

# Leukodystrophies

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**LEUKODYSTROPHIES - uncommon genetic biochemical defects of:**

- a) **myelin formation (synthesis)** → **DYSMYELINATION** (→ loss of defective myelin); abnormal lipids incorporated into defective myelin are *metachromatic*.
  - b) **myelin maintenance (turnover)** → **DEMYELINATION** (e.g. many *sudanophilic* leukodystrophies).  
 N.B. sudanophilia is produced when Sudan black reacts with neutral fat breakdown products of myelin; since myelin breakdown is result of variety of metabolic or acquired insults, *sudanophilia provides no useful information about pathogenesis!*
- it is very difficult to distinguish demyelination from dysmyelination (both processes frequently operate together).
  - defects involve *lysosomal* or *peroxisomal* enzymes.
  - AUTOSOMAL RECESSIVE disorders (except *classic adrenoleukodystrophy* - X-linked).
  - **variants** are recognized for many disorders (involve separate genetic loci) - follow principle “*earlier age at onset, more severe clinical course*”.
  - **onset**: first months of life ÷ 20s.
  - **clinical - progressive encephalopathy**.
  - progressive; late result is atrophy (at times severe).
  - **neuroimaging with contrast enhancement** (MRI is superior to CT) - diffuse symmetrical involvement of white matter with increased water content:  
 CT - abnormally low density;  
 T2-MRI - increased signal;  
 T1-MRI - decreased signal.
  - **hypomyelination** - MRI closely resembles immature brain;
  - **dysmyelination** - very bright T2-weighted images (much brighter than normal nonmyelinated white matter);
  - **demyelination** - irregular, often asymmetrical areas of increased T2-weighted signal (not as bright as in dysmyelination).
  - SECONDARY or DESTRUCTIVE processes (**demyelination**) are often **asymmetrical!**
  - **symmetry with central distribution\*** is dominant feature in PRIMARY white matter disorders (**hypo-, dys-myelination**).
- \*subcortical U-fibres are involved rather late in disease process.
- N.B. only very few diseases have sufficiently characteristic MRI findings to allow specific diagnosis! (e.g. adrenoleukodystrophy); initial diagnosis largely clinical!
- not yet curable.

Type	Name	Enzyme Defect	Storage Material	Genetics	Age of Onset
<b>PELIZAEUS-MERZBACHER disease</b>					
1	Classic	Mutations in <b>proteolipid protein (PLP)</b> – CNS <b>myelin component</b> .	Sudanophilic material	X-linked (Xq21.3-q22)	Infantile
2	Connatal (Seitelberger disease)			X-linked?	Birth
3	Transitional			Sporadic	Infantile
4	Adult (Löwenberg-Hull disease)			AD	Adult
5	Variant			Not known	Variable
<b>COCKAYNE'S syndrome</b>					
6	Classic	Not known ( <b>DNA excision repair</b> )	Sudanophilic material	AR ( <i>ERCC8</i> gene)	6-12 months
<b>ALEXANDER'S disease</b>					
7	Classic infantile	Not known (dysfunction of <b>astrocytes?</b> )	Not known	Not known	Infants
8	Juvenile				7-14 yrs
9	Adult				Young adults
<b>CANAVAN'S disease</b>					
10	Classic infantile	Aspartoacylase	N-acetylaspartate	AR (17p)	Infants
11	Neonatal			Sporadic	Newborns
12	Juvenile			Sporadic	5 yrs-teens
<b>GLOBOID CELL LEUKODYSTROPHY (KRABBE'S disease)</b>					
13	Classic, infantile	<b>Galactocerebroside β-galactosidase</b> ( <b>lysosomal</b> enzyme)	Galactose cerebroside, psychosine	AR	3-8 months
14	Late onset		Galactose cerebroside		Children, may be adults
<b>METACHROMATIC LEUKODYSTROPHY (MLD)</b>					
15	Classical late infantile (Greenfield)	<b>Arylsulfatase A</b> ( <b>lysosomal</b> enzyme)	Sulfatide	AR (22q13.3-qter)	Late infantile (18-24 months)
16	Juvenile (Scholz)				4-10 yrs
17	Adult (Austin)				Adult
<b>ADRENOLEUKODYSTROPHY (ALD)</b>					
18	Multiple peroxisomal enzyme deficiency (Zellweger syndrome)	Dihydroxyacetone phosphate acetyltransferase	Very long-chain fatty acids	AR	Neonatal
19	Neonatal ALD (Ulrich's disease)	<b>Peroxisomal</b> oxidation (enzyme unknown)		AR	Neonatal
20	Classic form (X-linked Siemerling-Creutzfeldt disease)	<b>Lignoceroyl-CoA ligase</b> ( <b>peroxisomal</b> enzyme)		X-linked recessive (Xq28)	4-10 yrs

