EXPERT REVIEWS

Childhood leukodystrophies: a clinical perspective

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Leukodystrophies are white matter disorders that are genetic in nature. In the young, they represent an important cause of progressive neurological disability. They are frequently recognized on MRI, but their identification remains a challenge. Their diagnosis is important for prognostication, palliative and experimental treatment, as well as family screening. The diagnostic strategy rests upon clinical clues and MRI patterns, complemented by appropriately selected electrophysiological and laboratory testing. Considerable overlap exists between white and gray matter disease, as neuronal degeneration will result in myelin loss. An understanding of the pathophysiology and natural disease evolution is necessary to understand the risks and benefits of experimental and palliative treatments.

Keywords: brain white matter • children • degenerative brain disease • metabolic genetic disease • MRI

The term 'leukodystrophy' refers to deterioration of white matter of the brain. The deterioration coincides with clinical regression of skills, and in the most severe cases neurological devastation. Leukodystrophies are genetic diseases with degeneration of myelin sheaths in the CNS and sometimes also in peripheral nerves. Their basic defect is directly related to the synthesis and maintenance of myelin membranes. Defects causing secondary myelin damage are called leukoencephalopathies. Most leukodystrophies manifest themselves during childhood or adolescence, are incurable and have a progressive course, leading to premature death. Diagnosis is important as palliative or experimental therapies may offer benefits, for reproductive counseling and family screening of currently unaffected individuals. The few treatments available are more effective in the early stages.

Making the diagnosis of a leukodystrophy requires knowledge of clinical features and neuroimaging. Familiarity with the typical age of onset of various phenotypes of leukodystrophies, as well as heightened vigilance to brain MRI patterns, is invaluable in the diagnostic algorithm. In addition, electrophysiological findings, specific laboratory tests and other special investigations may be needed to arrive at a precise diagnosis. The list of defined leukodystrophies and genetic leukoencephalopathies to consider in the young (Table 1) is extensive and is still growing. In this article, we review the current knowledge on recognition and management of these disorders from a pediatric viewpoint. In view of the complex designations of the disorders, we have resorted to using abbreviations that are increasingly found in the literature.

Clinical features & the diagnosis of a leukodystrophy

Age of onset

The leading symptoms of a leukodystrophy are neurological and appear, with few exceptions, in previously healthy children. The clinical onset is frequently insiduous, and symptoms then usually progress slowly, with possible periods of stagnation. Seemingly vague (and otherwise unexplained) progressive motor or mental symptoms in a young person may direct suspicion towards a leukodystrophy.

Table 1 is a near exhaustive list of leukodystrophies and genetic leukoencephalopathies occurring in the young. A single one of these genetically defined diseases can have widely variable phenotypes that may manifest, depending on the severity of mutations, at any age between infancy and adulthood. This bewildering variety of diagnostic possibilities requires a clinical strategy. Starting from the age of the patient at the onset of symptoms, certain types of leukodystrophies can be considered (Table 2).

General physical features

Most patients with leukodystrophies do not have any physical abnormality. Some have a large head (Alexander disease, Canavan disease, megalencephalic leukodystrophy with cysts and vanishing

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Table 1. Childhood leukodystrophies and genetic leukoencephalopathies[†].

Leukodystrophy	Abbreviation	MIM	Mutated genes	Hints from clinical findings or routine studies	Diagnostic tests	Ref.
Alexander disease	AD	203450	*GFAP*	Sporadic macrocephaly in infantile-type. Can suggest brain stem tumor in juvenile-type	MG	[38]
Aicardi–Goutières syndrome	AGS	225750	*TREX1*	Acquired microcephaly. CT: calcifications	MG	[39,40]
Canavan disease	CD	271900	*ASPA*	Macrocephaly in infantile-type	NAA (MRS, urine), MG	[41]
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	CADASIL	125310	*NOTCH3*	Dominant family history or sporadic Hemorrhagic strokes	MG	[42]
Cerebrotendinous xanthomatosis	CTX	213700	*CYP27A1*	Xanthomas, cataracts. MRI: cerebellar lesions, CT: calcifications. Treatable	Plasma cholestanol, MG	[43]
Chromosome 18q deletion syndrome	18q-	601808		Multiple malformations	Chromosomes	[44]
Congenital disorders of glycosylation	CDG			Heterogeneous group of disorders	Atypical transferrins in blood (in some patients)	[45]
Cystical leukoencephalopathy without megalencephaly	CYS	612951	*RNASET2*	MRI: cystic lesions	MG	[46]
Folate receptor defect	FOL	136430	*FOLRI1*	MRI: hypomyelination	CSF folate low	[47]
Fucosidosis	FUC	230000	*FUCA1*	Coarse facial features, MRI: hypomyelination	Fucosidase	[48]
Giant axonal neuropathy type I	GAN	256850	*GAN*	Curly hair, PNS involved	MG	[49]
Globoid leukodystrophy (Krabbe disease)	GLD	245200	*GALC*	Rapid downhill course in previously normal infant, PNS involved, milder juvenile forms	Galacto-cerebrosidase	[50]
Glycine leukoencephalopathy	GLY			MRI: rapidly progressive vacuolating encephalopathy	CSF glycine	[51]
Hypomyelination with atrophy of the basal ganglia and cerebellum	H-ABC	612438		MRI: hypomyelination, characteristic anatomic pattern		[52]
Hypomyelination and congenital cataract	HCC	610532	*FAM126A*	MRI: hypomyelination, cataracts and possible PNS involvement	MG	[53]
Hypomyelination, hypodontia, hypogonadotropic hypogonadism	HHHH	612440		Tooth anomalies, retarded puberty, MRI: hypomyelination	Endocrinological studies	[54]
Hypomyelination with monocarboxylate transporter 8 deficiency	H-MCT8	300523	*SLC16A2*	MRI: hypomyelination, abnormal thyroid function (T3 resistance)	MG	[55]
Hypomyelination with tremor and ataxia	TACH			Regression starts at age 1–5 years		[56]
Infantile neuroaxonal dystrophy	INAD	256600	*PLA2G6*	PNS involved	MG	[57]
Leukoencephalopathy with brain stem and spinal cord involvement and elevated lactate	LBSL	611105	*DARS2*	MRI: pattern characteristic, lactate elevated (MRS)	MG	[3]

