Leukodystrophies
Classification, Diagnosis, and Treatment
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Background: The leukodystrophies are a heterogeneous group of diseases, which primarily affect white matter. Symptomatic patients are frequently misdiagnosed and the leukodystrophies are collectively under recognized. However, with ongoing research and increased availability of neuroimaging, our understanding of these diseases is increasing at a steady rate. Recent advances in the diagnosis and treatment of certain forms of leukodystrophy should prompt increased awareness of these diseases in clinical practice.

Review Summary: The clinical features, pathophysiology, and therapeutic approach to these diseases are described. Particular emphasis is placed on genetic and pathophysiologic mechanisms, imaging patterns, screening of other family members and, where available, treatment options and resources.

Conclusions: With more widespread use of neuroimaging, both pediatric and adult neurologists will increasingly be confronted with white matter disorders. Neurologists should have an approach to the recognition, diagnosis, and management of white matter diseases in general and the leukodystrophies in specific.

Key Words: leukodystrophy, X-linked adrenoleukodystrophy, metachromatic leukodystrophy, vanishing white matter disease, Alexander disease, Krabbe disease, magnetic resonance imaging

Leukodystrophies are hereditary disorders of white matter, which are invariably progressive in nature. The first clinical description of inherited white matter disease appeared 100 years ago, consisting of familial occurrence, early onset spasticity, and a rapidly progressive course with fatal outcome. Pathologic examination revealed extensive demyelination that gave rise to the term “leukodystrophy” (leuko—white, dystrophy—degenerating). Disorders such as metachromatic leukodystrophy (MLD) and globoid cell leukodystrophy (also known as Krabbe disease) owe their names to the unusual morphology or staining reactions seen on histopathological specimens. Analysis of stored substrates within white matter subsequently helped to unravel the underlying enzymatic defects. However, many diseases that affect white matter remain poorly characterized with an unknown biochemical or molecular basis. Because many of these disorders demonstrate a failure in myelination or hypomyelination rather than a loss of previously acquired myelin, the term leukodystrophy is in actuality too narrow, and the broader term “leukencephalopathy” is probably more appropriate (though the term leukodystrophy remains in use today).

With progress in magnetic resonance imaging (MRI) technology and molecular genetics, new forms of leukodystrophy have been identified. These are not limited to childhood but also include adult-onset leukodystrophy. In addition, MR spectroscopy has allowed detection of abnormal or excessive brain metabolites, offering insight into pathophysiology and disease progression. MRI has also markedly increased the awareness of hereditary white matter diseases associated with hypomyelination, in addition to the previously described classic leukodystrophies. New disease entities based on MRI and clinical patterns have been defined through the committed collaboration of centers around the world.

The likelihood of encountering a patient in clinical practice depends on the prevalence of individual leukodystrophies and whether one is a pediatric or adult neurologist. Once considered extremely rare and refractory to treatment, leukodystrophies are now known to occur more frequently, and collectively, their incidence rivals that of multiple sclerosis (MS). Metabolic interventions such as enzyme replacement and cell-based therapies are becoming a therapeutic possibility and will hopefully lead to improved clinical outcomes.

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Clinical Presentation of Childhood-Onset Leukodystrophies

The insidious nature of symptom onset makes diagnosis in the early stages difficult, requiring a high index of suspicion and vigilant screening of the family history. There are few pathognomonic clinical features that set the leukodystrophies apart from other disorders. Particularly in early childhood, it can be difficult to discern whether a condition is static or truly progressive. Leukodystrophy patients are generally not dysmorphic. With the exception of infantile cases they exhibit normal early development before losing skills as myelin deteriorates. Personality changes and subtle cognitive decline may be the earliest signs and often precede the loss of previously acquired motor skills. More focal clinical signs may then appear, such as lower limb spasticity, ataxia, swallowing dysfunction, enunciation difficulties, movement disorders, optic atrophy or seizures. Although there is significant overlap in symptomatology, certain clinical signs can be clues to particular leukodystrophies. Adrenal insufficiency is seen almost exclusively with X-linked adrenoleukodystrophy (X-ALD). A coexistent peripheral neuropathy often occurs in Krabbe disease and MLD. Megalencephaly is characteristic for Canavan and Alexander disease.

In all cases of early neurologic regression, one should rule out infectious and toxic etiologies as well as other demyelinating conditions. A thorough neurologic examination and family history can be invaluable. In X-linked disorders, a maternal uncle may be wheelchair bound; in autosomal recessive disorders, more distant affected relatives can be identified—valuable clues to the diagnosis. Ultimately, it is often not until a brain MRI demonstrates symmetric confluent demyelination that a progressive leukencephalopathy is even suspected. The pattern of white matter involvement on MRI aids tremendously in honing the differential diagnosis, as do metabolites detected on MR spectroscopy, and most patients receive a definitive diagnosis within weeks of their brain MRI. The differential diagnosis of symmetric conflu ent white matter diseases of childhood is listed in Table 1.
The typical adult with a leukodystrophy presents with progressive cognitive or neuropsychiatric difficulties, often associated with pseudobulbar palsy or progressive lower limb spasticity.

