Leukodystrophy Overview

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Summary

Clinical characteristics. Leukodystrophies are heritable myelin disorders affecting the white matter of the central nervous system with or without peripheral nervous system myelin involvement. Involvement of the white matter tracts almost universally leads to motor involvement that manifests as hypotonia in early childhood and progresses to spasticity over time. This may lead to variable motor impairment, from mild spastic diplegia to severe spastic quadriplegia that limits purposeful movement. In addition, motor dysfunction is likely to significantly impair vital functions including swallowing, chewing, and (in some cases) respiration. Other findings that vary by disorder include extrapyramidal movement disorders (e.g., dystonia and/or dyskinesias), ataxia, seizures, and delay in cognitive development or change in cognitive function over time.

Diagnosis/testing. Establishing the specific leukodystrophy present in a given individual usually involves:

- Obtaining a medical history and detailed family history
- Performing a physical examination and neurologic examination
- Review of brain MRI findings:
  - T2-weighted hyperintensity in the white matter is the MRI finding required for diagnosis of a leukodystrophy.
  - T1-weighted signal may be variable: iso- or hyper- intense T1-weighted signal is consistent with a hypomyelinating leukodystrophy; hypointense T1-weighted signal is consistent with a demyelinating leukodystrophy.
- Performing specialized laboratory testing, often including molecular genetic testing (either stepwise single gene testing or use of a multi-gene panel targeted to the leukodystrophies).
**Genetic counseling.** Leukodystrophies with an identified genetic cause may be inherited in an autosomal dominant manner, an autosomal recessive manner, or an X-linked recessive manner. Genetic counseling regarding risk to family members depends on accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing. Prenatal testing for pregnancies at increased risk is possible for some types of leukodystrophy if the pathogenic variant(s) in the family are known. Many leukodystrophies are still without an identified genetic cause; once a genetic cause is identified, other inheritance patterns may emerge.

**Management.** Treatment of manifestations: Treatment is symptomatic and ideally occurs in a multidisciplinary setting by specialists experienced in the care of persons with a leukodystrophy. Pharmacologic agents are used to manage muscle tone and block neuronal signaling to muscle (chemodenervation). Intensive physical therapy is used to improve mobility and function. Pharmacologic treatment of dystonia and dyskinesias may result in significant functional improvement. Treatment of ataxia, seizures, and cognitive issues is provided in the usual manner, depending on the needs of the individual.

**Prevention of primary manifestations:** In a few leukodystrophies primary disease manifestations can be prevented by hematopoietic stem cell transplantation (HSCT) or bone marrow transplantation (BMT) early in the disease course.

**Surveillance:** Routine assessment of growth and nutritional status; physical examination and/or serial x-rays of the hips and spine to monitor for orthopedic complications; and routine history re signs and symptoms of seizures.

**Agents/circumstances to avoid:** Mild head injuries and infection as these may exacerbate disease manifestations.

**Evaluation of relatives at risk:** When primary prevention of a leukodystrophy is possible (e.g., by HSCT or BMT), it is appropriate to offer testing to asymptomatic at risk relatives who would benefit from early diagnosis and consideration of early treatment.

**Definition of Leukodystrophy**

The term leukodystrophy, as well as associated terms such as dysmyelination, demyelination, and leukoencephalopathy, are applied to a broad group of disorders.

In this *GeneReview* chapter, the following definition is used: Leukodystrophies are heritable myelin disorders affecting the white matter of the central nervous system with or without peripheral nervous system myelin involvement.

Leukodystrophies share the following findings:

- Abnormalities of the glial cell or myelin sheath, such that neuropathology – when known – is characterized primarily by involvement of oligodendrocytes, astrocytes, and other non-neuronal cell types. Of note, in many leukodystrophies the underlying disease mechanism is unknown.

- MRI findings (see Figure 1)
  - T2-weighted hyperintensity in the white matter must be present.
  - T1-weighted signal may be variable: iso- or hyperintense T1-weighted signal is consistent with a hypomyelinating leukodystrophy; hypointense T1-weighted signal is consistent with a demyelinating leukodystrophy.

**Clinical Manifestations of Leukodystrophies**

A number of leukodystrophies that meet the definition used in this *GeneReview* chapter are listed in Table 1.

Involvement of the white matter tracts almost universally leads to motor involvement that manifests as hypotonia in early childhood and progresses to spasticity over time. This may lead to variable motor impairment, from mild spastic diplegia to severe spastic quadriplegia that limits purposeful movement. In addition, motor dysfunction is likely to
significantly impair vital functions including swallowing, chewing and (in some cases) respiration. Spasticity may result in orthopedic complications such as scoliosis and large joint luxation.