[†]Most disorders are inherited autosomal recessively, exceptions are mentioned in particular diseases.
CSF: Cerebrospinal fluid; CT: Computed tomography; MIM: Mendelian Inheritance in Man; MRS: Magnetic resonance spectroscopy; MG: Molecular genetic analysis; NAA: *N*-acetyl aspartate; PNS: Peripheral nervous system.

Table 1. Childhood leukodystrophies and genetic leukoencephalopathies† (cont.).

Leukodystrophy	Abbreviation	MIM	Mutated genes	Hints from clinical findings or routine studies	Diagnostic tests	Ref.
Leukoencephalopathy with calcifications and cysts	LCC	612199		Retinopathy, MRI: cysts, CT: calcifications		[58]
Leukoencephalopathy with metaphyseal chondrodysplasia	LMCD	300660		Broad knees and wrists, X-linked	Bone x-ray	[59]
Megalencephalic leukodystrophy with cysts	MLC	604004	*MLC1*, *GlialCAM*	Macrocephaly, MRI: cystic lesions, progression: slow. Variants without *MLC1* defect may be benign. Pathogenic mutations in *GlialCAM* may be recessive or dominant	MG	[60,61]
Metachromatic leukodystrophy	MLD	250100	*ARSA*	PNS variably involved	Arylsulfatase A, urinary sulfatides, MG	
Metachromatic leukodystrophy with multiple sulfatase deficiency	MLD–MSD	272200	*SUMF1*	Coarse facial features, skin (ichthyosis), lymphocyte granules on light microscopy	Multiple sulfatases, MG	[62]
Mitochondrial disorders	MIT			Large heterogeneous group of disorders, frequently multi-organ symptoms	CSF lactate may be elevated (MRS)	[63–65]
Organic acid disorders				Large heterogenous group of disorders. Macrocephaly possible	Urinary organic acids	[66]
Progressive cavitating leukoencephalopathy	PCL		*NDUFS1*	MRI: cystic lesions, affecting corpus callosum	MG	[62,67,68]
Pelizaeus–Merzbacher disease	PMD	312080	*PLP1*	Congenital transitory stridor and nystagmus, MRI: hypomyelination, X-linked	MG	
Pelizaeus–Merzbacher-like disease type I	PMDL1	608804	*GJC2*/ *GJA12*	Hypomyelination	MG	[69]
Pelizaeus–Merzbacher-like disease type II	PMDL2	260600	*AIMP1*	Hypomyelination		[2,70]
Sialic acid storage disease	SSD	269920	*SLC17A5*	Clinically intermediate between severe neonatal storage disease and the more benign Salla disease, MRI: hypomyelination	Free sialic acid in urine, CSF	[71]
Trichothiodystrophy	TTDP	601675	*ERCC2*/ *XPD*, *ERCC3*/ *XPB*	Skin, hair and nail abnormalities, photosensitivity	MG	[72]
Vanishing white matter disease	VWMD	603896	*EIF2B1-5*	Deterioration triggered by stress, MRI pattern characteristic, white matter signal CSF-like	MG	[73]
X-linked adrenoleukodystrophy	X-ALD	300100	*ABCD1*	Behavioral change in boys, MRI: contrast enhancement, X-linked	Very-long-chain fatty acids in blood	

†Most disorders are inherited autosomal recessively, exceptions are mentioned in particular diseases.
CSF: cerebrospinal fluid; CT: Computed tomography; MIM: Mendelian Inheritance in Man; MRS: Magnetic resonance spectroscopy; MG: Molecular genetic analysis; NAA: *N*-acetyl aspartate; PNS: Peripheral nervous system.

white matter disease). Very rarely (fucosidosis and metachromatic leukodystrophy [MLD] with multiple sulfatase deficiency) they have dysmorphic features and skeletal abnormalities that resemble those seen in mucopolysaccharidoses. Dental abnormalities are seen in some forms of hypomyelination (Figure 1).

Neurologic features

Neurological symptoms of leukodystrophies consist of progressive motor symptoms (mostly spasticity) and changes in cognition and language. Peripheral nerve involvement is present in certain forms (MLD, globoid cell leukodystrophy and some

Table 2. Leukodystrophies to consider in relation to age of patient at onset.