Similar to childhood-onset leukodystrophies, certain clinical presentations are more common in specific disorders. Foremost among these is progressive spastic paraparesis with detrusor instability, which is a well-recognized presentation of the noninflammatory form of X-ALD, termed adrenomyeloneuropathy (AMN), but also occurs in Krabbe disease and MLD. Isolated adrenal insufficiency may be seen with X-ALD. Ill-defined pain syndromes may occur in X-ALD, particularly in female heterozygotes. Peripheral neuropathy may be the presenting feature of MLD, Krabbe disease, and X-ALD. A “pure” psychiatric presentation with psychosis may occur in adults with any leukodystrophy, but particularly with MLD. As in children, leukodystrophies in adults may also come to be diagnosed when a brain MRI unexpectedly shows significant white matter abnormalities. Last, leukodystrophies may be diagnosed through screening of asymptomatic family members. The differential diagnosis of symmetric confluent white matter abnormalities in adults is outlined in Table 2.

### TABLE 1. Most Frequently Encountered Childhood-Onset Hereditary Leukoencephalopathies and the Differential Diagnosis of Confluent White Matter Imaging Abnormalities in Children

<table>
<thead>
<tr>
<th>Heritable Leukoencephalopathies of Childhood</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood cerebral X-linked adrenoleukodystrophy</td>
<td>Primary CNS inflammation (AD, MS)</td>
</tr>
<tr>
<td>Vanishing white matter disease</td>
<td>Primary CNS infection (encephalitis)</td>
</tr>
<tr>
<td>Hypomyelinating disorders</td>
<td>CNS neoplasia (glial tumors, lymphoma)</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Toxic leukoencephalopathy (radiation, chemotherapy, biologic therapies)</td>
</tr>
<tr>
<td>Globoid cell leukodystrophy (Krabbe disease)</td>
<td>Vanishing white matter disease/ovarioleukodystrophy</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>Unclassifiable leukodystrophies</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>Alexander disease</td>
</tr>
<tr>
<td>Unclassifiable leukodystrophies</td>
<td>Leukodystrophy with neuroaxonal spheroids</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system; AD, acute demyelinating encephalomyelitis; MS, multiple sclerosis.

### TABLE 2. Most Frequently Encountered Adult-Onset Hereditary Leukoencephalopathies and the Differential Diagnosis of Confluent White Matter Imaging Abnormalities in Adults

<table>
<thead>
<tr>
<th>Heritable Leukoencephalopathies of Adulthood</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenomyeloneuropathy (AMN)</td>
<td>Infiltrative tumors (gliomas, gliomatosis cerebri, primary CNS lymphoma)</td>
</tr>
<tr>
<td>Adult cerebral X-linked adrenoleukodystrophy</td>
<td>Toxic leukoencephalopathy (radiotherapy, chemotherapy, organic solvents, biologic therapies, drugs of abuse)</td>
</tr>
<tr>
<td>Female heterozygote form of adrenoleukodystrophy</td>
<td>Metabolic leukoencephalopathy (anoxia, carbon monoxide, mitochondrial)</td>
</tr>
<tr>
<td>Unclassifiable leukodystrophies</td>
<td>Infection (encephalitis, HIV)</td>
</tr>
<tr>
<td>Vanishing white matter disease/ovarioleukodystrophy</td>
<td>Leukodystrophy, progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Trauma (diffuse axonal injury)</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>Vascular pathologies (ischemic, inflammatory, CADASIL)</td>
</tr>
<tr>
<td>Leukodystrophy with neuroaxonal spheroids</td>
<td>CNS inflammation (MS), ADEM, systemic disorders with CNS involvement</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system; HIV, human immunodeficiency virus; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MS, multiple sclerosis; ADEM, acute demyelinating encephalomyelitis.

### CLINICAL PRESENTATION OF ADULT-ONSET LEUKODYSTROPHIES

The clinical manifestations of leukodystrophies in adults are broadly similar to those in children, relating to dysfunctional cerebral and/or spinal cord white matter. Overall, the “typical” adult with a leukodystrophy presents with progressive cognitive or neuropsychiatric difficulties, often associated with pseudobulbar palsy or progressive lower limb spasticity. The pace of symptom onset may vary from relatively acute to subacute or insidious. Cerebral dysfunction is typically characterized by impaired attention and forgetfulness, psychomotor slowing, impaired executive and visuospatial skills, changes in personality, and emotional disturbances typical of a subcortical dementia. There is a notable lack of “cortical” abnormalities such as aphasia, neglect, or apraxia. Acute presentations may be precipitated by trauma, infection, or toxins. Patients who present acutely are commonly misdiagnosed, since a genetic disorder is often not considered in adults. The clinical picture may be additionally confounded by concurrent substance abuse, psychiatric disease, or incorrect pre-existing diagnostic labels such as fibromyalgia or multiple sclerosis. When advanced, the leukodystrophies lead to progressive abulia, spasticity, frontal release signs, incontinence, and cortical signs and symptoms. In the late stages, patients may progress into a state of akinetic mutism, stupor, coma, and ultimately death.