Significant pyramidal dysfunction (i.e., spasticity) may sometimes mask or overshadow the presence of extrapyramidal movement disorders such as dystonia and/or dyskinesias. For example, in MCT8-specific thyroid hormone cell transporter deficiency dystonia is a prominent finding.

Ataxia is a predominant finding in some leukodystrophies and can be disabling; for example, childhood ataxia with central nervous system hypomyelination/vanishing white matter (CACH/VWM) and hypomyelination with hypogonadotropic hypogonadism and hypodontia (4H syndrome).

Seizures are an often late manifestation of leukodystrophies, with the exception of rare leukodystrophies (e.g., Alexander disease) in which they are often a presenting feature.

Delay in cognitive development or change in cognitive function over time, while far less pronounced than motor dysfunction, can be common in the child or adult with leukodystrophy. Because progressive loss of cognitive function is slow in the majority of leukodystrophies, dementia is not an early feature.

**Prevalence of Leukodystrophies**

Epidemiologic data on the frequency of leukodystrophies overall are limited [Heim et al 1997, Bonkowsky et al 2010]. Furthermore, it is difficult to infer from these studies with any certainty the relative frequency of specific leukodystrophies.

Better information on prevalence is available for leukodystrophies that are seen regularly in specialized clinics and in general child neurology practices; these include Alexander disease [van der Knaap et al 1999], X-linked adrenoleukodystrophy [Bezman et al 2001] and metachromatic leukodystrophy.

As disorders such as certain adult-onset-only leukodystrophies and hypomyelinating leukodystrophies become better defined, the heterogeneity of the inherited white matter disorders is increasingly recognized.

It is important to note that in approximately 50% of individuals with a white matter disorder the specific etiology is unknown because of the heterogeneity and complexity of these disorders [Schiffmann & van der Knaap 2009].

**Differential Diagnosis of Leukodystrophies**

**Heredable disorders with significant white matter involvement** that are not leukodystrophies are listed in Table 2 (pdf); they include the following:

- **Inherited vasculopathies** that can result in white matter signal abnormalities, including inherited abnormalities of the vessel wall, such as CADASIL and COL4A1 and COL4A2-related disorders, which can give rise to multifocal white matter abnormalities. In end-stage disease, confluent signal abnormalities in the periventricular and deep white matter may be seen, typically with multifocal abnormalities in central gray matter structures and brain stem. Because these are not primary glial cell disorders, they are not considered to be leukodystrophies.

- **CNS diseases with primary involvement of neurons in the cerebral cortex or other gray matter structures** (in which brain MRI also reveals significant white matter abnormalities). Typical findings are significant encephalopathy and seizures.

  - The infantile variants of disorders like GM1 gangliosidosis, GM2 gangliosidosis, and neuronal ceroid-lipofuscinosis may have significant white matter abnormalities because the disease, which is primarily neuronal, also disrupts the normal process of myelination. Later-onset variants of these disorders eventually affect the cerebral white matter; mild signal abnormalities are related to Wallerian degeneration with loss of axons and myelin.
In other disorders, such as MCT8-specific thyroid hormone cell transporter deficiency, myelination can be extremely delayed but progress over time to become almost complete.

- **Inborn errors of metabolism** with significant secondary white matter abnormalities, such as organic acidemias, disorders of amino acid metabolism and many others. See Table 2 (pdf).

- **Disorders that affect both white and gray matter.** Examples in which both white matter injury and gray matter lesions are observed include mitochondrial disorders such as MELAS (*mitochondrial encephalopathy with lactic acidosis and seizures*), POLG-related disorders, and familial hemophagocytic lymphohistiocytosis.

**Other disorders with significant white matter involvement** include the following:

- **Acquired CNS myelin disorders** that result in demyelination, such as multiple sclerosis and those of infectious, post-infectious, and autoimmune etiology. Although not heritable in a Mendelian fashion, some of these disorders may have multifactorial etiologies that include a genetic predisposition.

- Disorders such as acute disseminated encephalomyelitis, multiple sclerosis, and neuromyelitis optica typically differ from heritable white matter disorders by their abrupt onset and multiphasic presentations. Brain MRI abnormalities are also more likely to be multifocal and patchy [Schiffmann & van der Knaap 2009], with variation or even improvement over time and with treatment.

- **Toxic injuries** of the myelin, such as those seen in heroin abuse or methotrexate-related toxicity

- **Central nervous system injury**, particularly in the perinatal period, which can result in significant white matter signal abnormalities that are typically irregular, and may result in loss of white matter volume

- Non-genetic vascular insults

**Evaluation Strategy for an Individual with a Leukodystrophy**

Once a leukodystrophy is considered in an individual, the following approach can be used to determine the specific leukodystrophy to aid in discussions of prognosis and genetic counseling.

Establishing the specific leukodystrophy (Table 1) present in a given individual usually involves obtaining a medical history and detailed family history; performing a physical examination and neurologic examination; review of brain MRI findings; and specialized laboratory testing, often including molecular genetic testing.

