**Leukodystrophies**

Last updated: September 5, 2017

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Enzyme Defect</th>
<th>Storage Material</th>
<th>Genetics</th>
<th>Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERLIZAEUS-MERZBACHER disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 Classic</td>
<td></td>
<td>Mutations in proteolipid protein (PLP) → CNS myelin component</td>
<td>Sudanhophilic material</td>
<td>X-linked (Xq21.3-q22)</td>
<td>Infantile</td>
</tr>
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<td>2 Connatal (Seitelberger disease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Transitional</td>
<td></td>
<td></td>
<td>Sudanhophilic material</td>
<td>X-linked?</td>
<td>Birth</td>
</tr>
<tr>
<td>4 Adult (Löwenberg-Hult disease)</td>
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<td></td>
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<td></td>
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<tr>
<td>5 Variant</td>
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<td></td>
<td>Not known</td>
<td>Not known</td>
<td>Variable</td>
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</table>

| **COCKayne’s syndrome** | | | | | |
| 6 Classic | Not known (DNA excision repair) | Sudanhophilic material | AR (ERCC5 gene) | 6-12 months |
| 7 Classic infantile | Not known | Not known | Infants |
| 8 Juvenile | | | Newborns |
| 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-teen |

| **GLOBOID CELL LEUKODYSTROPHY (KRAEBE’s disease)** | | | | | |
| 13 Classic, infantile | Galactocerebrosidase | Galactocerebrosidase (lysosomal enzyme) | Galactose cerebroside | 3-8 months |
| 14 Late onset | | | Galactose cerebroside | Children, may be adults |

| **METACHROMATIC LEUKODYSTROPHY (MLD)** | | | | | |
| 15 Classic, late infantile (Greenfield) | Arylsulfatase A | Biosynthetic pathway | AR (22q13.3-qter) | Late infantile (18-24 months) |
| 16 Juvenile (Scholz) | | | | |
| 17 Adult (Austin) | | | | |

| **ADRENOLEUKODYSTROPHY (ALD)** | | | | | |
| 18 Multiple peroxisomal enzyme deficiency (Zellweger syndrome) | | | | |
| 19 Neonatal ALD (Ulrich’s disease) | Peroxisomal oxidation (enzyme unknown) | Very long-chain fatty acids | AR | Neonatal |
| 20 Classic form (X-linked Sperling-Creatfild disease) | Lignoceroyl-CoA acetyltransferase | | AR | X-linked recessive (Xq28) |

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

a) myelin formation (synthesis) → **DYSMYELINATION** (→ loss of defective myelin); abnormal lipid-incorporated into defective myelin are **metachromatic**.

b) myelin maintenance (turnover) → **DENYELINATION** (e.g. many sudanophilic leukodystrophies).

N.B. sudanophilia is produced when Sudan black reacts with neutral fats.

- *it is very difficult to distinguish demyelination from dysmyelination (both processes frequently operate together).*
- *defects involve **lysosomal** or **peroxisomal** enzymes.*
- *AUTOSONAL 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: few months of life ÷ 20y.*
- *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 increased water content; CT - abnormally low density; T2-MRI - increased signal; T1-MRI - decreased signal.*

**hypomyelination** - MRI closely resembles immature brain;
**demyelination** - very bright T2-weighted images (much brighter than normal nonmyelinated white matter);
**denyelination** - 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 cerebral distribution** is dominant feature in primary white matter disorders (hypo-, dys-myelination!)

*subcortical U-fibers 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 clinically!

**not yet curable.**
ADRENOLEUKODYSTROPHY

- Peroxisomal leydigodystrophies see table above >>
  b) single peroxisomal enzyme defect (lignoceryl-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 lignoceryl-CoA ligase deficiency – inability to oxidize very long chain fatty acids (esp. C25 and C26) within peroxisomes.
- characteristic intracellular lamellar sudanophilic inclusions (in CNS white matter, peripheral nerves, adrenal zona fasciculata and reticularis, testes) - cholesterol esters with striking excess of saturated unbranched VLCFA.
- adrenal cortex – balloononed cells, striated cytoplasm and specific microvacuoles; → adrenal atrophy.
- CNS & PNS
  1) exsive diffuse demyelination (sparing subcortical U-fibers)
  2) perivascular mononuclear infiltration.