Patient age at onset of symptoms	Leukodystrophies (in order of probability)
Infantile (first year of life)	Globoid cell leukodystrophy Pelizaeus–Merzbacher disease Canavan disease Vanishing white matter disease Megalencephalic leukodystrophy with cysts Aicardi–Goutières syndrome Hypomyelination with atrophy of the basal ganglia and cerebellum
Late infantile (1–5 years)	Metachromatic leukodystrophy Alexander disease Vanishing white matter disease Megalencephalic leukodystrophy with cysts Hypomyelination with atrophy of the basal ganglia and cerebellum Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate Giant axonal neuropathy type I
Juvenile	X-linked adrenoleukodystrophy Metachromatic leukodystrophy Vanishing white matter disease Megalencephalic leukodystrophy with cysts Alexander disease Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate
Adolescence, young adulthood	Metachromatic leukodystrophy Vanishing white matter disease Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate

hypomyelinating disorders) and may lead to the unusual combination of spasticity and reduced muscle stretch reflexes. Early or recalcitrant seizures can occur, but are an unusual feature of disorders mainly affecting brain white matter.

Neuroimaging & the diagnosis of a leukodystrophy

An MRI of the head is the most important ancillary test in a patient suspected of having a leukodystrophy. The minimal requirement for a standard investigation is T1- and T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images. The usefulness of other techniques depends on individual circumstances and is discussed below.

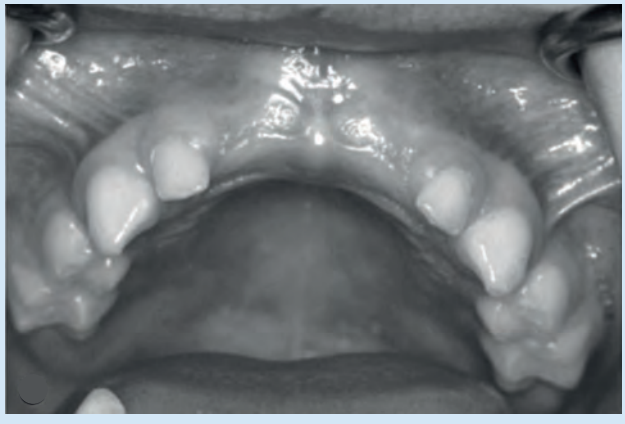

Figure 1. Hypodontia in hypomyelination, hypodontia, hypogonadotropic hypogonadism (HHHH syndrome). Reproduced with permission from [74]. © 2005, Wolters Kluwer Health.

The correlation of MRI results with clinical findings can vary widely. The evaluation of certain patterns and localizations of lesions is crucial in differentiating the metabolic/degenerative characteristics of a disorder from purely inflammatory, tumorous or vascular etiologies. In infancy, the rapid changes in myelination must be taken into account. A comprehensive MRI-based approach to the diagnosis of white matter disorders has recently been published [1]. Its authors suggest a stepwise image analysis using the following discriminators:

First, is hypomyelination (delayed myelination or permanent hypomyelination) or some other brain white matter pathology present? In young infants, the deposition of myelin can best be followed on T1-weighted images. A child over 1.5 years of age has accumulated enough myelin to let the white matter appear dark on T2-weighted images. A high signal on T2-weighted images is, therefore, abnormal for cerebral white matter after this age. The important differentiation between delayed myelination and permanent hypomyelination (and also the recognition of ongoing demyelination) can be made on two MRIs with a significant time interval.

Second, are the white matter abnormalities confluent and bilateral, essentially symmetric, as is typical of genetic white matter disorders, or multifocal and asymmetric as frequently seen in acquired disorders?

Third, if confluent white matter abnormalities are present, where is their predominant localization? The major preferential localizations are frontal, parieto-occipital, periventricular,

Box 1. Childhood leukodystrophies according to major neuroimaging patterns.

Disorders with confluent MRI lesions
- Alexander disease†
- Canavan disease
- Globoid cell leukodystrophy
- Leukoencephalopathy with metaphyseal chondrodysplasia
- Metachromatic leukodystrophy
- Metachromatic leukodystrophy with multiple sulfatase deficiency
- Mitochondrial disorders
- X-linked adrenoleukodystrophy

Disorders with cavitating MRI lesions
- Cystical leukoencephalopathy without megalencephaly
- Glycine leukoencephalopathy
- Leukoencephalopathy with calcifications and cysts
- Megalencephalic leukodystrophy with cysts
- Progressive cavitating leukoencephalopathy

Disorders with hypomyelination
- Fucosidosis
- Folate receptor defect
- Hypomyelination with atrophy of the basal ganglia and cerebellum
- Hypomyelination and congenital cataract
- Hypomyelination, hypodontia, hypogonadotropic hypogonadism
- Hypomyelination with monocarboxylate transporter-8 deficiency
- Pelizaeus–Merzbacher disease
- Pelizaeus–Merzbacher-like disease
- Sialic acid storage disorder
- Tremor-ataxia with central hypomyelination

Disorders with Calcifications
- Aicardi–Goutières syndrome
- Cerebrotendinous xanthomatosis
- Leukoencephalopathy with calcifications and cysts

†Infantile type.

subcortical, diffuse cerebral and in the posterior fossa, each of which are associated with certain forms of leukodystrophy.