Note: Adherence to the diagnostic approach discussed in this section notwithstanding, a specific diagnosis cannot be established in a clinical (i.e., not research) setting in a significant number of individuals with a leukodystrophy [van der Knaap et al 1999, Schiffmann & van der Knaap 2009].

**Medical History**

A history of certain clinical features may be helpful in identifying a specific leukodystrophy; however, in the majority of cases, only nonspecific loss of function (primarily motor) occurs and medical history alone does not provide insight into a specific diagnosis.

In the hypomyelinating leukodystrophies helpful diagnostic clues may, for example, be the following:

- Congenital cataract: hypomyelination and congenital cataract (HCC)

- Hypodontia and/or hypogonadotropic hypogonadism: *POLR3*-related leukodystrophy

- Severe seizures: sialic acid storage disorders

In the demyelinating leukodystrophies helpful diagnostic clues may, for example, be the following:
• Recurrent vomiting: Alexander disease
• Adrenal dysfunction: X-linked adrenoleukodystrophy (X-ALD)
• Early-onset autonomic dysfunction: AD adult-onset leukodystrophy (ADLD)
• Chronic cerebrospinal fluid lymphocytosis or (more often) recurrent “aseptic meningitis”: Aicardi-Goutières syndrome
• Abrupt loss of function after a fever or fall: childhood ataxia with central nervous system hypomyelination/vanishing white matter (and possibly other leukodystrophies)

**Family History**

A detailed three-generation family history focusing on individuals with hypotonia, spasticity, dystonia, seizures, ataxia, and/or delay in cognitive development or change in cognitive function over time.

• Because most leukodystrophies are autosomal recessive, special attention to parental consanguinity and medical problems in sibs is warranted.

• Evaluation of relatives and/or review of their medical records may be needed.

**Physical Examination and Neurologic Examination**

In most instances physical findings do not suggest a specific diagnosis; however, certain findings may direct the reader to further explore specific underlying etiologies:

• Macrocephaly; see Table 6 (pdf)
• Abnormal dentition: POLR3-related leukodystrophy or oculodentodigital dysplasia (ODDD)
• Palatal myoclonus in adults: Alexander disease
• Xanthomas: cerebrotendinous xanthomatosis (CTX)
• Abnormalities of skin pigmentation: X-linked adrenoleukodystrophy (X-ALD)
• Ichthyosis: Sjögren-Larsson syndrome
• Vascular retinal abnormalities: cerebroretinal microangiopathy w/calcifications & cysts (CRMCC)
• Cherry red spot on retinal examination: disorders such as GM1 and GM2 gangliosidosis

**Brain MRI Findings**

**Step 1**

Establish whether the pattern of brain MRI abnormalities is consistent with a hypomyelinating leukodystrophy or a demyelinating leukodystrophy (Figure 1) [van der Knaap et al 1999, van der Knaap & Valk 2005, Schiffmann & van der Knaap 2009].

**Step 2**

Within the hypomyelinating and demyelinating leukodystrophies, determine if patterns of involvement suggest specific diagnoses.

**Hypomyelinating leukodystrophy.** Note specific patterns on neuroimaging that include the following (Figure 2):
• Improvement of myelination over time (e.g., as seen in MCT8-specific thyroid hormone cell transporter deficiency; see Figure 2A→B)

• Severe atrophy of cortical gray matter (variably seen in primary neuronal disorders as well as a limited number of classic leukodystrophies; see Figure 2C)

• Persistent hypomyelination without atrophy of cortical gray matter (e.g., in Pelizaeus-Merzbacher disease; see Figure 2D)

• Cerebellar atrophy (e.g., in POLR3-related leukodystrophy [4H syndrome]; see Figure 2E)

• Basal ganglia involvement (e.g., in HABC syndrome; see Figure 2F)

Demyelinating leukodystrophy

• Identify the region in which white matter abnormalities predominate.

• Distinguish confluent from multifocal lesions (Figure 3):
  • Confluent white matter lesions are extensive white matter abnormalities in significant portions of the brain, often affecting specific regions or tracts, although not necessarily perfectly symmetrically.
  • Multifocal white matter lesions are more discrete, often asymmetric and involving a limited area. Multifocal abnormalities have a specific differential diagnosis.