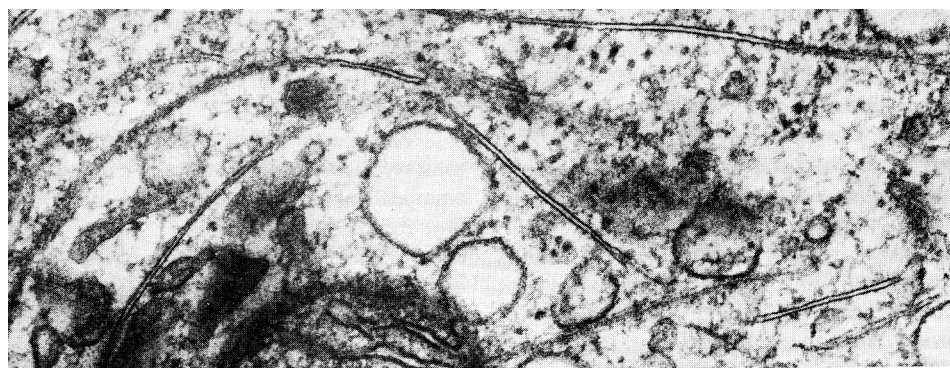
## ADRENOLEUKODYSTROPHY

- **PEROXISOMAL leukodystrophies:** see table above >>

- b) **single peroxisomal enzyme defect** (lignoceroyl-CoA ligase) – **classical (X-linked) adrenoleukodystrophy** (XALD), **adrenomyeloneuropathy**.
- c) **disorders of peroxisome assembly / biogenesis** - **neonatal adrenoleukodystrophy** (NALD, Ulrich's disease), **multiple peroxisomal enzyme deficiency** (Zellweger's syndrome).

### PATHOPHYSIOLOGY

- peroxisomal *lignoceroyl-CoA ligase* deficiency → inability to oxidize **very long chain fatty acids** (esp. C:25 and C:26) within peroxisomes.
- **characteristic intracellular lamellar *sudanophilic inclusions*** (in CNS white matter, peripheral nerves, adrenal zona fasciculata and reticularis, testis) - cholesterol esters with striking excess of saturated unbranched VLCFA.
- **adrenal cortex** – ballooned cells, striated cytoplasm and specific microvacuoles; → **adrenal atrophy**.
- **CNS & PNS:**
  - 1) **extensive diffuse demyelination** (sparing subcortical U-fibers)
  - 2) perivascular mononuclear infiltration.



Electron micrograph of the characteristic curvilinear profiles seen in adrenoleukodystrophy.

### CLINICAL FEATURES

N.B. affected individuals in same family may have quite different clinical courses!

- I. **Adrenal insufficiency** (degree varies considerably): fatigue, intermittent vomiting, salt craving, hyperpigmentation (most prominent in skin folds).
- II. **Progressive psychomotor decline**

#### Neonatal adrenoleukodystrophy

- dysmorphic coarse features, poor mental development, early seizures, retinopathy, hepatomegaly.
- very protracted course.

#### Classical (X-linked) adrenoleukodystrophy - more fulminating disorder!

- locus Xq28 is near loci for **hemophilia A** and **red-green color blindness** (defects in red-green color discrimination are frequent in ALD patients, suggesting *contiguous gene syndrome*).
- 4% female carriers are symptomatic.
- patients are boys with normal early development!
- **childhood variant** (onset at 4-10 yrs): **behavioral change** (abnormal withdrawal, aggression, poor memory, difficulties in school) → rapid regression of auditory discrimination, spatial orientation, speech, and writing → seizures → spastic paraparesis / quadriparesis, dysphagia, visual loss (demyelination along entire visual pathway), progressive dementia → **vegetative state** within 2 years of onset → **death** (e.g. from adrenal crisis) 1-10 yrs after onset.
- **adolescent variant** – onset at 10-21 yrs.