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 congenital 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, poor memory, difficulties in school) → rapid regression of auditory discrimination, spatial orientation, speech, and writing → seizures → spastic paraparesis / quadriparesis, dysphagia, dysmorphic coarse features, poor mental development, early seizures, retinopathy, hepatomegaly,
- very protracted course.

Adrenoleukodystrophy - 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 hypodense & hypodense band-like demyelination regions proceeding in characteristic posterior-to-anterior pattern (begin in patients-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.

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

TREATMENT

1. Dietary treatment:
   - dietary avoidance of VLCFA (4:1 mixture of GLYCEROL TRIOLEATE and GLYCEROL TRIBRUCATE) in amniotic fluids or chorionic villus sampling.
   - Lorenzo's oil (4:1 mixture of GLYCEROL TRIOLEATE and GLYCEROL TRIBRUCATE) 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.

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 myotatic 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.
  - heterozygotes have activity 10 times more than patients.
  - carriers have activity 25-50% of normal.
- 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. T2 - MRI - black arrow shows confluent hyperintense signal in diseased white matter. So shrunken is this ribbon of white matter that gyral and sulcal shapes next to ventricle (open arrows).

TREATMENT

- bone marrow transplantation.
**GLOBOID CELL LEUKODYSTROPHY (s. KRABBE disease)**

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

**PATHOPHYSIOLOGY**
- autosomal recessive lysosomal enzymatic defect - galactocerebroside-β-galactosidase, s. β-galactocerebroside (gene on chromosome 14) → accumulation of galactocerebroside, psychosine (s. galactose sphingosine)*.
- cytotoxic compound that causes oligodendroglial 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 froumi 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 hypotonus with obvious ophthalmoplegia.
- by 9 months of age, blindness (optic atrophy), deafness, cerebellar ataxia, seizures → 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 - centrum semi-ovale hypodensity.
  - MRI - white matter involvement of cerebrum & cerebellum.
  - nerve conduction velocities KV.

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

**PELIZAEUS-MERZBACHER disease**
- sudanophic 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.

**Clinical features**
- 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, dystonia, 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**

- **Conventional 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.

- **Typical variant** - intermediate severity between classic and conventional 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-activity 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**
- **aplasia/cystic deficiency** (gene on 17p) → N-acetylaspatic acid accumulation.
- changes are limited to white matter (extensive demyelination), axial 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, dystonia.
- death in vegetative state by 3-4 years of age.
- **Neonatal form** - deathly within few weeks (lethargy, hypotonia, diminished spontaneous movement, dysphagia).
- **Juvenile form** (onset after 5 years of age): ataxia, tremor, prosis, dementia, progressive cerebellar symptoms, spasticity, loss of vision.
- other organ systems are sometimes involved (diabetes mellitus, hyperaldosteronism, heart block).
- extends into adolescence.

**DIAGNOSIS**
- N-acetylaspartat 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 saki).
- 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 multysystem disease.
- mutation in ERCC5 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 cachetic 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 facial fat, long hair, extreme thinness of body, acne, and high arched palate).
- 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) eye - retinitis pigmentosa, optic atrophy, lenticular cataracts, corneal opacities, impaired lacrimation.
5) anomalies of renal function.

**DIAGNOSIS**
- exomaging - stripped calcification of basal ganglia and cerebellum.
- CSP 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.
**LEUKODYSTROPHIES**

- **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 periventricular locations).
  - Rosenthal fibers are not pathognomonic (occur in pilocytic astrocytoma, 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 >>