Specific patterns on neuroimaging in confluent disorders include (Figure 4):

• Diffuse cerebral involvement (e.g., as seen in megalencephalic leukodystrophy with subcortical cysts; see Figure 4A)

• Frontal involvement (e.g., in Alexander disease; see Figure 4B)

• Parieto-occipital involvement (e.g. in X-linked adrenoleukodystrophy; see Figure 4C)

• Temporal involvement (e.g., in Aicardi-Goutières syndrome; see Figure 4D)

• Subcortical involvement (e.g., in Kearns-Sayre syndrome; see Figure 4E)

• Periventricular involvement (e.g., in metachromatic leukodystrophy; see Figure 4F)

• Brain stem involvement (e.g., in adult polyglucosan body disease with heterogeneous involvement of the brain stem; see Figure 4G)

• Cerebellar/cerebellar peduncle involvement (e.g., in AD adult-onset leukodystrophy (ADLD) with involvement of the middle cerebellar peduncles; see Figure 4H)

• Large, asymmetric lesions (e.g., in hereditary diffuse leukoencephalopathy with spheroids [HDLS]; Figure 4I)

Diagnostic algorithm. For algorithms based on MRI findings, see Figure 5 (demyelinating and other conditions) and Figure 6 (hypomyelinating conditions) [Schiffmann & van der Knaap 2009].

Step 3

Look for the following associated features which, in addition to the pattern of findings on brain MRI, can assist in recognition of a specific leukodystrophy:

• White matter rarefaction and cysts (Table 3) seen on FLAIR imaging (e.g., in vanishing white matter disease: childhood ataxia with central nervous system hypomyelination/vanishing white matter; Figure 7A)
- Calcium deposits and hemosiderin deposits (Table 4) visible on CT, and not easily distinguishable on MRI (e.g., in Aicardi-Goutières syndrome; see Figure 7B)
- Contrast enhancement (Table 5) on T1-weighted imaging within the abnormal white matter (e.g., in X-linked adrenoleukodystrophy; see Figure 7C)
- Leukoencephalopathy with macrocephaly (Table 6)
- Cortical gray matter lesions (Table 7) (e.g., in POLG-related disorders; see Figure 7D)
- Cerebellar abnormalities (Table 8) seen in the dentate nucleus (e.g., in L-2-hydroxyglutaric aciduria; see Figure 7E)
- Thinning of the corpus callosum (Table 9), in particular, of the genu (e.g., in hereditary spastic paraplegia 11; see Figure 7F)
- Non-calcifying basal ganglia lesions (Table 10) (e.g., in Alexander disease; see Figure 7G, signal abnormality of the basal ganglia and frontal white matter)
- Brain stem involvement (Table 11) (e.g., in AD adult-onset leukodystrophy (ADLD); see Figure 7H)
- Spinal cord involvement (Table 12) (seen in many disorders, including LBSL; see Figure 7I, an example of involvement of tracts within the spinal cord)

**Specialized Laboratory Testing (including Molecular Genetic Testing)**

If the findings on brain MRI are consistent with a specific leukodystrophy, consider biochemical or molecular genetic testing for that disorder (Table 1). Note: Molecular genetic testing may be performed either as single gene testing in a stepwise fashion based on the information gained during the evaluation or, if available, as a multi-gene panel.