#### Adrenomyeloneuropathy - **adult variant** of XALD – onset after age of 21 yrs.

- predominantly **spinal cord & peripheral nerve** involvement developing for decades (slowly progressive spastic paraparesis, bladder dysfunction, hypogonadism).
- **brain** unaffected.
- adrenal insufficiency may have been present since childhood.

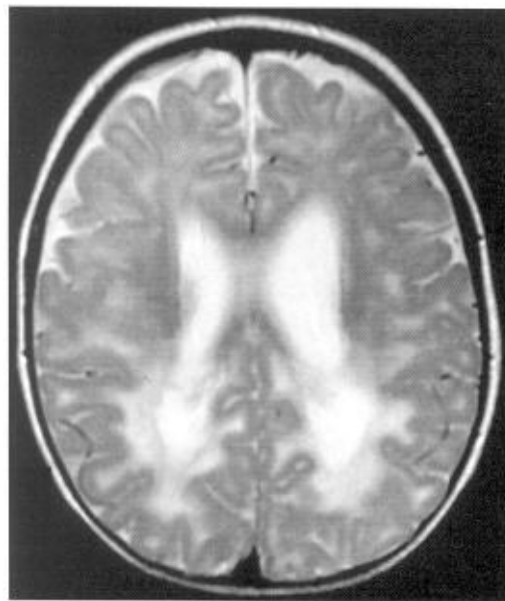
### DIAGNOSIS

- unbranched saturated **very long chain fatty acids (VLCFA)**↑ in plasma & cultured skin fibroblasts.

- also positive in 85% female carriers.

N.B. people taking *ketogenic diet* may show [VLCFA]↑ in plasma but not cultured skin fibroblasts.

- **CSF** ≈ MS (protein↑ may be higher).
- **neuroimaging** - symmetric **hyperdense & hypodense band-like demyelination regions** proceeding in characteristic POSTERIOR-TO-ANTERIOR pattern (begin in **parieto-occipital white matter**).
  - enhancement along leading (anterior) edge of demyelination.
- **adrenal function tests** (esp. ACTH stimulation test) - primary adrenal insufficiency (even in absence of clinical signs).
- **DNA probe** is available for gene screening.



PRENATAL DIAGNOSIS – [VLCFA] in amniotic fluid cells or chorionic villus sampling.

### TREATMENT

1. **Dietary treatment:**
    - *dietary avoidance of VLCFA* does not lead to biochemical change because of endogenous synthesis.
    - **Lorenzo's oil** (4:1 mixture of GLYCEROL TRIOLEATE and GLYCEROL TRIERUCATE) lowers endogenous VLCFA synthesis → normalized [VLCFA] in plasma within 4 weeks;
      - N.B. this biochemical change does not have clinical correlate!
      - **neurologically intact patients** → possibly reduced frequency and severity of subsequent neurological disability.
      - **symptomatic patients** - results are disappointing.
  2. Bone marrow **transplants** before neurologic deterioration.
  3. **Steroid replacement** (at least, during stressful periods) for adrenal insufficiency.
- **immunosuppression** (with cyclophosphamide) does not alter clinical course.

## METACHROMATIC LEUKODYSTROPHIES (s. SULFATIDE LIPIDOSES)

- most common leukodystrophy!