Another approach to the clinical presentation of leukodystrophies is to consider the differential diagnosis of confluent, often symmetric, white matter abnormalities on MRI (Tables 1 and 2). Although this general appearance is indicative of diffuse white matter injury, it is not necessarily pathognomonic for the heritable leukodystrophies. Still, the specific pattern of white matter involvement on MRI can be suggestive of a particular leukodystrophy (Fig. 1). Because of the diffuse nature of white matter damage in leukodystrophies, confluent imaging abnormalities are more typical than multifocal or asymmetric imaging abnormalities. Canavan disease shows diffuse subcortical involvement with T2 prolongation extending into the internal and external capsules. The MR appearance of Pelizaeus-Merzbacher disease (PMD) is one of lack of myelination similar in appearance to that of a newborn, without frank evidence of white matter destruction. A parieto-occipital pattern of abnormal T2 hyperintensity is seen with X-ALD and GLD, but only in X-ALD does this lesion enhance after administration of contrast (Fig. 2). Other diagnostic considerations when contrast enhancement is present include infections, MS, acute demyelinating encephalomyelitis, and Alexander disease (the latter tends to have an anterior-predominant pattern of white matter...
GLD is often also associated with abnormal T2 signal within the basal ganglia and thalami. In the early stages, VWMD characteristically spares the midline. In general, most symptomatic leukodystrophy patients have abnormal MRI scans, but at times clinical deterioration may precede subtle evidence of demyelination on MRI as seen in infantile cases of MLD. Figure 2 presents examples of typical imaging findings in specific leukodystrophies.

CLINICAL FEATURES AND PATHOPHYSIOLOGY: FROM GENE TO BIOCHEMISTRY AND PATHOLOGY

Modern genetics has allowed us to identify abnormal genes responsible for a number of leukodystrophies and thereby assess the impact of these mutations on organ function and pathology. This has led to increased understanding of the pathophysiological basis of hereditary white matter diseases. Table 3 summarizes the typical clinical, imaging, and pathophysiological features of the most commonly recognized leukodystrophies.

The myelin sheath is a complex structure composed of lipid (80% of weight) and protein (20%) components, arranged as strategically placed proteins alternating with lipid layers. The lipid layers consist of a bimolecular layer of hydrocarbon chains, cholesterol, phospholipids, and galactolipids (mainly galactocerebroside and sulfatide). The galactolipids and cholesterol are mostly in the outer layer of the cell membrane, exposed to the extracellular space and interacting with extracellular water, whereas the hydrophobic phospholipids are located on the cytoplasmic side of the membrane. Hydrocarbon chains of specific length (primarily long-chain fatty acids) are interposed between the inner and outer membranes. More than half of these hydrocarbon chains are unsaturated, resulting in a more stable cell membrane. Both cholesterol and the protein components are critical to membrane stability. Consequently, the membrane may become unstable because of alterations in either hydrocarbon chains or protein components. A large number of proteins are incorporated into the myelin sheath. The 2 major proteins are proteolipid protein (PLP, 50% of myelin protein weight) and myelin basic protein (MBP, 35%). PLP is composed of 4 helices that span the cell membrane, extending from the extracellular space, where it has a homophilic interaction with adjacent PLP molecules, leading to tight apposition of outer membranes of adjacent spirals of myelin. MBP is located on the cytoplasmic side of myelin membranes. It is postulated that MBP stabilizes the myelin spiral by interacting with negatively charged phospholipids at the cytoplasmic surface of the lipid membrane.

X-Linked Adrenoleukodystrophy

Adrenoleukodystrophy is an X-linked disorder characterized biochemically by impaired metabolism of very long chain fatty acids (VLCFA), an integral part of myelin. X-ALD is the most prevalent leukodystrophy encountered in clinical practice, with an estimated overall frequency of 1:17,000 across most ethnic groups. Patients have no dysmorphic features and exhibit normal early development but then lose skills and regress as myelin deteriorates. Like other leukodystrophies, the insidious nature of symptom onset makes diagnosis in the early stages difficult, requiring a high index of suspicion in most cases. For example, boys with X-ALD may initially show just a subtle personality change, or a toddler will learn to walk but then plateau. Usually, it is only with the development of a second symptom, such as eye deviation or

FIGURE 1. Algorithm for the use of MRI patterns in distinguishing disorders with white matter involvement. CTX indicates cerebrotendinous xanthomatosis; VWMD, vanishing white matter disease; PMD, Pelizaeus-Merzbacher disease; MCL, megalencephalic leukoencephalopathy with subcortical cysts; X-ALD, X-linked adrenoleukodystrophy; HIE, hypoxic-ischemic encephalopathy; MLD, metachromatic leukodystrophy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MS, multiple sclerosis; PKU, phenylketonuria; HDLS, hereditary diffuse leukoencephalopathy with spheroids; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate.