**Table 1.**

Leukodystrophies Meeting Strict Diagnostic Criteria

<table>
<thead>
<tr>
<th>Name of Disorder</th>
<th>Mode of Inheritance</th>
<th>Gene ¹</th>
<th>Biochemical Testing / Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>18q deletion syndrome</td>
<td>Most often <em>de novo</em> deletion; may be inherited</td>
<td></td>
<td>Chromosome analysis for 18q microdeletion involving <em>MBP</em></td>
</tr>
<tr>
<td>Adult polyglucosan body disease (APBD)</td>
<td>AR</td>
<td><em>GBE1</em></td>
<td>Histopathologic examination of muscle, nerve, axillary skin: pathologic polyglucosan accumulation</td>
</tr>
<tr>
<td>Aicardi-Goutières syndrome (AGS)</td>
<td>Usually AR; may be AD</td>
<td><em>TREX1</em> RNASEH2A RNASEH2B RNASEH2C <em>SAMHD1 ADAR</em></td>
<td>CSF analysis: lymphocytosis, ↑ interferon-α, ↑ pterins</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>AD</td>
<td><em>GFAP</em></td>
<td></td>
</tr>
<tr>
<td>AD adult-onset leukodystrophy (ADLD)</td>
<td>AD</td>
<td><em>LMNB1</em></td>
<td></td>
</tr>
<tr>
<td>Name of Disorder</td>
<td>Mode of Inheritance</td>
<td>Gene</td>
<td>Biochemical Testing / Other</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>Cerebroretinal microangiopathy w/calcifications &amp; cysts (CRMCC) ²</td>
<td>Likely AR</td>
<td></td>
<td>Clinical &amp; neuroradiologic features</td>
</tr>
</tbody>
</table>
| Canavan disease                                                                  | AR                  | ASPA    | In urine, plasma, CSF, & amniotic fluid: ↑ N-acetylaspartic acid in urine  
In skin fibroblasts: deficient aspartoacylase enzyme activity  |
| Cerebrotendinous xanthomatosis (CTX)                                             | AR                  | CYP27A1 | In plasma & CSF: ↑ cholestanol concentration,  
↓ chenodeoxycholic acid  
In bile, urine, plasma: ↑ concentration bile alcohols & glyconjugates  
In fibroblasts, liver, leukocytes: ↓ sterol 27-hydroxylase activity  |
| Childhood ataxia w/CNS hypomyelination / vanishing white matter (CACH/VWM)      | AR                  | EIF2B1-5| In urine, fibroblast, lysosomes: ↑ free sialic acid               |
| Free sialic acid storage disorders ³                                              | AR                  | SLC17A5 | On urinary oligosaccharide assay: ↑ fucose-containing glycoconjugates  
In leukocytes or fibroblasts: deficient α-fucosidase activity  |
| Fucosidosis                                                                      | AR                  | FUCA1   |                                                                 |
| Hypomyelination w/atrophy of the basal ganglia & cerebellum (H-ABC)             | Likely AD           | TUBB4A  | Clinical & neuroradiologic features                             |
| Hypomyelination and congenital cataract (HCC)                                    | AR                  | FAM126A |                                                                 |
| Krabbe disease                                                                   | AR                  | GALC    | In leukocytes or fibroblasts: deficient galactocerebrosidase activity  
See footnote 4                                                                  |
<p>| L-2-hydroxyglutaric aciduria                                                     | AR                  | L2HGDH  | In plasma, urine, CSF: ↑ concentration of L-2-hydroxyglutaric acid (and lysine)  |
| Leukoencephalopathy w/brain stem &amp; spinal cord involvement &amp; lactate elevation (LBSL) | AR                  | DARS2   |                                                                 |
| Leukoencephalopathy w/thalamus and brain stem involvement &amp; lactate elevation (LTBL) | AR                  | EARS2   |                                                                 |
| Megalencephalic leukodystrophy w/subcortical cysts (MLC)                         | AR                  | MLC1    |                                                                 |
|                                                                     |                     | HEPACAM (MLC2) |                                                                 |</p>
<table>
<thead>
<tr>
<th>Name of Disorder</th>
<th>Mode of Inheritance</th>
<th>Gene</th>
<th>Biochemical Testing / Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metachromatic leukodystrophy (MLD)</td>
<td>AR</td>
<td>ARSA</td>
<td>In leukocytes, fibroblasts: ↓ arylsulfatase A activity In urine: ↑ sulfatides</td>
</tr>
<tr>
<td>PSAP-related MLD (^5)</td>
<td></td>
<td>PSAP</td>
<td>In leukocytes, fibroblasts: normal arylsulfatase A activity In urine: ↑ sulfatides</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency (MSD)</td>
<td></td>
<td>SUMF1</td>
<td>↓ activity of other sulfatas In urine: ↑ mucopolisaccharides, ↑ urinary sulfatides</td>
</tr>
<tr>
<td>Hereditary diffuse leukoencephalopathy w/spheroids (HDLS) (^6)</td>
<td>AD</td>
<td>CSF1R</td>
<td></td>
</tr>
<tr>
<td>Oculodentodigital dysplasia (ODDD)</td>
<td>Usually AD; may be AR</td>
<td>GJA1</td>
<td></td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease (PMD)</td>
<td>XL</td>
<td>PLP1</td>
<td></td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher-like disease 1 (PMLD1)</td>
<td>AR</td>
<td>GJC2</td>
<td></td>
</tr>
<tr>
<td>Peroxisome biogenesis disorders, Zellweger syndrome spectrum (PBD, ZSS) (^7)</td>
<td>AR</td>
<td>PEX genes</td>
<td>Plasma VLCFA, phytanic &amp; pristanic acid, plasma &amp; urine concentration of picoenic acid &amp; bile acids aid to distinguish different forms of peroxisomal disorders</td>
</tr>
<tr>
<td>Pol III-related leukodystrophies (^8)</td>
<td>AR</td>
<td>POLR3A</td>
<td>POLR3B</td>
</tr>
<tr>
<td>RNAse T2-deficient leukoencephalopathy</td>
<td>AR</td>
<td>RNASET2</td>
<td></td>
</tr>
<tr>
<td>Single-enzyme deficiencies of peroxisomal fatty acid beta oxidation (^9)</td>
<td>AR</td>
<td>Dibifunctional protein deficiency: HSD17B4</td>
<td>Plasma VLCFA, phytanic &amp; pristanic acid, plasma &amp; urine concentration of picoenic acid &amp; bile acids aid to distinguish different forms of peroxisomal disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peroxisomal acyl-CoA-oxidase deficiency: ACOX1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCPx deficiency: SCP2</td>
<td></td>
</tr>
<tr>
<td>Sjögren-Larsson syndrome</td>
<td>AR</td>
<td>ALDH3A2</td>
<td>In urine: abnormal metabolites of leukotriene B4 In cultured skin fibroblasts, leukocytes: deficiency of fatty aldehyde dehydrogenase activity (FALDH) and/or of fatty alcohol:NAD oxidoreductase (FAO)</td>
</tr>
<tr>
<td>SOX10-associated disorders</td>
<td>AD</td>
<td>SOX10</td>
<td></td>
</tr>
<tr>
<td>Name of Disorder</td>
<td>Mode of Inheritance</td>
<td>Gene</td>
<td>Biochemical Testing / Other</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>---------------------</td>
<td>--------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>X-linked adrenoleukodystrophy (X-ALD)</td>
<td>XL</td>
<td>ABCD1</td>
<td>On plasma VLCFA assay: C26:0, ↑ ratio of C24:0 to C22:0, ↑ ratio of C26:0 to C22:0</td>
</tr>
</tbody>
</table>