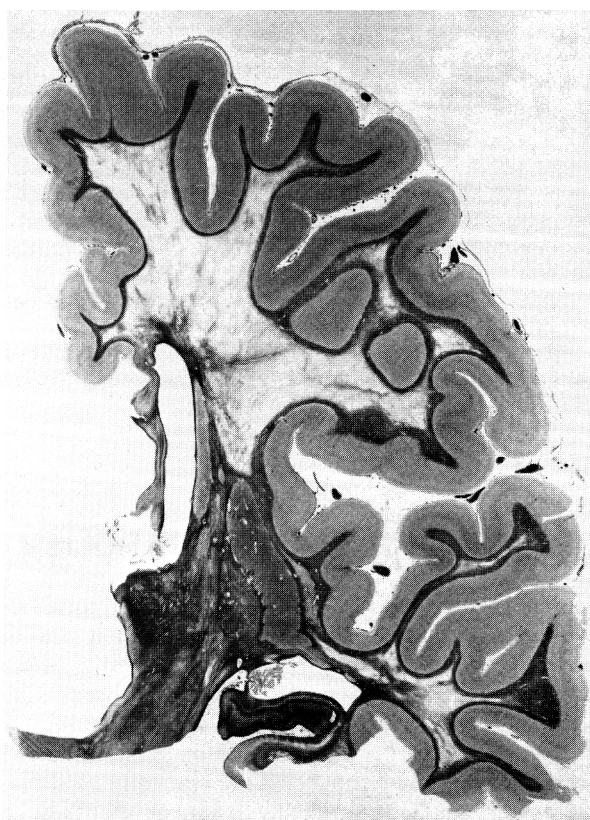
see table above >>, also p. 759 >>, p. 761 >>

### PATHOPHYSIOLOGY

- **METACHROMATIC** - staining properties of accumulating lipid *sulfatides* (brown hue with toluidine blue rather than usual blue of myelin).
- autosomal recessive **lysosomal enzymatic defect** - *arylsulfatase-A* (myelin catabolism enzyme) in 22q13.3-qter.
- sulfatides accumulate in lysosomes of:
  - 1) oligodendrocytes and Schwann cells → demyelination.
  - 2) kidneys, pancreas, adrenal glands, liver, gallbladder.

Arylsulfatase has 3 isoenzymes - A, B, and C.

- MULTIPLE SULFATASE DEFICIENCY (mucopolysaccharidosis) - markedly reduced activity of arylsulfatases A and B.



Metachromatic leukodystrophy. Demyelination is extensive. Subcortical fibers in cerebral hemisphere are spared. (Luxol-fast-blue, PAS stain.)

### CLINICAL FEATURES

**Classical late infantile form** (onset at 18-24 months → **subacute** decline over 6-12 months): megalencephaly, intellectual deterioration, seizures, peripheral neuropathy, ataxia, gait disturbance, hypotonia, bulbar signs.

- in terminal stage, **switching point** occurs: hypotonia → hypertonia (frank spasticity), involuntary movements.
- patients die by 5-10 years of age (some reach vegetative trough and live well into their teens).

**Juvenile form** (onset at 4-10 years): bradykinesia and poor school performance (daydreaming, confusion, emotional lability) → spastic gait, ataxia, extrapyramidal dysfunction, increased myotactic reflexes, generalized convulsions.

- deterioration is usually **chronic** (often not bedridden even 5-10 years after onset) - live for ≥ 20 years.

**Adult form** (onset after puberty): personality and mental changes → slowly progressive **frank dementia**, psychosis → pyramidal & cerebellar changes.

- no peripheral neuropathy.

