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
PELIZAEUS-MERZBACHER disease					
1	Classic	Mutations in **proteolipid protein (PLP)** – CNS myelin component.	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
COCKAYNE'S syndrome					
6	Classic	Not known (DNA excision repair)	Sudanophilic material	AR (*ERCC8* gene)	6-12 months
ALEXANDER'S disease					
7	Classic infantile	Not known (dysfunction of astrocytes?)	Not known	Not known	Infants
8	Juvenile				7-14 yrs
9	Adult				Young adults
CANAVAN'S disease					
10	Classic infantile	Aspartoacylase	*N*-acetylaspartate	AR (17p)	Infants
11	Neonatal			Sporadic	Newborns
12	Juvenile			Sporadic	5 yrs-teens
GLOBOID CELL LEUKODYSTROPHY (KRABBE'S disease)					

Type	Name	Enzyme Defect	Storage Material	Genetics	Age of Onset
13	Classic, infantile	**Galactocerebroside β-galactosidase** (lysosomal enzyme)	Galactose cerebroside, psychosine	AR	3-8 months
14	Late onset		Galactose cerebrosides		Children, may be adults
METACHROMATIC LEUKODYSTROPHY (MLD)					
15	Classical late infantile (Greenfield)	**Arylsulfatase A** (lysosomal enzyme)	Sulfatide	AR (22q13.3-qter)	Late infantile (18-24 months)
16	Juvenile (Scholz)				4-10 yrs
17	Adult (Austin)				Adult
ADRENOLEUKODYSTROPHY (ALD)					
18	Multiple peroxisomal enzyme deficiency (Zellweger syndrome)	Dihydroxyacetone phosphate acetyltransferase	Very long-chain fatty acids	AR	Neonatal
19	Neonatal ALD (Ulrich's disease)	Peroxisomal oxidation (enzyme unknown)		AR	Neonatal
20	Classic form (X-linked Siemerling-Creutzfeldt disease)	**Lignoceroyl-CoA ligase** (peroxisomal enzyme)		X-linked recessive (Xq28)	4-10 yrs

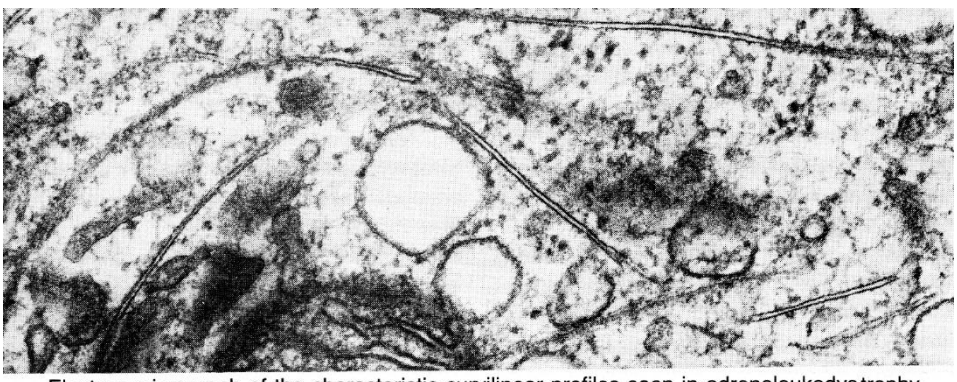
ADRENOLEUKODYSTROPHY

- 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.