AD = autosomal dominant
AR = autosomal recessive
XL = X-linked
VLCFA = very long-chain fatty acid
Disorders listed in alphabetical order; naming as per GeneReviews
1. Genetic testing is available for many of these genes.
2. This disorder now appears to be distinct from Coats plus caused by pathogenic variants in CTC1, encoding conserved telomere maintenance component 1.
3. Includes Salla disease; infantile sialic acid storage disease, intermediate form
4. Defects in PSAP causing a deficiency in the activator protein of SapA-d essential for the action of GALC have been reported.
5. Pathogenic variants in PSAP result in deficiency in SapB-d, an activator protein essential for ARSA activity.
6. Also known as adult-onset leukodystrophy w/ neuroaxonal spheroids & pigmented glia; may include hereditary diffuse; pigmentary type of orthochromatic leukodystrophy w/pigmented glia (POLD)
7. Includes neonatal adrenoleukodystrophy; infantile Refsum disease
8. Includes hypomyelination, hypodontia, hypogonadotropic hypogonadism (4H syndrome); ataxia, delayed dentition, and hypomyelination (ADHD); tremor-ataxia with central hypomyelination (TACH); leukodystrophy with oligodontia (LO); and hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC).
9. Includes D-bifunctional protein (DBP) deficiency; sterol carrier protein-2 (SCPx) deficiency; peroxisomal acyl-CoA-oxidase deficiency

**Genetic Counseling**

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional.* —ED.

**Mode of Inheritance**

Leukodystrophies with an identified genetic cause may be inherited in an autosomal dominant manner, an autosomal recessive manner, or an X-linked recessive manner; other inheritance patterns may be identified as more genetic causes of leukodystrophy are discovered.

If a proband has a specific syndrome associated with a leukodystrophy, counseling for that condition is indicated.

**Risk to Family Members — Autosomal Dominant Inheritance**

**Parents of a proband**

- Most individuals diagnosed as having autosomal dominant leukodystrophy have an affected parent, although occasionally the family history is negative.
- Family history may appear to be negative because of early death of a parent, failure to recognize autosomal dominant leukodystrophy in family members, late onset in a parent, reduced penetrance of the mutated allele in an asymptomatic parent, or a *de novo* pathogenic variant.
Sibs of a proband

- The risk to sibs depends on the genetic status of the proband's parents.
- If one of the proband's parents has a mutated allele, the risk to the sibs of inheriting the mutated allele is 50%.

Offspring of a proband. Individuals with autosomal dominant leukodystrophy have a 50% chance of transmitting the mutated allele to each child.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents are obligate heterozygotes and therefore carry a single copy of a pathogenic variant.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.

Offspring of a proband. All offspring are obligate carriers.

Risk to Family Members — X-Linked Inheritance

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the pathogenic variant.
- Women who have an affected son and another affected male relative are obligate heterozygotes. These females may be affected, sometimes with only certain features of the disease, or with milder symptoms. Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism. Rarely, the unaffected father of an affected female may have germline mosaicism.
- A mother of an affected female who has a pathogenic variant may have favorably skewed X-chromosome inactivation that results in her being unaffected or mildly affected.
- An individual who is the only affected family member (i.e., a simplex case) may have a de novo pathogenic variant.

Sibs of a proband. The risk to sib depends on the carrier status of the mother:

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the variant will be affected; female sibs who inherit the variant will be carriers and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a proband
Daughters of an affected male will be obligate carriers and may or may not be affected; none of his sons will be affected.

Each child of an affected female has a 50% chance of inheriting the pathogenic variant.

Because of possible skewing of X-chromosome inactivation, variable phenotypes in females are possible.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband’s parents.

Related Genetic Counseling Issues

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for leukodystrophy are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- Myelin Disorders Bioregistry Project
  Email: myelindisorders@cnmc.org

Management

Treatment of Manifestations

Although the underlying mechanisms of leukodystrophies are diverse, many manifestations are similar across this group of disorders. In the great majority of cases, primary treatment is not possible, but management of symptoms can improve the comfort and care of individuals with these complex disorders.