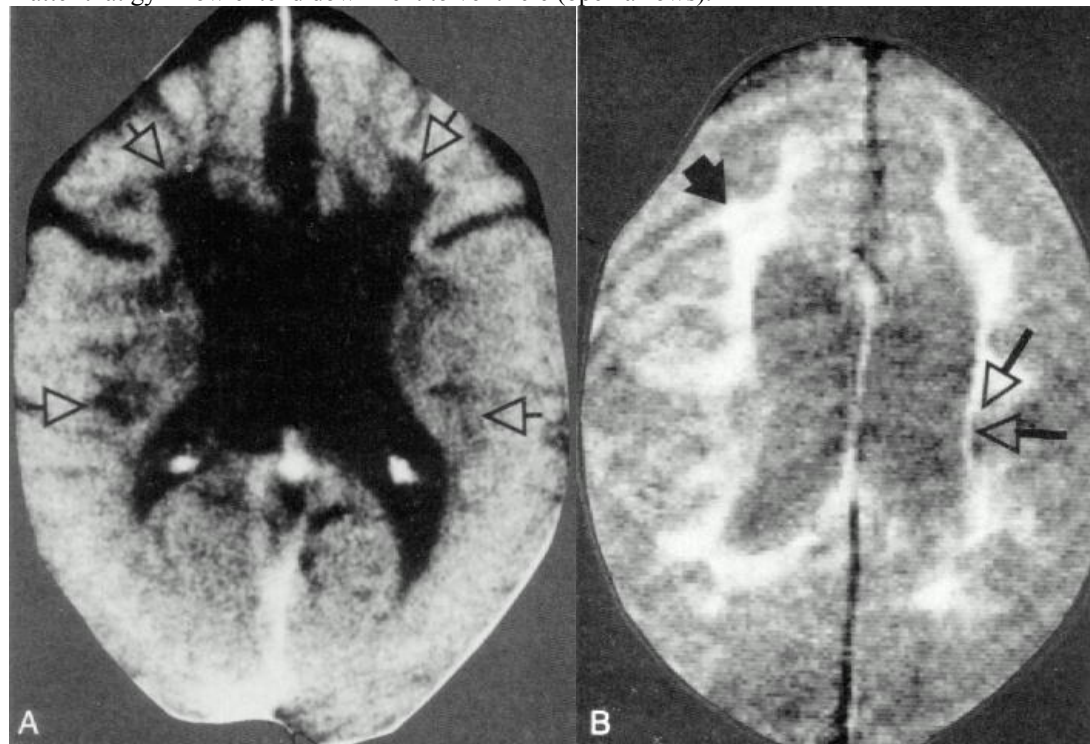
### DIAGNOSIS

- **CSF** protein 150-300 mg/100 ml with no qualitative abnormalities.
  - *arylsulfatase-A* activity↓ in **urine** or in **leukocytes**.
    - carriers have activity 25-50% of normal.
    - heterozygotes have activity 10 times more than patients.
- N.B. patients with **genetic deficiency of sulfatide activator protein** (required for arylsulfatase A) may have MLD, but commonly used enzyme assays may fail to diagnosis this.
- **metachromatic granules** in **urine**.
  - decreased nerve conduction velocities!!!
  - **metachromatic material** in **nerve biopsy**.

### Adult MLD

A. CT - open arrows indicate symmetrical lesions of markedly decreased absorption in white matter.

B. T<sub>2</sub>-MRI - black arrow shows confluent hyperintense signal in diseased white matter. So shrunken is this ribbon of white matter that gyri now extend down next to ventricle (open arrows).



### TREATMENT

- bone marrow transplantation.

## GLOBOID CELL LEUKODYSTROPHY (s. KRABBE disease)

see p. 759 >>, p. 761 >>

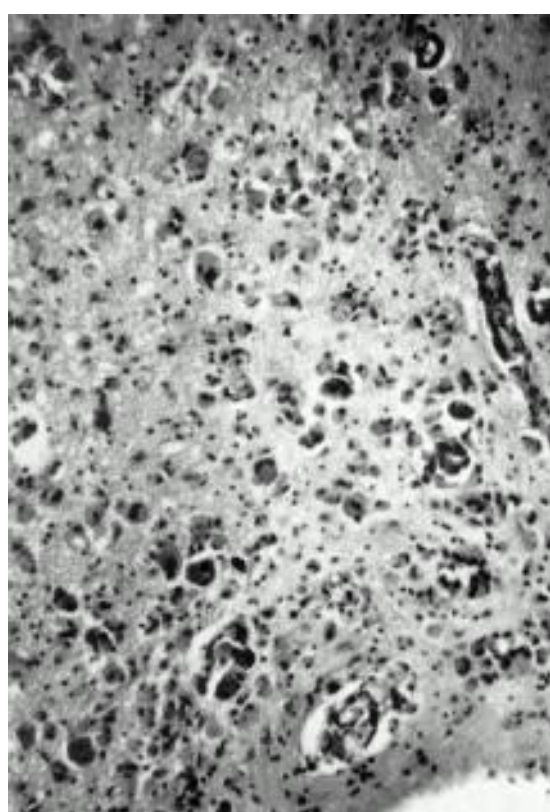
- distributed worldwide; no gender, racial, or ethnic proclivities.

