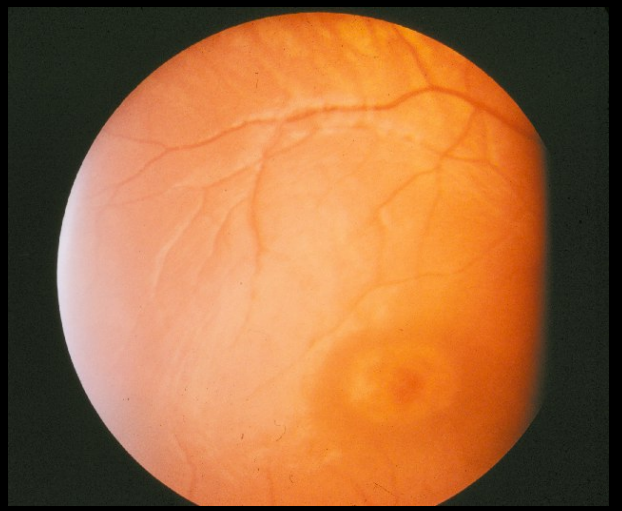
- In this group of genetic disorders, lipopigment is deposited in neurons and some visceral tissues
- Disorders are classified by age of onset and rapidity of progression
- Most types occur after age 2 years
- Most of the disorders are characterized by dementia and blindness
  - Seizures are common in the late infantile forms
- Diagnosis is made by:
  - Characteristic clinical history
  - Ophthalmologic findings
  - Cerebral atrophy
  - Electron microscopic findings of skin, conjunctiva or rectum
  - Genetic testing available for some forms

Neuronal Ceroid Lipofuscinosis

Clinical

Neuronal Ceroid Lipofuscinosis
Ophthalmologic Findings

- Typical findings include:
  - Attenuation of vessels
  - Optic atrophy
  - Pigmentary degeneration of the macula and retina

Neuronal Ceroid Lipofuscinosis
Variants

- Infantile form (Santavuori type)
  - Onset prior to age 2 years
  - Visual impairment, myoclonus are the initial features
  - Rapid regression, hypotonia, ataxia follow
- Late infantile form (Bielschowsky-Jansky)
  - Onset between 2-4 years
  - Seizures rather than blindness are the initial symptom
  - Regression follows with relentless progression
- Juvenile form (Spielmeyer-Vogt-Sjögren disease)
  - Mean age of onset is 6 years
  - Initial symptoms are decreasing vision followed by the development of dementia and seizures

Mitochondrial disorders

- Disorders of the energy-producing organelles
- Mutations in mitochondrial or nuclear DNA
  - May be recessive or X-linked
  - genetic testing available for some forms
- Highly variable manifestations
  - Any organ or system may be involved
  - Different manifestations at different ages
  - CNS and PNS often involved