Ideally, the child or adult with a leukodystrophy is managed in a multidisciplinary setting by providers experienced in the care of persons with a leukodystrophy.

Spasticity. Pharmacologic agents are used to manage muscle tone and block neuronal signaling to muscle (chemodenervaton). Intensive physical therapy is used to improve mobility and function.

Extrapyramidal manifestations. Dystonia and dyskinesias may cause significant disability; pharmacologic treatment may result in significant functional improvement.

Ataxia. No specific treatment of ataxia exists, although rehabilitative measures can be of great assistance.

Seizures. Seizures should be treated with typical anticonvulsants and are rarely refractory, except on occasion at the end of life.

Cognitive developmental delay/encephalopathy. It is important to advocate for persons with a leukodystrophy in school or at work to avoid limitations related to their motor disabilities. Augmentative communication may be used to address speech deficits. Accommodations for cognitive delays and fine motor disabilities should be used as needed.
Orthopedic. Attention should be given to the prevention and treatment of orthopedic problems, such as hip dislocation and scoliosis.

Feeding. Swallowing dysfunction and pulmonary problems resulting from the increased risk of aspiration are common as the disease progresses. Decreased nutritional intake and failure to thrive may also occur. The decision to place a gastrostomy tube for nutrition is based on the overall health status of the individual, expected disease course, and family and patient wishes.

Prevention of Primary Manifestations
Primary disease manifestations can be prevented in a few of the leukodystrophies: in X-linked adrenoleukodystrophy, Krabbe disease, and metachromatic leukodystrophy, for example, hematopoietic stem cell transplantation (HSCT) or bone marrow transplantation (BMT) may be beneficial if performed early in the disease course. Patients with these disorders should be referred to specialized centers for consideration of HSCT or BMT [Eichler et al 2009].

Surveillance
Standard surveillance includes the following:

- Routine measurement of weight and height to assess growth and nutritional status
- Physical examination and/or serial x-rays of the hips and spine to monitor for orthopedic complications
- Routine history re signs and symptoms of seizures

Certain disorders require specialized surveillance, for example monitoring for the development of hydrocephalus in Alexander disease.

Agents/Circumstances to Avoid
In a number of leukodystrophies anecdotal evidence suggests episodic worsening of manifestations with mild head injuries and infection. While this has been clearly documented only for childhood ataxia with central nervous system hypomyelination/vanishing white matter, it appears prudent to avoid these triggers when possible.

Evaluation of Relatives at Risk
See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation
Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

References

Literature Cited


Chapter Notes

Revision History

- 6 February 2014 (me) Review posted live
- 14 February 2012 (av) Original submission
Figure 1.
Hypomyelinating leukodystrophy has T2-weighted hyperintensity (↑) and T1-weighted iso- (→) or hyperintensity (↑) of affected white matter. Demyelinating leukodystrophy has T2-weighted hyperintensity (↑) and T1-weighted hypointensity (↓) of affected white matter.
Figure 2.

Hypomyelinating leukodystrophy – patterns on MRI

A→B. Improvement of myelination over time in MCT8-specific thyroid hormone cell transporter deficiency seen in a male with documented SLC16A2 (MCT8) pathogenic variants at age two years (A) and age 4.5 years (B)

C. GM1 gangliosidosis with hypomyelination accompanied by early loss of white matter volume

D. Persistent and severe hypomyelination seen in a school-aged child with Pelizaeus-Merzbacher disease

E. Cerebellar atrophy seen in POLR3-related leukodystrophy (4H syndrome); arrow indicates atrophy.

F. Basal ganglia involvement seen in H-ABC syndrome; arrow indicates atrophy of the putamen, a classic finding in this disorder.
**Figure 3.**

Confluent white matter lesions are extensive white matter abnormalities in significant portions of the brain, often affecting specific regions or tracts, although not necessarily perfectly symmetrically. Multifocal white matter lesions are more discrete, often asymmetric and involving a limited area.
Figure 4.
Demyelinating leukodystrophy – patterns on MRI