FIGURE 2. Magnetic resonance imaging findings in patients with specific hereditary leukodystrophies: (A) X-linked adrenoleukodystrophy, (B) Metachromatic leukodystrophy, (C) Krabbe disease, (D) Canavan disease.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Clinical Features</th>
<th>Distinct Imaging Features</th>
<th>Diagnostic Tests</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenoleukodystrophy</td>
<td>X-linked recessive</td>
<td>Cerebral: behavioral changes, motor regression, acute progression AMN: chronic progressive spastic paraparesis</td>
<td>Cerebral: predominantly posterior-perventricular, contrast enhancement AMN: corticospinal tract involvement</td>
<td>Plasma very long chain fatty acids; ABCD1 mutation</td>
<td>Cerebral: brain inflammation AMN: oxidative stress?</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Autosomal recessive</td>
<td>Behavioral changes, pyramidal signs, ataxia</td>
<td>Diffuse white matter abnormalities with sparing of U-fibers</td>
<td>Arylsulfatase A in leukocytes; high urinary excretion of sulfatides</td>
<td>Accumulation of sulfatides within lipid membranes</td>
</tr>
<tr>
<td>Globoid cell leukodystrophy (Krabbe disease)</td>
<td>Autosomal recessive</td>
<td>Developmental regression, spasticity, opisthotonus; late-onset milder</td>
<td>Posterior-predominant perventricular; no enhancement</td>
<td>Galactosylceramide β-galactosidase in leukocytes</td>
<td>Psychosine cytotoxic to oligodendroglia?</td>
</tr>
<tr>
<td>Vanishing white matter disease</td>
<td>Autosomal recessive</td>
<td>Ataxia, spasticity, deterioration following minor head trauma and febrile illness</td>
<td>Progressive rarefaction and cystic degeneration of white matter</td>
<td>Mutation in eIF2B α, β, γ, δ, or e</td>
<td>Abnormal unfolded protein response?</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>De novo mutations in majority</td>
<td>Megenalencephy, psychomotor regression, ataxia and seizures; adults with bulbar symptoms</td>
<td>Diffuse white matter abnormalities, often with anterior predominance</td>
<td>GFAP gene mutation</td>
<td>Toxic aggregates of GFAP?</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>Autosomal recessive</td>
<td>Megenalencephy, hypotonia, psychomotor regression</td>
<td>Diffuse subcortical signal abnormalities; increased NAA on MRS</td>
<td>Aspartoacylase gene mutation</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>Leukodystrophy with neuroaxonal spheroids</td>
<td>Unclear- most cases sporadic but familial inheritance described</td>
<td>Adult onset disease may masquerade as MS or dementia</td>
<td>Symmetric confluent or multifocal white matter signal abnormalities</td>
<td>Neuroaxonal spheroids and pigmented glia on brain biopsy</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>Pelizaeus Merzbacher disease</td>
<td>X-linked recessive</td>
<td>Infantile onset in majority; nystagmus, impaired vision, ataxia, seizures</td>
<td>Symmetric confluent white matter signal abnormalities</td>
<td>PLP1 gene mutation</td>
<td>Poorly formed myelin</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher-like disease</td>
<td>Unclear, but probably autosomal recessive</td>
<td>Indistinguishable from PMD</td>
<td>Symmetric confluent abnormalities</td>
<td>GJA12 gene mutation</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>Megalencephalic leukencephalopathy with subcortical cysts</td>
<td>Unclear, but probably autosomal recessive</td>
<td>Megenalencephy, slowly progressive ataxia and spasticity, seizures</td>
<td>Subcortical cysts in temporal poles and frontotemporal regions</td>
<td>MCL1 gene mutation</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>Leukencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate</td>
<td>Autosomal recessive</td>
<td>In early adulthood cerebellar ataxia, spasticity, cognitive impairment</td>
<td>Brainstem and spinal cord involvement and elevated lactate on MRS</td>
<td>DARS2 gene mutation</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>Aicardi-Goutieres syndrome</td>
<td>Predominantly autosomal recessive, except subtype 5 which is autosomal dominant</td>
<td>Neonatal form presents with microcephaly, spasticity, dystonia, marked developmental delay and regression; later-onset variants with milder phenotype</td>
<td>Extensive calcification, cerebral hypoplasia, white matter signal abnormalities</td>
<td>TREX1 and RNASEH2A-C gene mutations</td>
<td>Dysfunctional DNA repair?</td>
</tr>
</tbody>
</table>

AR indicates autosomal recessive; AD, autosomal dominant; AMN, adrenomyeloneuropathy; ABCD1, ATP-binding cassette, subfamily D, member 1; eIF, eukaryotic translation initiation factor; GFAP, Glial fibrillary acidic protein; NAA, N-acetylaspartic acid; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; PMD, Pelizaeus Merzbacher disease; PLP, proteolipid protein; GJA12, gap junction protein; MCL, Megalencephalic leukencephalopathy with subcortical cysts; DARS2, mitochondrial aspartyl-tRNA synthetase; TREX-3-prime@repair exonuclease 1; RNASEH2A-C—aspartyl-tRNA synthetase.

motor difficulties, that a neurologic disease is suspected. Careful probing of the family history often reveals other family members with neurologic conditions on the maternal side of the family. However, usually not until a brain MRI demonstrates symmetric confluent demyelination is X-ALD considered. The pattern of posterior-predominant white matter involvement, often with a contrast-enhancing rim or edge, aids tremendously in the diagnostic work up, as do metabolites detected on MR spectroscopy.
Adrenoleukodystrophy is an X-linked disorder characterized biochemically by elevated very long chain fatty acids.