### PATHOPHYSIOLOGY

- autosomal recessive **lysosomal enzymatic defect** - *galactocerebroside- $\beta$ -galactosidase*, s.  *$\beta$ -galactocerebrosidase* (gene on chromosome 14) → accumulation of *galactose cerebroside*, *psychosine* (s. *galactose sphingosine*)\*.

\*cytotoxic compound that causes oligodendrocyte injury

- myelin loss in CNS & PNS.
- white matter is atrophic and gliotic (firm-rubbery on palpation).
- GLOBOID CELLS** (found deep in white matter around and within vessels) are of two types (equally important in pathogenesis):
  - Epithelioid cells** - round, medium size, mononuclear.
  - Globoid bodies** – large (20-50  $\mu$ ), irregular, often multinucleated.
    - cytoplasm stains positively with PAS and only faintly with Sudan black.
    - no metachromasia!
    - electron microscopy - electron-dense granules within cytoplasm (fine filaments in both electron-dense linear or curved tubular profiles is distinctive sign in Krabbe's disease).



- PNS involvement (segmental demyelination) varies; histiocytes with foamy cytoplasm and tubular inclusions are present instead of globoid cells.

### CLINICAL FEATURES

- purely neurological syndrome (vs. other leukodystrophies).  
Patients are normal at birth!

**Classic infantile form** (onset at 3-8 months): irritability, intermittent fever, episodic limb or trunk rigidity, heightened startle responses, feeding problems, vomiting, seizures → severe **hypertonus** with obvious opisthotonos.

- by 9 months of age, **blindness** (optic atrophy), **deafness**, **decerebrate vegetative state**.
- death at age  $\approx$  2 years.

**Late-onset form** (onset in infancy, childhood, or even in adult life) - extremely uncommon!: cortical blindness, optic atrophy, pyramidal spasticity, slowly progressive dementia.

- rate of regression is relatively slow.

### DIAGNOSIS

- **enzymatic assays**:

Disease or carrier state - assays on **WBC**, **serum**, **fibroblasts**.

Prenatal diagnosis - assays of **amniotic fluid**.

- CSF protein $\uparrow$
- CT** - periventricular hyperdensities.
- MRI** - white matter involvement of cerebrum & cerebellum.
- nerve conduction velocities $\downarrow$

### TREATMENT

- no curative treatments; various attempts to enhance enzyme activity:
  - liposomes containing beta-galactosidase.
  - bone marrow transplantation.

## PELIZAEUS-MERZBACHER disease

- sudanophilic leukodystrophy with **almost total absence of normal myelination**.

### PATHOPHYSIOLOGY

**Classic form** - mutations in **proteolipid protein (PLP)** gene (Xq21.3-q22);

- PLP (integral membrane protein) accounts for 50% of CNS myelin proteins.
- PLP holds outer myelin leaflets together at intraperiod line.

N.B. one mutation in this gene causes variant as **familial spastic paraplegia (SPG2)**

- tigroid pattern in CNS** (on myelin stains) - patches of **oligodendrocyte loss with sudanophilic demyelination** interspaced with **perivascular islands of relatively intact myelin**

islands of spared myelin against nonmyelinated background

- no sparing of U-fibers!
- axons and neurons are usually well preserved.
- peripheral nerves are well myelinated!

### CLINICAL FEATURES

**Classic form**

- more prominent in males.
- onset in first few months of life: **slow, rotary "cogwheel" nystagmus** (nearly diagnostic!) and **head tremor** → ataxia, attention tremor, choreoathetosis, spasticity, dysarthria, optic atrophy, seizures, mild degree of dementia.
- by school age, affected boy is usually mute and confined to wheelchair → little further deterioration.
- death is delayed until early adulthood (from intercurrent illness).

### Variants

**Connatal form (Seitelberger disease)** - *more severe* than classic form (brain, cerebellum, brain stem, and spinal cord are essentially devoid of myelin); present at birth; death within first year of life.

**Transitional form** – *intermediate severity* between classic and connatal forms; death by 5-10 yrs.

**Adult form (Löwenberg-Hull disease)** - *very slow course*, no ocular abnormalities, characteristic episodic psychotic events.