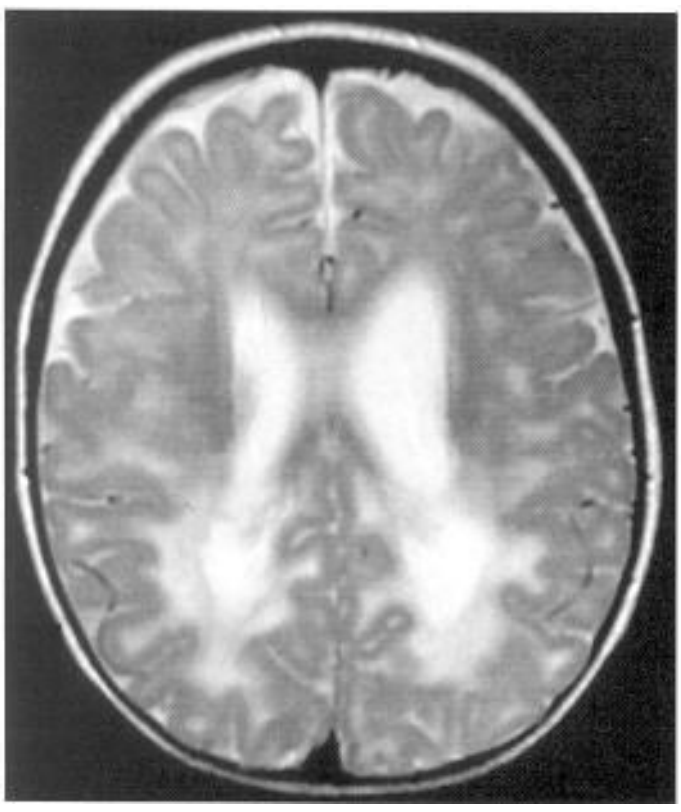
- predominantly ***spinal cord & peripheral nerve*** involvement developing for decades (slowly progressive spastic paraparesis, bladder dysfunction, hypogonadism).
- ***brain*** unaffected.
- adrenal insufficiency may have been present since childhood.

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)

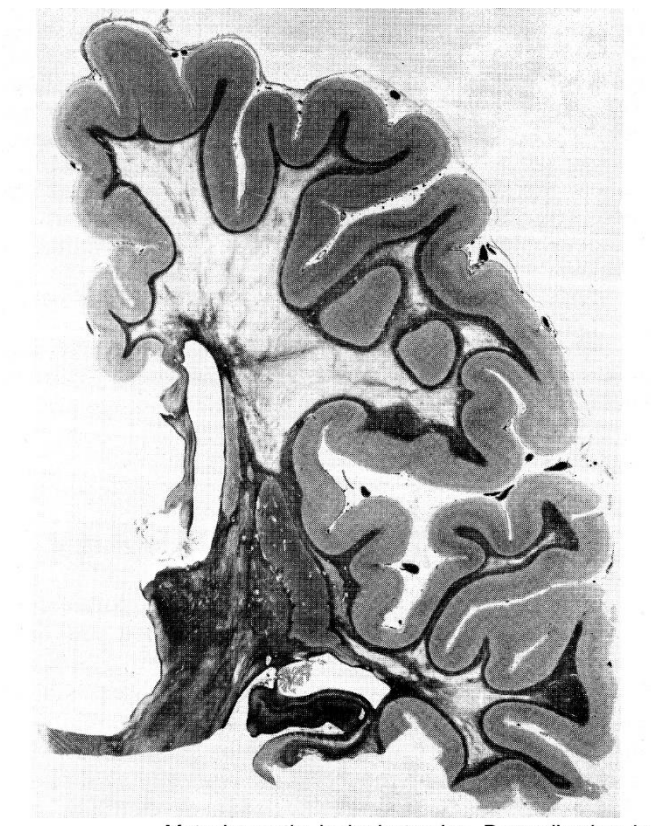
- most common leukodystrophy! see table above >>, also p. 759 >>, p. 761 >>

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.