There are several distinct phenotypes in X-ALD. The most prevalent manifestation is that of a slowly progressive paraparesis with sphincter disturbances because of involvement of the long tracts in the spinal cord, referred to as AMN. This is due to an axonal degeneration that is primarily noninflammatory in nature. Beyond this, X-ALD can also manifest as acute inflammatory brain demyelination, particularly but not exclusively in childhood. The affected boys develop normally until 4 to 8 years of age, then suffer dementia and progressive neurologic decline that leads to a vegetative state and death. More than 70% of all male patients will have adrenal insufficiency. Female heterozygotes can also have symptoms resembling AMN, but they never develop cerebral demyelination.

In males, as AMN progresses, symptoms and signs of cerebral dysfunction often supervene. Approximately 20% of patients with an AMN phenotype will develop, after a variable period of 5 to 10 years, a more severe phenotype, termed adult cerebral ALD (AC-ALD). AC-ALD is a progressive inflammatory demyelinating disease. Despite similarities in the MRI lesion pattern, disease progression may be slower in adults compared with that observed in affected children. Patients often develop neuropsychiatric signs first, followed by dementia, ataxia, seizures, and ultimately death in many. The rate of decline may vary from insidious and chronic, simulating Alzheimer disease or frontotemporal dementia, to more fulminant deterioration, where treating physicians legitimately consider an infective, inflammatory, toxic, or paraneoplastic cause. Rarely, adults may present with the cerebral variant without a premonitory AMN syndrome.

Female heterozygotes of X-ALD may also manifest a progressive spastic paraparesis with bowel and bladder dysfunction. Far from being mere “carriers” of disease, they may exhibit a myelopathy that can be insidious, slowly progressive, or static. Overall, approximately two-third of symptomatic female heterozygotes display an AMN-like syndrome. Prominent symptoms are those of ill-defined pain and vague sensory abnormalities. Given the wide differential diagnosis of spastic paraparesis, the most common manifestation is that of a slowly progressive paraparesis with bowel and bladder dysfunction. In particular, differentiation from hereditary spastic paraparesis may be difficult. The paraparesis in progressive spastic paraparesis with bowel and bladder dysfunction is not distinguishable from other causes of progressive spastic paraparesis. In particular, differentiation from hereditary spastic paraparesis may be difficult. The paraparesis in X-ALD carriers tends to be insidious and chronic in nature, unlike the frequently fulminant or subacute presentation of AC-ALD.

Female heterozygotes of X-linked adrenoleukodystrophy may also manifest a progressive spastic paraparesis with bowel and bladder dysfunction.

In X-ALD, the gene defect is at the locus for ABCD1, which codes for adrenoleukodystrophy protein, a peroxisomal transmembrane transporter protein.

Metachromatic Leukodystrophy

MLD is an autosomal recessive disorder caused by a deficiency in lysosomal arylsulfatase A (ARSA), which catabolizes sulfatides. The incidence of MLD is approximately 1 per 40,000 live births. Diagnosis of MLD is based on the measurement of ARSA activity in leukocytes. However, about 15% of normal people have low ARSA activity without clinical symptoms, because of gene polymorphisms in the ARSA encoding gene. Hence, correct diagnosis requires additional proof of abnormally high urinary excretion of sulfatides or molecular analysis of the ARSA gene. There are 3 clinical phenotypes, based on the age of disease onset. Late-infantile MLD is the most common form and usually appears between 18 and 24 months, often shortly after a child takes his or her first steps. The juvenile form emerges between 4 and 16 years, and the adult form, which accounts for approximately 20% of all cases, is defined by the onset of disease beyond 16 years of age. The clinical symptoms vary by age of onset. In childhood, patients usually present with a disturbance in gait and go on to develop ataxia, spastic quadriplegia, optic atrophy, and peripheral neuropathy. Symptoms eventually progress to a cerebellar state in most cases. In the adult form of MLD, the initial symptoms are often psychiatric and may lead to a diagnosis of schizophrenia. Motor manifestations tend to occur later in the clinical course, and progressive intellectual deterioration sets in after a variable period of neuropsychiatric illness. Peripheral neuromuscular complications such as neuropathy or myopathy can also occur in adults but are less frequent than in infants or children. Other manifestations of adult MLD include optic atrophy and dystonia. MLD heterozygotes...
typically have a normal elemental neurologic examination and electroencephalogram (EEG) but may show deficits on formal neuropsychological testing, particularly on tasks of spatial or constructional skills. In the adult form of MLD, the initial symptoms are often psychiatric and may lead to a diagnosis of schizophrenia.

In MLD, the defective enzymatic activity of ARSA causes intracellular accumulation of sulfatide. How this accumulation leads to the characteristic demyelination with subcortical sparing of U-fibers is unknown. Interruption of the integrity of a stable lipid bilayer as a result of abnormal myelin composition may play an important role. Dysfunction of the myelin sheath may result from defective resorption of sulfatides from the inner compartment of the myelin membrane. In addition, the cytotoxic effect of lyso-sulfatide, a sulfatide metabolite, may contribute to oligodendrogial dysfunction and death.

