Leukodystrophies

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

1. **myelin formation (synthesis)** → **dysmyelination** (→ loss of defective myelin); abnormal lipids incorporated into defective myelin are ***metachromatic***.
2. **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)** |
| 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 >>](#ADRENOLEUKODYSTROPHY)

1. **single peroxisomal enzyme defect** (lignoceroyl-CoA ligase) – **classical (X-linked) adrenoleukodystrophy** (XALD), **adrenomyeloneuropathy**.
2. **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.



Clinical Features

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

* + 1. **Adrenal insufficiency** (degree varies considerably): fatigue, intermittent vomiting, salt craving, hyperpigmentation (most prominent in skin folds).
		2. **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 (beginin ***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.
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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.
1. Bone marrow **transplants** before neurologic deterioration.
2. **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 >>](#METACHROMATIC_LEUKODYSTROPHY), also [p. 759 >>](http://www.neurosurgeryresident.net/USMLE%202%5CBiochemistry%2C%20Metabolic%20Disorders%20%28501-900%29%5C759.jpg), [p. 761 >>](http://www.neurosurgeryresident.net/USMLE%202%5CBiochemistry%2C%20Metabolic%20Disorders%20%28501-900%29%5C761.jpg)

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.

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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. T2 -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 >>](http://www.neurosurgeryresident.net/USMLE%202%5CBiochemistry%2C%20Metabolic%20Disorders%20%28501-900%29%5C759.jpg), [p. 761 >>](http://www.neurosurgeryresident.net/USMLE%202%5CBiochemistry%2C%20Metabolic%20Disorders%20%28501-900%29%5C761.jpg)

* 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).
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* 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:

1. liposomes containing beta-galactosidase.
2. 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 >>](http://www.neurosurgeryresident.net/Dem.%20Demyelinating%20disorders%5CDem.%20Bibliography.pdf)

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