A rough classification of leukodystrophies according to their presentation on neuroimaging is shown in Box 1.

Certain typical MRI patterns are seen in several different leukodystrophies, for example, the streaky 'tigroid' appearance of central white matter in MLD and globoid cell leukodystrophy (Figure 2), or the sparing of the subcortical U-fibers as seen, for example, in X-linked adrenoleukodystrophy (X-ALD) and MLD. Streaky patterns are related to the anatomy of the Virchow–Robin spaces in the brain and the accumulation of storage material or fluid around blood vessels. Other patterns are so characteristic as to practically allow a diagnosis. This may be possible, in such cases as juvenile Alexander disease (AD) (Figure 3) and vanishing white matter disease. Hypomyelination is observed in a growing number of genetic disorders that have frequently been classified by recognition of their characteristic MRI pattern [2].

Contrast enhancement is seen in leukodystrophies with an inflammatory component, particularly in X-ALD (Figure 4). Cystic lesions are best detected using FLAIR studies (Figure 5). Magnetic resonance spectroscopy (MRS) is helpful for detecting elevated *N*-acetyl aspartate (NAA) in Canavan disease, or lactate in leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate [3], and other mitochondrial disorders [4]. A decreased NAA peak indicates neuronal involvement occurring in primary white matter disease. Massive swelling of the optic nerves may be seen in infantile globoid cell leukodystrophy (Figure 6). Peripheral nerves can also be thickened in this disorder, and spinal roots may show contrast enhancement. When detecting calcifications, CT is superior to MRI.

A quantitative scoring of MRI lesions has been devised for X-ALD and is widely used to assess eligibility for treatments such as hematologic stem cell transplantation [5,6]. Analogous scores have also been used to describe the lesions in patients with globoid cell leukodystrophy [7] and MLD [8].

Careful image analysis, making use of standard works on myelination disorders [9] and sometimes asking for an expert opinion, will save much time and unnecessary expensive laboratory studies.

Electrophysiology & leukodystrophies

Evoked potentials and nerve conduction velocities, particularly after the first decade, often reveal symmetric involvement of long spinal tracts and peripheral nerves, and are thus helpful in differentiating leukodystrophies from other demyelinating disorders. Furthermore, the presence of peripheral nerve involvement on nerve conduction studies (NCS) can prove valuable in differentiating certain leukodystrophies from others. For instance, patients with X-ALD show normal nerve conduction velocities, while patients with metachromatic or globoid cell leukodystrophy commonly display abnormalities.

Nerve conduction studies

In Krabbe disease, the severity of abnormalities in NCS appears to correlate with clinical severity [10,11]. In general, NCS more frequently reveals abnormalities in symptomatic patients than evoked responses. In general, the degree of MRI abnormality correlates with that seen on NCS and clinical severity. Thus NCS, in combination with neuroimaging studies, appear to be the most sensitive laboratory measures to help assess the severity and the phenotypic classification of globoid cell leukodystrophy.

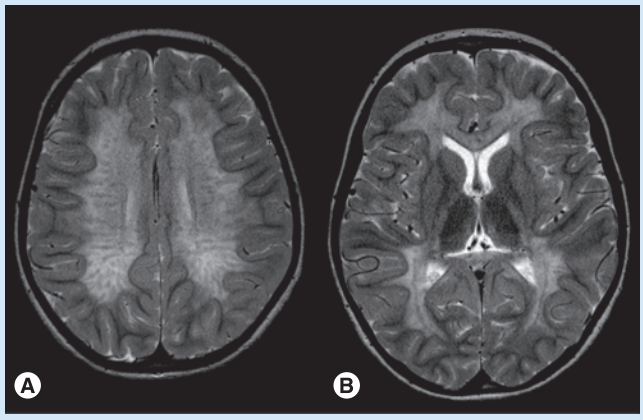

Figure 2. MRI in juvenile metachromatic leukodystrophy.
(A) The central white matter shows signal hyperintensity and a streaky pattern, while the subcortical U fibers are spared.
(B) Involvement of corpus callosum and posterior limb of internal capsule.

Evoked potentials

For boys with X-ALD, brainstem auditory evoked responses (BAER) are usually normal in the first decade of life. BAER later become abnormal in the course of the disease when demyelinating lesions extend in the brainstem and spinal cord. Visual-evoked potentials (VEP) in X-ALD become abnormal once there are extensive demyelinating lesions in the occipital white matter, somatosensory-evoked potentials and motor-evoked responses even later in the course of the disease. Even patients with a normal MRI may have an abnormal neurophysiologic pattern identical to that seen in adrenomyeloneuropathy (AMN) patients (evidently milder in term of abnormalities); usually BAER are first to be abnormal, then somatosensory-evoked potential of the lower limbs and then motor-evoked responses to lower limbs [12].

Laboratory tests in leukodystrophies

Laboratory tests ordered prior to a thorough evaluation of clinical and imaging findings are frequently of low yield and cause high costs. There is no routine all-encompassing laboratory protocol for a suspected leukodystrophy. The utility of individual tests is established through the findings on a focused clinical exam and suspicion arising from an analysis of the imaging pattern. Tests used to establish or confirm a specific diagnosis are listed in Table 1 (last column). A number of tests that may be useful to do relatively early in the diagnostic process include those listed below (Table 3).