**Globoid Cell Leukodystrophy (Krabbe Disease)**

Krabbe disease is caused by a deficiency in the lysosomal enzyme cerebroside β-galactocerebrosidase, which catalyzes galactocerebrosides. The manifestations of Krabbe disease are due to accumulation of galactocerebrosides and β-galactosylsphingosine, which in turn leads to loss of oligodendrocytes. The incidence of Krabbe disease is estimated at 1:100,000 births. Infantile Krabbe disease presents in the first 6 months of life as hyperirritability, increased muscular tone, fever, and developmental arrest. As the disease progresses, there is further cognitive decline, myoclonus, opisthotonus, nystagmus, and optic atrophy. Patients diagnosed in infancy rarely survive beyond 2 years. In an estimated 10% of cases, symptoms begin after the patient has begun to walk; these are considered “late-onset.” Several authors have described cases of late-onset Krabbe disease in patients as old as 84, though clearly infantile onset dominates this disease. Adults present with a variety of central and peripheral motor symptoms, but most eventually develop progressive cognitive decline, seizures, and cortical blindness. Central motor signs include spasticity, ataxia, and weakness. Of late-onset patients, 20% have abnormal peripheral nerve conduction studies with uniform slowing of conduction velocities.

In Krabbe disease, substrate accumulation secondary to the genetic defect figures prominently in pathogenesis. Excess galactosylceramide is consumed by phagocytic macrophages which take on their characteristic “globoid” appearance. As opposed to MLD, in which ceramide is consumed by phagocytic macrophages which take on their genetic defect figures prominently in pathogenesis. Excess galactosylcerebroside within Krabbe disease may also accumulate in the subcortical gray matter, in basal ganglia, and in thalamic and subependymal regions. These fibers are located within astrocytes, cells that are closely related to blood vessels. A transgenic mouse overexpressing GFAP produces Rosenthal fibers and, more importantly, up-regulates stress-response genes such as alpha-β-...
crystallin as well as Nrf2. Thus, the stress response may be accentuated in astrocytes due to up-regulation of GFAP.42

Alexander disease is caused by a mutation in the gene for glial fibrillary acid protein.

Canavan Disease
Canavan disease is an autosomal recessive leukodystrophy that usually presents with megalencephaly and hypotonia in infancy.43 At onset, there is very low tone in the neck muscles and trunk, with concurrent hyperextension of legs and flexion of arms. Although the megalencephaly may initially contribute to poor head control, progressive motor dysfunction, and cognitive symptoms become apparent over time. Progression may be variable, but death usually results within a few years of symptom onset. Some adult patients with increased N-acetylaspartic acid (NAA) in urine may represent another as of yet poorly characterized spectrum of the disorder.

Canavan disease is caused by a deficiency in aspartoacylase (ASPA), which leads to elevation in NAA. NAA is only present in the nervous system, localized primarily in neurons and considered a marker of the functional integrity of neurons. MR spectroscopy allows detection of the metabolite in vivo. The enzyme ASPA cleaves NAA into acetate and aspartate, and its deficiency leads to a decrease in acetate. Because acetate is necessary for myelin synthesis, this deficiency is thought to disturb myelination. At autopsy, the enlarged brains show spongy degeneration and hypomyelination.

Hereditary Diffuse Leukoencephalopathy With Spheroids
Unlike the other diseases discussed, hereditary diffuse leukoencephalopathy with spheroids is almost exclusively diagnosed in adults. The clinical features in adulthood are rather homogeneous and include deterioration in behavior and personality with concurrent cognitive decline and seizures.44 In an advanced stage, patients exhibit bilateral but often asymmetric pyramidal signs. Though putatively hereditary with an autosomal dominant inheritance, establishing a diagnosis is made more difficult by the apparently sporadic nature of most cases. The reported disease onset ranges from 15 to 65 years, but most often occurs in the 20- to 50-year age interval. Like other leukodystrophies, hereditary diffuse leukoencephalopathy with spheroids can be mistakenly attributed to other more common neurologic disorders.45 Diagnosis is formally established by brain biopsy or autopsy. Nohrenhancing T2 hyperintense white matter abnormalities may be strikingly asymmetric.

Hereditary diffuse leukoencephalopathy with spheroids is almost exclusively diagnosed in adults.

Pelizaeus-Merzbacher Disease
PMD is an X-linked recessive dysmyelination disorder caused by mutations in the PLP1 gene. In contrast to other leukodystrophies such as MLD and X-ALD, in which myelin is formed but subsequently destroyed, PMD is characterized by a failure to form myelin, i.e., hypomyelination. PMD is the prototype of hypomyelinating leukodystrophies because of an inborn error of myelin formation. Clinical features usually consist of nystagmus and impaired motor development within the first months of life followed by ataxia, dystonia, dysarthria, and progressive spasticity. The clinical spectrum ranges from severe infantile-onset disease to childhood-onset spastic paraparesis.46 One of the patients originally described by Pelizaeus lived into the sixth decade, and since then there have been a number of case reports of adult-onset PMD characterized by tremor, ataxia, dementia47 and progressive spastic paraplegia.48 Like X-ALD, some heterozygous females have manifestations of the disorder, such as progressive personality change or gait disorder.48,49

Pelizaeus-Merzbacher disease is an X-linked recessive dysmyelination disorder caused by mutations in the proteolipid protein 1 gene.