### DIAGNOSIS

- CT** – hypomyelination (resembles immature brain), cerebellar atrophy.
- MRI**:
  - persistent myelin islands
  - reversal of normal gray-white matter signal relationships consistent with dysmyelination.
  - low-intensity signals from lentiform nucleus (iron deposition).
- normal CSF protein!

- normal nerve conduction velocities!
- diagnosis can be made by **cerebral biopsy**.
- PRENATAL DIAGNOSIS (in family with known mutation) - **DNA analysis** of chorionic villi samples.

**TREATMENT**

- no curative therapy.

**CANAVAN disease (s. SPONGY DEGENERATION of nervous system)**

- spongiform leukoencephalopathy.

**PATHOPHYSIOLOGY**

- **aspartoacylase** deficiency (gene on 17p) → **N-acetylaspartic acid** accumulation.
- changes are limited to white matter (*extensive demyelination*); axonal fibers and oligodendroglia are not extensively affected.
- **vacuoles** (excessive fluid accumulation) in variety of brain cells (esp. astrocytes) - SPONGY APPEARANCE.
- **gigantic abnormal mitochondria** (dense filamentous granular matrix and distorted cristae) in watery cytoplasm of hypertrophied astrocytes (Alzheimer type II astrocytes).
- brain is enlarged (increased water content) – megalencephaly.
- vacuoles enlarge and split myelin sheath to form cysts that communicate with extracellular space → extensive demyelination → extensive gliosis.

**CLINICAL FEATURES**

**Classic infantile form** - occurs predominantly in Ashkenazi Jews and Saudi Arabians.

- begins within few months of birth: **megalencephaly**, apathy, hypotonia → spasticity, decorticate and decerebrate posturing, seizures, optic atrophy, dysautonomia.
- death in vegetative state by 3-4 years of age.

**Neonatal form** - deadly within few weeks (lethargy, hypotonia, diminished spontaneous movement, dysphagia).

**Juvenile form** (onset after 5 years of age): ataxia, tremor, ptosis, dementia, progressive cerebellar symptoms, spasticity, loss of vision.

- other organ systems are sometimes involved (diabetes mellitus, hyperaldosteronism, heart block).
- extends into adolescence.

**DIAGNOSIS**

- **N-acetylaspartate** in plasma & urine.
- **enzyme deficiency** in cultured skin fibroblasts.
- **CT & MRI** – enlarged brain, increased lucency of white matter, poor demarcation of gray and white matter → **severe brain atrophy** (with ventricular enlargement and gaping sulci).
- CSF and nerve conduction velocities are normal.
- PRENATAL DIAGNOSIS and CARRIER DETECTION by **DNA analysis** are available in > 90% cases.

**TREATMENT**

- no curative therapy.
- generous use of antiepileptic drugs and antibiotics.

**COCKAYNE syndrome**

- progressive multisystem disease.

- mutation in **ERCC8** gene (important in **DNA excision repair**).

**PATHOPHYSIOLOGY**

- no consistently specific biochemical abnormalities.
- **tigroid pattern** of patchy demyelination among preserved islands of myelin (similar to Pelizaeus-Merzbacher disease).
- brain is small (< 500 g) with **extremely thin (atrophic) white matter**.
- **calcifications** in globus pallidus & cerebellum, **mineralization** of small arteries.
- cerebral cortex may contain diffuse proliferation of bizarre multinucleated astrocytes.
- **PNS** - segmental demyelination with preservation of axons.
- pronounced involvement of **multiple systems!!!**

**CLINICAL FEATURES**

- normal at birth.
  - onset at 6-12 months.
  - most survive at least into 2<sup>nd</sup> decade.
- 1) **skin** - photosensitive dermatitis.
  - 2) **CNS** - **mental retardation** (most do not speak, but pleasant personality), progressive UMN & cerebellar dysfunction, normal-pressure hydrocephalus, neural deafness.
  - 3) **bones** - peculiar **cachectic appearance** with facial-somatic dysplasia (extreme dwarfism, arresting facies with large ears, long aquiline beaklike nose, deep set eyes, thin lips, jutting chin, loss of severely carious teeth, microcephaly, kyphosis, joint deformities);
    - abnormally advanced bone age.
    - body proportions, although miniature, are appropriate for child's age.
    - shedding of deciduous teeth and puberty occur on time (although testes and breasts are underdeveloped).
  - 4) **eyes** - retinitis pigmentosa, optic atrophy, lenticular cataracts, corneal opacities, impaired lacrimation.
  - 5) anomalies of **renal** function.