Evaluation of other organ function in leukodystrophies

Ophthalmology

Cataracts can be seen in association with cerebrotendinous xanthomatosis and certain forms of hypomyelination (Table 1). On retinal examination, the presence of a 'cherry red spot' can help distinguish infantile and/or macrocephalic patients from infantile GM2 gangliosidosis (Tay–Sachs and Sandhoff disease).

Endocrinology

X-linked adrenoleukodystrophy can also manifest as Addison's disease without evidence of neurological involvement [13,14]. Such patients are referred to as the 'Addison-only' phenotype. More than 70% of all male patients will have adrenal insufficiency. Usually glucocorticoids are more affected than mineralocorticoids. X-ALD is estimated to be the cause of adrenal insufficiency in approximately 35% of patients with idiopathic Addison's disease [15]. Prior studies have demonstrated Addisonian crisis as a common cause of acute presentation of childhood X-ALD.

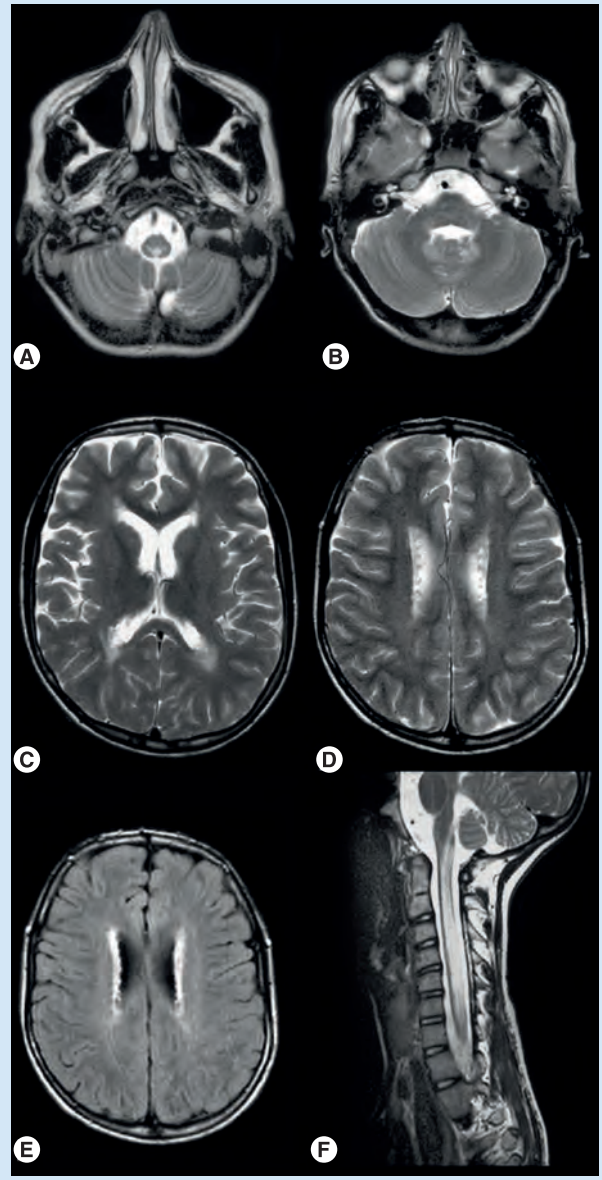

Figure 3. MRI in juvenile Alexander disease. (A) Signal abnormalities in the medulla, **(B)** the hilus of the dentate nucleus, and **(C)** a thin periventricular rim. **(D & E)** Peculiar garland-like structures are present along the ventricular wall. **(F)** Swelling and prominent signal abnormality of the cervical spinal cord. Reproduced with permission from [78]. © 2006, Wolters Kluwer Health.

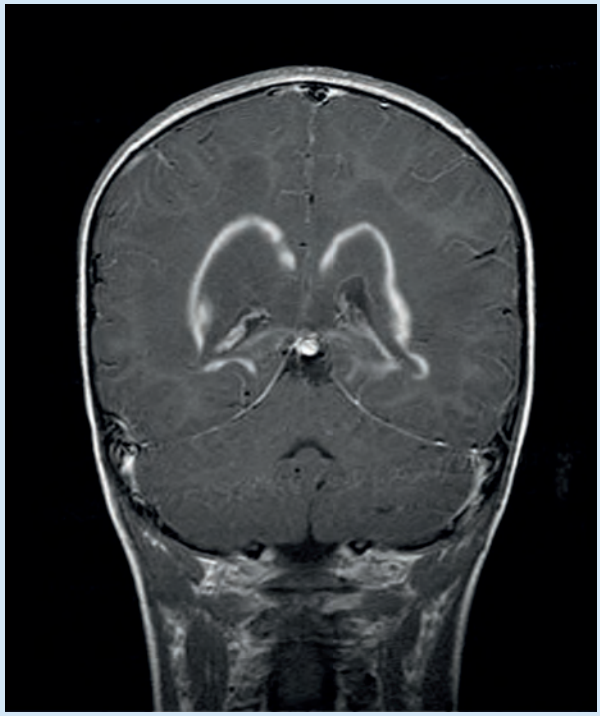

Figure 4. MRI in X-linked adrenoleukodystrophy. Contrast enhancement around a bilateral zone of white matter.