In PMD, mutations in the PLP1 gene on chromosome Xq22 are associated with a lack of PLP in conjunction with deficits in the other protein component of myelin, such as myelin basic protein. About 20% of individuals with a clinical and radiologic PMD phenotype do not have PLP1 mutations; these individuals are deemed to have “Pelizaeus Merzbacher-like disease” (PMLD, see below). Up to one third of patients carry an identifiable mutation in the coding region of PLP1, whereas the majority of patients have increased PLP1 dosage resulting from duplication of genomic fragments containing the entire PLP1. The most common mutation is gene duplication. Less frequent genetic findings are missense mutations, insertions, and deletions. Both excessive production of PLP, as in gene duplications, or conformational change of the protein, because of missense mutations, are detrimental to myelination. Abnormal PLP is thought to impair protein trafficking and to induce apoptosis in oligodendroglia, leading to hypomyelination and impaired brain development.

Recessive Hypomyelinating Leukoencephalopathy (Pelizaeus-Merzbacher-like Disease)
Recessive hypomyelinating leukoencephalopathy (RHL), also known PMLD, is a genetically heterogeneous disorder within the group of hypomyelinating leukoencephalopathies. PMLD usually presents in infancy or early childhood with nystagmus, impaired motor development, ataxia, choreoathetoid movements, dysarthria, and progressive spasticity. A symptomatic 15-year-old girl heterozygote presenting with progressive pendular nystagmus, spastic gait disturbance, atethosis, and dysarthria has also been described.49 Mutations of the gap junction protein α12 gene are known to cause one autosomal recessive subtype of PMLD. The gene was localized to chromosome 1q41-q42 by genome-wide linkage scan. Gap junction proteins assemble into intercellular channels through which signaling ions and small molecules are exchanged.

Vacuolating Megalencephalic Leukoencephalopathy With Subcortical Cysts
Vacuolating megalencephalic leukoencephalopathy with subcortical cysts (MLC) is another recently recognized leukodystrophy caused by mutations in the MLC1 gene.51 The core clinical features of this rare disease include megalencephaly noted in infancy, spastic motor disability, ataxia, occasional seizures, mild cognitive decline, and slow progression. There are emerging reports of adults with this syndrome, usually presenting with spasticity and ataxia, sometimes...
associated with megalencephaly.\textsuperscript{52,53} Neuroimaging shows bilateral extensive white-matter changes with characteristic cysts in the temporal regions.

MLC1 is an oligomeric plasma membrane protein of unknown function expressed mainly in glial cells and neurons. It shares its localization at astrocytic endfoot with the dystrophin-associated glycoprotein complex. MLC1 mutations produce folding defects and reduce protein levels in vivo.\textsuperscript{54} Therefore, the disorder is thought to belong to the class of conformational diseases.

**Leukoencephalopathy With Brainstem and Spinal Cord Involvement and Elevated White Matter Lactate**

This novel leukoencephalopathy syndrome, first described in 2003, is an autosomal recessive disease commonly manifesting in early childhood.\textsuperscript{55,56} Affected individuals develop progressively severe cerebellar ataxia, spasticity, and dorsal column dysfunction, sometimes with a mild cognitive deficit or decline. Mutations in DARS2, which encodes mitochondrial aspartyl-tRNA synthetase, have been found to be responsible. MR spectroscopy characteristically reveals decreased NAA and increased lactate in the white matter.

**Aicardi-Goutieres Syndrome**

Aicardi-Goutieres syndrome (AGS) is a genetically heterogeneous autosomal recessive group of inherited encephalopathies with 5 subtypes. Classic AGS is characterized by cerebral atrophy, white matter abnormalities, intracranial calcifications, chronic CSF lymphocytosis, and elevated CSF alpha-interferon.\textsuperscript{57} Broadly speaking, 2 clinical presentations have been delineated: an early onset neonatal form, highly reminiscent of congenital infection seen particularly with TREV1 mutations, and a later-onset presentation, sometimes occurring after several months of normal development and occasionally associated with remarkably preserved neurologic function. Severe neurologic dysfunction becomes clinically apparent in infancy, and manifests as progressive microcephaly, spasticity, dystonic posturing, profound psychomotor retardation, and often death in early childhood. Outside the nervous system, thrombocytopenia, hepatoplenomegaly, and elevated hepatic transaminases along with intermittent fever may also erroneously suggest an infective process.\textsuperscript{58} AGS subtype 1 is transmitted in an autosomal recessive pattern and is caused by mutations in the TREV1 gene on chromosome 3p21. TREV1 is involved in DNA repair. The other subtypes are caused by mutations in nuclease genes, namely RNASEH2B gene (AGS subtype 2), RNASEH2C gene (AGS subtype 3), RNASEH2A gene (AGS subtype 4), and an autosomal dominant subtype caused by a TREX1 gene mutation (AGS subtype 5).

**MANAGEMENT AND TREATMENT**

The management of leukodystrophies can be divided into (a) general therapies applicable to all progressive white matter disorders and (b) therapies for specific disorders. Disease-specific therapies may be further subdivided into presymptomatic, early symptomatic, and late symptomatic treatment. Presymptomatic disease is typically found by family screening in at-risk individuals or, less often, by incidentally found MR abnormalities in an asymptomatic individual.