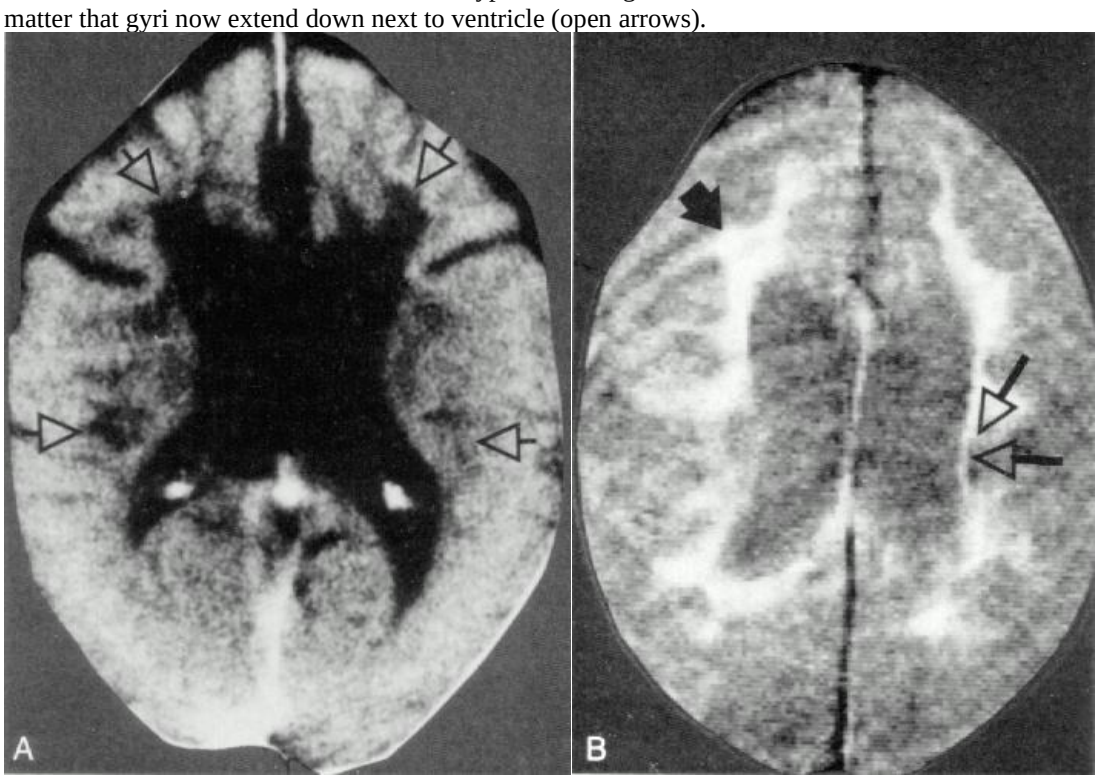
- no peripheral neuropathy.

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_2 -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 >>

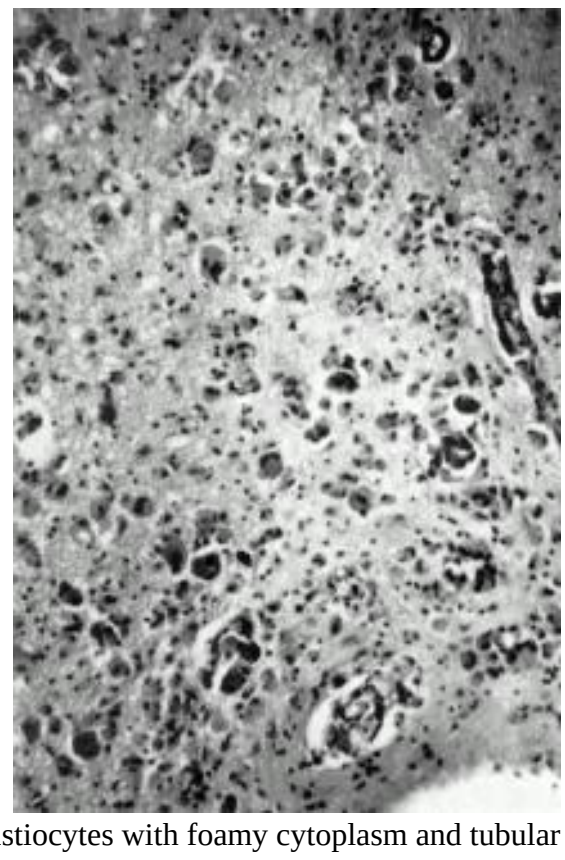
- distributed worldwide; no gender, racial, or ethnic proclivities.