Besides adrenal dysfunction, other endocrine systems, such as that of the ovaries, can be affected in leukodystrophy patients. Primary or secondary ovarian failure can be seen to be associated with all degrees of neurologic severity in vanishing white matter disease [16]. In rare severe variants, growth failure, cataracts, hepatosplenomegaly, pancreatitis and kidney hypoplasia can occur [17].

GI issues

The association of gallbladder papillomatosis with MLD is well known. Less well known is the occurrence of intestinal bleeding in this context. Recently, a child with hemobilia was reported who required cholecystectomy [18]. Caution regarding this life-threatening condition is necessary. Feeding and swallowing issues are a common feature of all advanced leukodystrophy patients and require evaluation by a multidisciplinary team.

Therapeutics in the leukodystrophies

While the prognosis for leukodystrophy patients is often dismal, this should not lead to therapeutic negligence and defeatism. There remains a valuable role in addressing both symptomatic management versus disease-modifying treatment with patients with leukodystrophies and their families. Many physicians recoil when confronted with a rare disorder and attribute all symptoms to the underlying disease and do not look for treatable causes.

Medical management

The prevention of secondary complications, such as infections and aspirations, are tantamount to preserving quality of life in leukodystrophy patients. Several studies have demonstrated improved survival in leukodystrophy patients over the last 50 years [19]. This may be attributed to improved medical management, such as the prudent use of antibiotics and gastric tube placement. Careful evaluation with swallowing studies should be a cornerstone in monitoring patients with advancing brain disease. Gallbladder-associated pain and vomiting in MLD may be alleviated using ursodeoxycholic acid.

The use of antispasmodics and pain medication can further relieve muscle spasms and unnecessary suffering in children that are often nonverbal and unable to localize pain or voice complaints. Unexplained irritability should always prompt a thorough evaluation for the source of pain (muscle spasms, latent fracture and visceral pain) [20]. A wide range of analgesics are available, but few careful studies. One study reported that caregivers stated improved irritability after use of gabapentin [21].

More than 70% of male X-ALD patients have adrenocrotical insufficiency. As the insufficiency can be latent, adrenocorticotropic hormone levels need to be followed routinely during childhood. As adrenal replacement can be life saving, families should be educated about the importance of stress dose steroids. Beyond glucocorticoid replacement, some patients require fludrocortisone and, in the case of hypogonadism, androgens.

Enzyme replacement & metabolic correction

Enzyme replacement has been successful in ameliorating disease in animal models of metachromatic and globoid cell leukodystrophy, but has not so far been successful in humans [22,23]. Both the larger volume of the human brain and the challenges of overcoming the BBB pose significant obstacles.

Lorenzo's oil is a combination of erucic and oleic acid that is taken orally and lowers levels of plasma very-long-chain fatty acids in X-ALD patients [24]. This is of value in asymptomatic boys, but

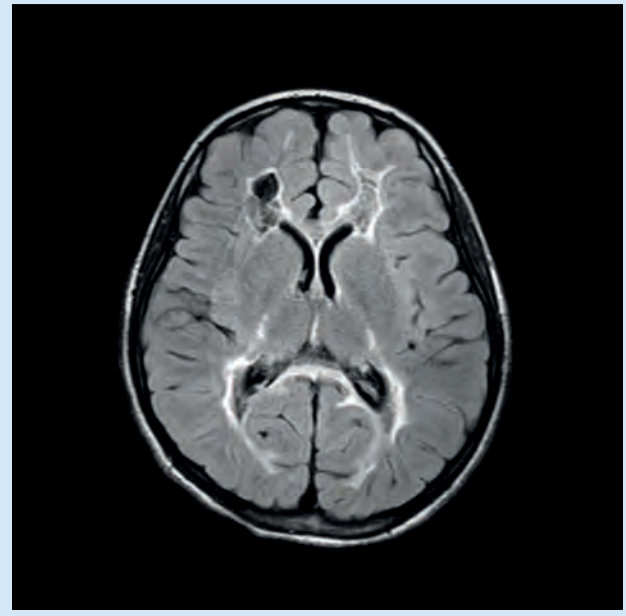

Figure 5. MRI in cystic leukodystrophy (fluid-attenuated inversion-recovery image).

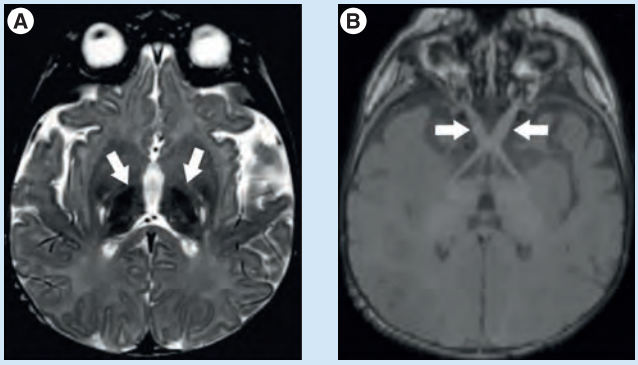

Figure 6. MRI in globoid cell leukodystrophy (Krabbe disease). (A) Signal changes in the bilateral thalami, **(B)** optic nerve enlargement.
Reproduced with permission from [79].

unfortunately does not arrest progression once brain demyelination has set in. In the latter case, even aggressive immune suppression has failed and only timely bone marrow transplantation can stabilize patients.