**General Therapies**

All individuals with a leukodystrophy benefit from supportive care, counseling of the individual and family, discussion of the role of family screening, and establishment of a specialist multidisciplinary care team. Education of the patient and caregivers about the disease by medical personnel and patient support groups is critical. When available and logistically feasible, the patient and family should seek help and advice from regional or national centers of expertise in the management of leukodystrophies. The multidisciplinary approach to care should optimize education, nutrition, control of seizures and behavioral difficulties, visual and mobility aids, and family support. Physical therapy, management of spasticity, pain control, respiratory physiotherapy, adequate control of pulmonary infections, and management of bladder dyssynergia, detrusor instability, and continence can greatly augment quality of life. Social support for family and caregivers can alleviate caregiver stress, and inpatient respite and rehabilitative care can be invaluable, particularly when the disease is advanced.

**Therapies for Specific Leukodystrophies**

**X-Linked Adrenoleukodystrophy**

The division of X-ALD into presymptomatic, early symptomatic, and late symptomatic disease is particularly useful when considering appropriate treatment. In the presymptomatic phase, evidence of adrenal insufficiency should be sought and treated, because physical stress and minor illness can lead to acute adrenal insufficiency. Patients should consider wearing a medical alert bracelet to notify others of their dependency on exogenous steroid therapy.

In presymptomatic children, dietary therapy is paramount to reduce the risk of inflammatory demyelination. This consists of dietary restriction of VLCFA combined with the oral intake of a 4:1 mixture of glyceryl trioleate and glyceryl trierucate oils, also referred to as Lorenzo’s oil. Both components of Lorenzo’s oil contain monounsaturated fatty acids, which have been shown to reduce endogenous synthesis of saturated very-long-chain fatty acids. Strict adherence to this 2-pronged dietary regimen has the biochemical effect of normalizing the plasma VLCFA levels within 4 weeks. The results of a recent multicenter international trial suggest that administration of Lorenzo’s Oil to boys who are less than 6 years old, are neurologically asymptomatic and have a normal MRI reduces the risk for subsequent neurologic involvement.\textsuperscript{59,60}

In the early symptomatic phase when MRI abnormalities have appeared, hematopoietic transplant can be considered. Allogeneic bone marrow transplantation has shown favorable effects when performed early in the course of cerebral involvement and when a well-matched donor is available.\textsuperscript{61,62} In the late symptomatic phase, the risk-benefit ratio of transplantation is less favorable. Here a less toxic regimen with use of antioxidants such as N-acetylcysteine may be more appropriate.

The current standard treatment of X-ALD is summarized in Table 4. Other approaches are still under investigation. The management of female heterozygotes is largely supportive. Lorenzo’s oil is not yet proven to be of benefit in female heterozygotes. Unfortunately, more than half of the patients with cerebral involvement who are diagnosed on the basis of symptoms are too advanced to benefit from currently available therapies.

**Metachromatic Leukodystrophy**

In selected patients, typically those who have not yet developed neurologic signs, bone marrow transplantation or hematopoietic stem cell transplantation may be effective for MLD. The therapeutic efficacy of bone marrow and stem cell transplantation is thought to rely on the migration of donor bone marrow-derived cells of the monoocyte-macrophage lineage into disease target organs, where they provide a source of deficient ARSA. In selected early stage patients with the juvenile or adult forms of MLD, bone marrow transplantation has been reported to delay onset and slow progression of disease.\textsuperscript{63} Preliminary animal work has shown that gene therapy where the gene encoding for ARSA is transferred into ARSA-deficient hematopoietic stem cells using viral vectors may be a promising alternative therapy for MLD.\textsuperscript{64} However, additional preclinical work on large animal models before clinical translation is
likely necessary. Clinical experience has shown no efficacy of bone marrow transplantation when performed in symptomatic patients with early onset disease or in the advanced stages of late-onset patients.

Globoid Cell Leukodystrophy

Therapy for globoid cell leukodystrophy is largely limited to symptomatic therapies and supportive care at the present time. Enzyme replacement therapy has not been attempted in this disorder. Bone marrow transplantation has not been systematically studied but has been performed in several patients with some success. One study of 5 patients with Krabbe disease who received hematopoietic stem cell transplantation demonstrated significant improvement in neurologic symptoms. In other reports, however, children with advanced infantile-onset disease have not shown improvement after transplantation. Bone marrow transplantation in a murine model of Krabbe disease increases life span and promotes remyelination of peripheral nerves. Other murine experiments suggest improvement with disease increases life span and promotes remyelination of peripheral nerves. Other murine experiments suggest improvement with l-cycloserine, which reduces sphingosine synthesis by inhibiting the enzyme 3-ketodihydrosphingosine synthase. Lastly, gene therapy research is ongoing but remains untested in humans.

Other Leukodystrophies

For the remaining leukodystrophies, no specific therapies have been established. These rare leukodystrophies are likely to continue to be treated by supportive measures alone until specific genetic defects are identified and understood. Failed therapeutic attempts in many leukodystrophies highlight the need for carefully conducted natural history studies prior to evaluating novel therapies. Given the clinical variability in most of these disorders, it is increasingly clear that one single approach will not bring about cure. Rather, therapies will likely vary by age group and may include combination therapies tailored to the specifics of genotype, metabolism and clinical presentation.

### REFERENCES