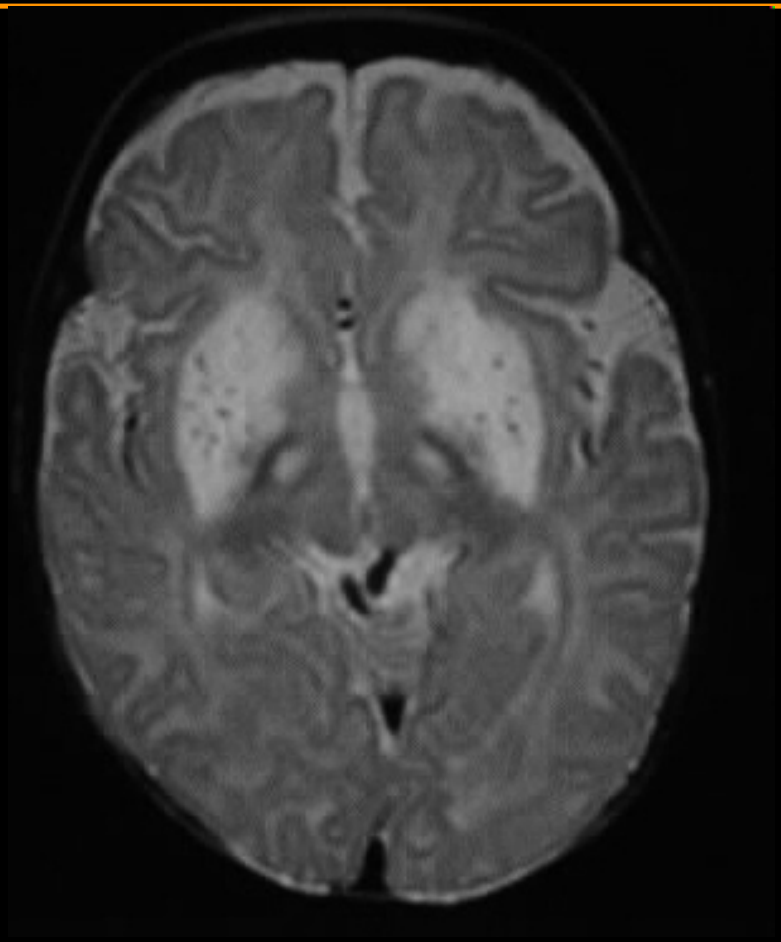
Mitochondrial disorders

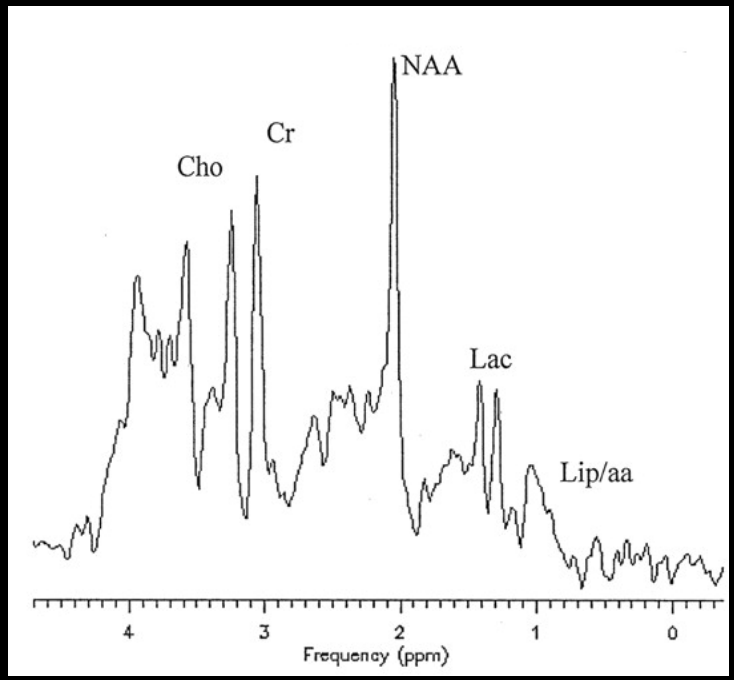
- **Named disorders with neurological involvement**
  - Leber's hereditary optic neuropathy (LHON)
  - Leigh syndrome = subacute sclerosing encephalopathy
  - Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP)
  - Myoneurogenic gastrointestinal encephalopathy (MNGIE)
  - Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
  - Myoclonus Epilepsy Associated with Ragged-Red Fibers (MERRF)

Mitochondrial disorders

- **Suspect in:**
  - Multisystem involvement
  - Multiple-neurological involvement
    - Vision / hearing / ataxia / seizures / neuropathy
  - Signs and symptoms that come and go
  - MRI lesions that may change over time
    - Grey and white matter
- Investigations
  - Often need liver and muscle biopsies to make diagnosis.
  - Blood and CSF lactate may be NORMAL!

MRI / MRS





Congenital disorders of glycosylation
(Previously known as “carbohydrate deficient glycoprotein syndrome”)

- N-glycosylation of a variety of tissue proteins is deficient or defective = disorders of sugar attachment
- Type I disorders involve disrupted synthesis of the lipid-linked oligosaccharide precursor.
- Type II disorders involve malfunctioning trimming/ processing of the protein-bound oligosaccharide chain
- 12 Type I variants and 6 Type II variants described

Congenital disorders of glycosylation

- Multiorgan and multisystem
  - Nervous system / intestines / skin / muscles / eyes
- Neurological manifestations
  - “malformations” – cerebellar “hypoplasia”
  - Ataxia
  - Seizures
  - Retinopathy and optic atrophy
- Transferrin isoforms

Neurotransmitter defects

- **genetic disorders that affect the synthesis, metabolism and catabolism of neurotransmitters**
  - **GABA**
    - Succinic Semialdehyde Dehydrogenase Deficiency (SSADH)
  - **Dopamine**
    - Tyrosine Hydroxylase Deficiency (TH)
    - Aromatic-L-Amino Acid Decarboxylase Deficiency (AADC)
    - Guanosine Triphosphate Cyclohydrolase I Deficiency (GTPCH)
    - Sepiapterin Reductase Deficiency (SR)

Neurotransmitter defects

- **Variable neurological symptoms, but suspect in**:
  - dystonia or tremor
  - hypotonia or rigidity
  - diurnal variation of movement disorder
  - oculogyric crises
  - excessive sweating
  - temperature instability
  - hypoglycemia

A word on testing

- A urine metabolic screen is a screen for a few things
- Plasma amino acids
- Urine amino and organic acids
- CSF amino acids
- CSF neurotransmitters
- CSF lactate and pyruvate
- Paired CSF and blood glucose
- Very Long Chain Fatty Acids
- Lysosomal enzymes
- Biopsies
  - Skin / muscle / liver
- Ophthalmology consult
- Metabolics consult

Very Long Chain Fatty Acids

- X-linked adrenoleucodystrophy (ALD)
- X-linked adrenomyeloneuropathy (AMN)
- peroxisomal biogenesis disorders of the Zellweger spectrum (Zellweger syndrome, neonatal ALD and infantile Refsum disease)
- isolated disorders of peroxisomal b-oxidation (D-bifunctional protein deficiency, acyl-CoA oxidase deficiency).

Lysosomal Enzymes

- GM1-gangliosidosis
- GM2-gangliosidosis type 1 (Tay-Sachs disease, b-hexosaminidase A deficiency)
- GM2-gangliosidosis type 2 (Sandhoff disease)
- Metachromatic leucodystrophy
- Krabbe disease
- Gaucher disease
- Niemann-Pick disease type A and B
- Acid lipase deficiency (Wolman disease, cholesterol ester storage disease)
- Fucosidosis
- a-Mannosidosis
- MPS-VII (Sly syndrome)
- Mucolipidosis type II (I-cell disease)
- Mucolipidosis type III (Pseudo-Hurler polydystrophy)
- Ceroid lipofuscinosis neuronal type 1 (infantile NCL)
- Ceroid lipofuscinosis neuronal type 2 (late-infantile NCL)
- Galactosialidosis
- Schindler's disease