Cell-based therapies

Bone marrow transplantation has been efficacious in certain genetic conditions for many years and is able to halt progression in the early stages of cerebral X-ALD [25–27]. The procedure seems less efficacious for MLD [28], as well as other leukodystrophies, and carries significant risks and hazards [29].

Less than two-thirds of males with X-ALD will ever develop cerebral disease and a minority of patients with early cerebral disease may even arrest spontaneously. As a result, bone marrow transplantation should not be regarded as a therapy that all asymptomatic boys with X-ALD should undergo. The success of bone marrow transplantation in the early stages of the disease has not been demonstrated in boys with more advanced disease.

Gene therapy using a lentiviral vector for the correction of autologous stem cells has recently been developed as a therapeutic method for X-ALD [30] and MLD. The use of autologous cells mobilized from peripheral blood reduces the risk of graft-versus-host complications. However, a risk remains of the most relevant hematopoietic stem cells not being corrected. Further close monitoring is warranted as there are reports of the integration of viral vectors causing cancer.

Definitive diagnosis of a leukodystrophy

Although leukodystrophies currently cannot be cured, it is of great importance to arrive at a definitive diagnosis in an individual patient. The diagnosis will put an end to a frequently long and distressing search for the cause of a child's abnormalities. It may allow the family to focus on palliative care or more aggressively pursue experimental treatments. All in all, the diagnosis can facilitate a more realistic view of the patient's further course, and appropriate family genetic counseling.

The initial sections of this article will facilitate the path to diagnosis by narrowing the spectrum of suspected disorders. It allows the physician and family to economize efforts and resources by ordering a relatively small number of diagnostic tests. At this point it may be useful to consult Table 3. An initial classification of a patient's findings as 'white matter disease', as opposed to gray matter disease, may be useful in many instances, but considerable overlap exists among these two groups: certain neuronal storage disorders can impress as 'leukodystrophy-like' on imaging because degeneration of neurons will also result in a loss of myelin.

Expert commentary

The field of leukodystrophies is growing owing to advances in MR diagnostics and an explosion of gene discovery over the last decade. We have outlined a clinical approach that remains indispensable, even with advances in technology. Leukodystrophies are caused by mutations in single genes and follow Mendelian genetics. Currently, genes underlying Mendelian traits are being discovered at a threefold higher rate compared with those for complex traits [31]. Therefore, we expect the number of identifiable leukodystrophies to increase in the coming years, as well as their burden on the healthcare system and society at large.

A clinical diagnosis is necessary: despite the array of new MRI and gene sequencing technologies, the clinical diagnosis remains tantamount. The age of onset and the pattern of neurological involvement dictates the workup and allows for a successful diagnosis. The diagnostic test alone is meaningless if not placed into a clinical context. Despite solid biochemical assays being available for most classic leukodystrophies, these tests do not distinguish between different phenotypes (e.g., the level of plasma very-long-chain fatty acids does not predict childhood cerebral adrenoleukodystrophy vs AMN). In other cases, the clinical description will help resolve false-positive and false-negative tests.

The diagnosis has consequences for clinical management: not unlike most other neurological disorders there is little chance for a cure in leukodystrophy patients. Yet treatments are available and the single gene mutations that impact specific enzyme and protein function allow for potential interventions (e.g., chenodeoxycholic acid in cerebrotendinous xanthomatosis). Symptomatic treatments for pain, spasticity and seizures are widely used but lack controlled studies in the field of leukodystrophies. A vast array of supplements are being utilized without good justification and with considerable cost burden to families or insurance schemes. In rare cases, the response to trials such L-dopa have been useful and revealed another diagnosis [32]. However, the success of treatments for disorders outside the CNS such as Gaucher and Pompe disease, remains out of reach. While often undervalued, the diagnosis and phenotypic designation can guide medical management and help families to make decisions on gastric tube placement and other life-prolonging procedures.

Quality of life often improves with diagnosis: in the early stages of disability the diagnosis can be horrifying and families are at times bewildered, incredulous and devastated. However, more often the diagnosis brings relief, particularly to those families who have been seeking a diagnosis for a long time. Although the disorder remains incurable and often not treatable, it brings closure and allows families to focus on palliative care and quality of life for their loved ones. There now exists a wide range of palliative care

Table 3. Some laboratory tests useful in diagnosing a leukodystrophy.

Laboratory study	Usefulness for diagnosing leukodystrophies
Blood	
Cellular elements	Lymphocyte granulation in MLD–MSD Anemia in MIT
VLCFA	Elevated in X-ALD (and other peroxisomal disorders)
Lysosomal enzyme activities	Arylsulfatase A low in MLD[†] Galacto-cerebrosidase low in GLD[‡] Fucosidase low in FUC (several other lysosomal storage disorders may show hypomyelination)
Lactate	Elevated in LBSL, other mitochondrial disorders
Asialotransferrins	Elevated in CDG
Cholestanol	Elevated in CTX
DNA preparation	Frequently useful
Urine	
Sulfatides[§]	Elevated in MLD
NAA (organic acids)	Elevated in CD
Organic acids	Organic acid disorders
Free sialic acid	Elevated in SSD
CSF	
Cellular elements	Elevated in AGS
Total protein	Elevated in GLD, MLD (young patients)
Asialotransferrins	Elevated in VWMD [77]
5-Methyltetrahydrofolate	Low in FOL (while normal in blood)
Lactate	Elevated in LBSL, other mitochondrial disorders
Interferon	AGS
Glycine (CSF:serum ratio)	Elevated in GLY
Free sialic acid	Elevated in SSD
Biopsies	
Skin	Generally useful for morphological studies and fibroblast[¶] cultivation MLD: demyelinated nerve fibers may be seen GLD: crystalloid inclusion bodies Other inclusion bodies of storage disorders
Peripheral nerve	Rarely indicated in leukodystrophies