**DIAGNOSIS**

- **neuroimaging** - stippled calcification of basal ganglia and cerebellum.
- CSF protein may be elevated.
- nerve conduction velocity ↓.
- skin fibroblasts show **defective DNA repair** when exposed to UV light.

**TREATMENT**

- treatment of normal pressure hydrocephalus (when it occurs) may be beneficial.

## ALEXANDER disease

- degenerative disorder of unknown origin.

### PATHOPHYSIOLOGY

- dysfunction of ASTROCYTES.

- **ROSENTHAL fibers** - elongated hyaline, eosinophilic inclusions found exclusively in astrocytic footplates.
  - contain B-crystal protein.
  - distributed throughout most of brain (particularly numerous in *subpial*, *subependymal*\*, and *perivascular* locations). \*may obstruct cerebral aqueduct
  - Rosenthal fibers are not pathognomonic (occur in pilocytic astrocytomas).
  - although astrocytes are distended, there is no evidence of abnormal storage material within neurons.
- **CNS demyelination** in regions rich in Rosenthal fibers – may be secondary event!; axon cylinders are preserved.
  - myelin loss is *most severe frontally* (characteristic frontal-to-occipital gradient).
  - demyelination of centrum semiovale is so severe that it may lead to cavitation.
- PNS is not involved.

### CLINICAL FEATURES

**Classic infantile form** (onset at 6 months of age)

- psychomotor retardation → progressive spasticity, unresponsive seizures, *megalencephaly* (due to enlarged brain ± frank hydrocephalus\*).
  - \*obstruction of aqueduct of Sylvius by Rosenthal fibers
- no optic atrophy!
- most die in vegetative state; average disease duration 2-3 years.

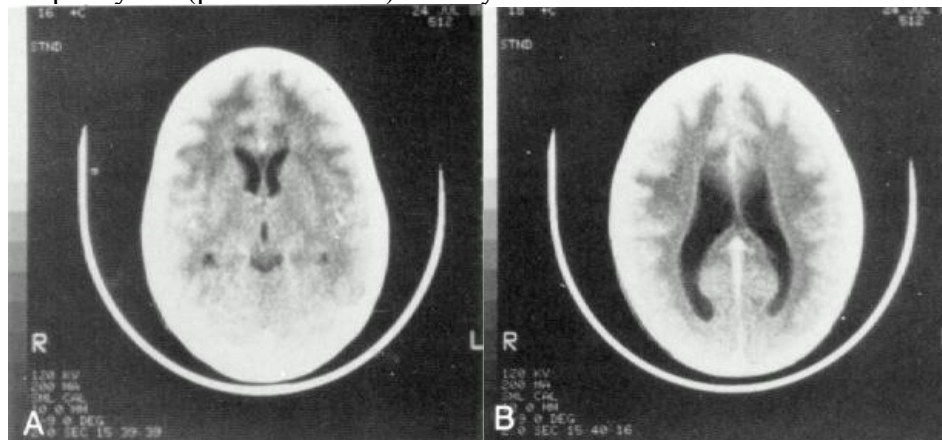
**Juvenile form** (onset at 7-14 yrs of age)

- bulbar and pseudobulbar dysfunction, nystagmus, ptosis, full facial palsy, tongue atrophy.
- mentation tends to remain intact!!!
- no seizures.
- average disease duration 8 years.

**Adult form** (onset in young adults) - clinically resembles MS (blurred vision, spasticity, nystagmus, dysarthria, dysphagia).

### DIAGNOSIS

- **CT** - marked demyelination with frontal predominance (frontal to occipital gradient) with increased subependymal (periventricular) density:



### TREATMENT

- supportive care (good nutrition, generous use of antibiotics and antiepileptics).

BIBLIOGRAPHY for ch. "Demyelinating Disorders" → follow this [LINK >>](#)