A. Diffuse cerebral involvement in an individual with megalencephalic leukodystrophy with subcortical cysts
B. Primarily frontal involvement in a child with Alexander disease; arrow indicates white matter abnormalities in the frontal region.
C. Primarily parieto-occipital involvement in a child with X-linked adrenoleukodystrophy; arrow indicates white matter abnormalities in the parieto-occipital region.
D. Primarily temporal involvement in an individual with Aicardi-Goutières syndrome; arrow indicates white matter abnormalities in the temporal region.
E. Primarily subcortical involvement in Kearns-Sayre syndrome; arrow indicates sparing of the white matter in the periventricular region.
F. Primarily periventricular involvement in an individual with metachromatic leukodystrophy; subcortical fibers
are spared; arrow indicates sparing of white matter in the subcortical region.
G. Primarily brain stem involvement in an individual with adult polyglucosan body disease with heterogeneous involvement of the brain stem; arrow indicates white matter abnormalities in the brain stem.
H. Primarily cerebellar and middle cerebellar peduncle involvement in an individual with autosomal dominant adult-onset leukodystrophy (ADLD); arrow indicates white matter abnormalities in the middle cerebellar peduncles.
I. Large, asymmetric lesions in an individual with hereditary diffuse leukoencephalopathy with spheroids (HDLS); arrow indicates asymmetric white matter abnormalities in the frontal region.
Figure 5.
Algorithm Part 1: Demyelinating and other conditions

Adapted from Schiffmann & van der Knaap [2009]
Mild T2-hyperintensity in combination with T1-hyperintensity (= normal signal), T1-iso-intensity or mild T1-hypointensity relative to gray matter structures.

**Improving = DELAYED MYELINATION**
- SOX10-associated disorders
- MC1R-related disorders
- Other neuronal disorders

**Permanent = HYPOMYELINATION**
- Cerebellar Atrophy INCONSTANT
- Basal Ganglia Anomalies
- Not or Late Atrophy; + Normal Basal Ganglia

- 4H syndrome (C atrophy can be INCONSTANT)
- HABC
- ODDD
- Salla disease
- Cockayne syndrome

- 18q minus syndrome
- HCC (NB: some regions may have low T1 signal)
- HEMS
- PMD
- PMLD
- Salla disease
- SOX10-associated disorders

**Infantile spinal acid storage disease**
- Aicardi-Goutières syndrome

**Prominent cerebral atrophy and slowly progressing myelination = FALSE HYPOMYELINATION**
- Early-onset neuronal degenerative disorders including:
  - Serine synthesis defects
  - NCL
  - Early-onset GM1 and GM2
  - Mitochondrial disorders
  - Fumaric hydratase deficiency
  - Band-like intracranial calcification with simplified gyration and polymicrogyria

- Neuronal form of malignant infantile osteopetrosis
- AGC1-related disorders
- HSPD1-related disorders
- AMPK-related disorders
- GPR56-related disorders

**DELAYED MYELINATION OR HYPOMYELINATION ± MULTIFOCAL LESIONS**
- 18q minus syndrome
- HCC
- Galactosemia type I
- Adenylsuccinate lyase deficiency
- Aspartylglucosaminuria
- GPR56-related disorders
- Dystroglycanopathies
- D-2-hydroxyglutaric aciduria

**Legend**
- 4H = Hypomyelination, hypodontia and hypogonadotropic hypogonadism
- HABC = Hypomyelination with atrophy of the basal ganglia and cerebellum
- HCC = Hypomyelination with congenital cataract
- HEMS = Hypomyelination of early myelinating structures
- ODDD = Oculodentodigital dysplasia
- PMD = Pelizaeus-Merzbacher disease
- PMLD = Pelizaeus-Merzbacher-like disease
- NCL = Neuronal ceroid-lipofuscinosis

Adapted from Schiffmann & van der Knaap [2009]

Figure 6.
Algorithm Part 2: Hypomyelinating conditions

Adapted from Schiffmann & van der Knaap [2009]
Features associated with specific leukodystrophies

A. White matter rarefaction and cysts on FLAIR imaging in vanishing white matter disease; arrow indicates cystic rarefaction within abnormal white matter.
B. Calcium deposits and hemosiderin deposits visible on CT in Aicardi-Goutières syndrome; not easily distinguishable on MRI; arrow indicates basal ganglia calcifications.
C. Contrast enhancement on T1-weighted imaging within abnormal white matter in X-linked adrenoleukodystrophy; arrow indicates contrast enhancement in the abnormal white matter.
D. Cortical gray matter lesions in POLG-related disorders; arrow indicates swollen appearance of the cortical mantle and loss of gray-white matter differentiation.
E. Cerebellar abnormalities seen in the dentate nucleus in L-2-hydroxyglutaric aciduria; arrow indicates symmetric hyperintensity.
F. Thinning of the corpus callosum (particularly of the genu) in hereditary spastic paraplegia 11; arrow indicates thin corpus callosum with anterior beaking typically seen in this disorder.

G. Non-calcifying basal ganglia lesions in Alexander disease; arrow indicates hyperintense signal within the basal ganglia.

H. Typical brain stem involvement in AD adult-onset leukodystrophy (ADLD); arrow indicates hyperintense lesions within the brain stem.

I. Spinal cord involvement in LBSL; arrow indicates hyperintense lesions within the spinal cord, affecting tracts longitudinally throughout the length of the visible cord.