[†]Beware of misinterpretation of low activity results, as healthy persons can have pseudodeficiency of the enzyme.
[‡]The use of a natural instead of artificial substrate is recommended [78].
[§]Urinary lipids can conveniently be collected on filter paper [79].
[¶]Can be used for biochemical studies and DNA preparation.
AGS: Aicardi–Goutières syndrome; CD: Canavan disease; CDG: Congenital disorders of glycosylation; CSF: Cerebrospinal fluid; CTX: Cerebrotendinous xanthomatosis; FOL: Folate receptor defect; FUC: Fucosidosis; GLD: Globoid cell leukodystrophy (Krabbe disease); GLY: Glycine leukoencephalopathy; LBSL: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MIT: Mitochondrial disorders; MLD: Metachromatic leukodystrophy; MSD: Multiple sulfatase deficiency; NAA: *N*-acetyl aspartate; SSD: Sialic acid storage disorder; VLCFA: Very-long-chain fatty acids; VWMD: Vanishing white matter disease; X-ALD: X-linked adrenoleukodystrophy.

options [20,33,34]. These include medical, psychiatric, psychological, educational and other options. Their impact will often depend on a thorough understanding of the nature of the disorder.

Opportunities for experimental treatments: while experimental treatments for leukodystrophies are in their infancy, one aspect is clear: the therapeutic window is often limited to early manifestations of the disease. In unaffected patients, the risk may not be justified. In more advanced patients, the disease may be too far gone and aggravated by the side effects of the intervention. Again, clinical judgment and the weighing of risks and potential benefits will guide the individual patient. As gene therapy and enzyme replacement emerge, physicians will increasingly face difficult questions that require an understanding of the pathogenesis, disease course and training in clinical trials. Ethical dilemmas are bound to occur.

Do not think 'rare'. Collectively the leukodystrophies rival the incidence of other demyelinating disorders, such as multiple sclerosis. Yet the relative rarity has shaped the mindset of many physicians and patients lament the fact that they have to educate residents and physicians in emergency rooms ('why do I have such a rare disease that not even my doctors know about?'). Many patients avoid hospitals because of a lack of trust that the medical establishment will be aware of their diagnosis. Certainly our age will increasingly depend on electronic services and the internet to disseminate information. Networks of expert healthcare providers will partner with disease foundations and serve patients and families, as well as general practitioners, as no one alone can be expected to keep up with the growth of information.

Five-year view

Research to date on leukodystrophies suggests several different avenues for study in the next 5 years. Advances in gene sequencing technologies, improved design of clinical trials, the development of new biomarkers and genetic animal models, improved identification of susceptibility factors and more efficient drug delivery are just a few of the reasons for progress.

Currently, out of nearly 7000 suspected or known Mendelian disorders identified based on clinical features, less than half have been linked to a gene [35]. In the leukodystrophies, more than a dozen clinically defined disorders exist whose genetic etiology has not been found. With the advances in next generation sequencing technology we expect this to change, as large volumes of sequence data will be delivered at low cost [36]. Even rare diseases in individual families will thereby have access to gene identification. Bioinformatics tools have been standardized for DNA sequencing and are making progress in the field of RNA.

The study of leukodystrophies remains challenging owing to the limited number of study subjects for clinical trials. The nature of leukodystrophies lends itself to the use of MRI as biomarker. Yet alternative study designs even without imaging should be considered (factorial and n-of-1 studies [37]). The prudent choice of outcome measures can allow study questions to be answered with fewer subjects. This can also be achieved by monitoring trials during their conduct.

Susceptibility factors for some leukodystrophies, such as head trauma and fever for vanishing white matter disease, have long been known. We expect natural history studies in the coming years to add more detail to these environmental factors, as well as experimental studies to elucidate genetic modifiers.

Overall we expect these advances to improve the prospects to forestall onset of illness and clinical decline in the growing number of leukodystrophies.

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Key issues

- Brain white matter abnormalities are a frequent cause of CNS symptoms in children.
- A great variety of gene defects contribute to brain white matter abnormalities of the young.
- Defects within the myelin sheath cause leukodystrophies, those outside cause metabolic leukoencephalopathies. They may resemble each other.
- Brain white matter and gray matter diseases may overlap.
- The disorders are incurable and most lead to progressive motor and mental disability.
- Suspicion for such a disorder is usually raised by MRI, but the definitive diagnosis is a challenge.
- A timely diagnosis is required for family counseling and optimizing palliative care and experimental treatments.
- Diagnosis starts from clues on physical examination and an awareness of MRI algorithm, and is complemented by targeted laboratory testing.
- Management is multidisciplinary. It involves pediatric disciplines, including child psychiatry and social support of families.

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