PATHOPHYSIOLOGY

- autosomal recessive lysosomal enzymatic defect - *galactocerebroside-β-galactosidase*, s. *β-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):
  1. **Epithelioid cells** - round, medium size, mononuclear.
  2. **Globoid bodies** – large (20-50 μ), 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 ≈ 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↑
- **CT** - periventricular hyperdensities.
- **MRI** - white matter involvement of cerebrum & cerebellum.
- nerve conduction velocities↓

TREATMENT

- no curative treatments; various attempts to enhance enzyme activity:
  a) liposomes containing beta-galactosidase.
  b) 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**:
  1) persistent myelin islands
  2) reversal of normal gray-white matter signal relationships consistent with dysmyelination.
  3) 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 2nd 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*, *CRANIOPHARYNGIOMAS*).
  - 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.

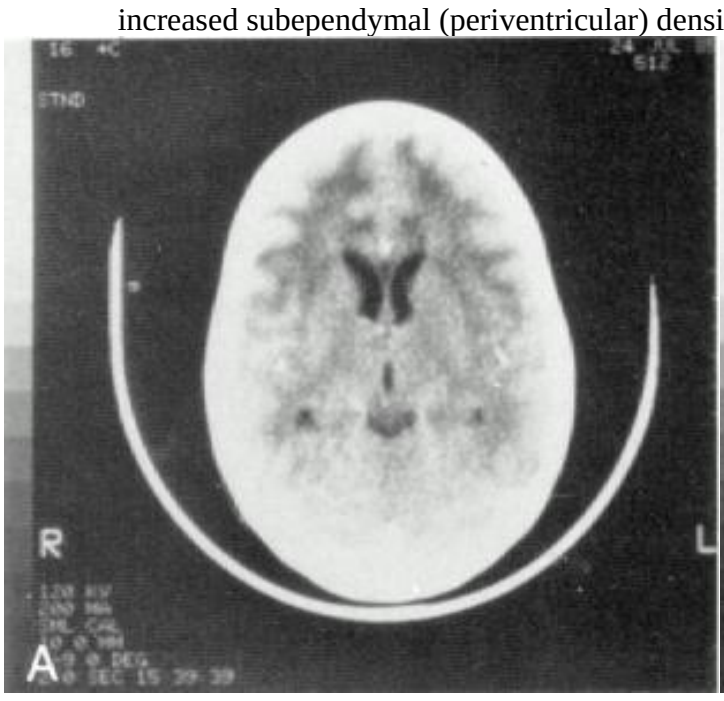
Juvenile form (onset at 7-14 yrs of age)

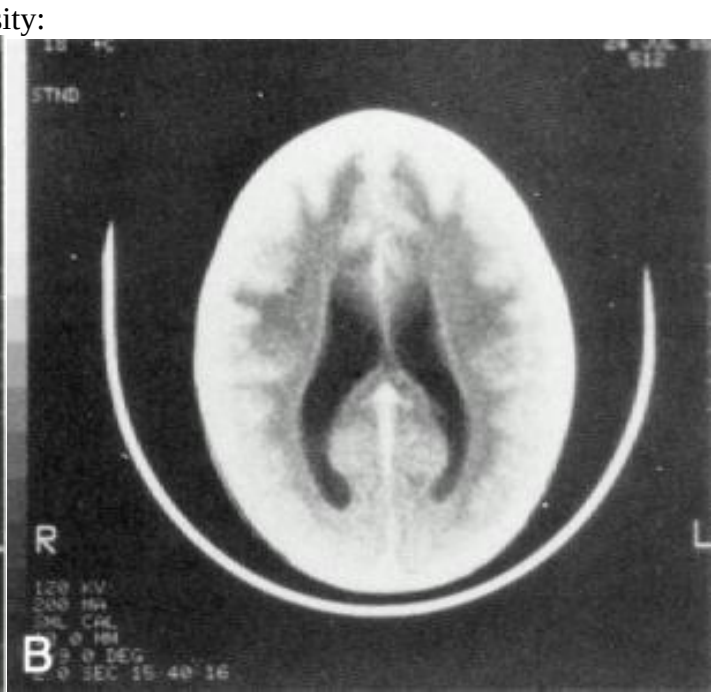
- bulbar and pseudobulbar dysfunction, nystagmus, ptosis, full facial palsy, tongue atrophy.
- mentation tends to remain intact!!!
- no seizures.
- average disease duration 8 years.

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 >>