

Emerging Treatments for Pediatric Leukodystrophies



Guy Helman, BS^{a,b}, Keith Van Haren, MD^c, Maria L. Escolar, MD^d,
Adeline Vanderver, MD^{a,b,e,*}

KEYWORDS

- Leukodystrophy • Genomics • Therapy • Symptomatic • Disease modifying
- Stem cell • Gene therapy

KEY POINTS

- Although leukodystrophies remain incurable, they are uniformly treatable disorders.
- Next-generation sequencing technologies have enhanced the ability to detect the underlying cause of disease and have permitted identification of pathologic mechanisms in many disorders.
- Several pilot and phase I, II, or III clinical trials are currently in progress for patients with leukodystrophy covering various disorders.
- Awareness and early recognition of the signs and symptoms of patients with leukodystrophy is of utmost importance for the small number with existing therapies.

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^a Department of Neurology, Children's National Health System, 111 Michigan Avenue, Northwest, Washington, DC 20010, USA; ^b Center for Genetic Medicine Research, Children's National Health System, 111 Michigan Avenue, Northwest, Washington, DC 20010, USA; ^c Department of Neurology, Lucile Packard Children's Hospital, Stanford University School of Medicine, 730 Welch Rd, Palo Alto, CA 94304, USA; ^d Department of Integrated Systems Biology, George Washington University School of Medicine, 2150 Pennsylvania Ave NW, Washington, DC 20037, USA; ^e Department of Integrated Systems Biology, George Washington University School of Medicine, 2150 Pennsylvania Ave NW, Washington, DC 20037, USA

* Corresponding author. Children's National Health System, 111 Michigan Avenue, Northwest, Washington, DC 20010.

E-mail address: avanderv@childrensnational.org

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The leukodystrophies are a heterogeneous group of inherited disorders with broad clinical manifestations and variable pathologic mechanisms.^{1,2} Although these disorders are individually rare, an incidence of 1 in 7000 suggests that these disorders are collectively more common than was once thought.^{1,3-5} In many cases, patients with leukodystrophy remain in the diagnostic category of unsolved disorders, despite significant improvements in diagnostic approaches.^{6,7} Even more important, only a few of these disorders have well-established treatments or therapies readily available to the leukodystrophy population.⁸ With this in mind, this article provides an update on the emerging treatments available to patients with leukodystrophy and the prospect for future therapies based on new molecular understanding of these conditions in the context of next-generation sequencing.

THE LEUKODYSTROPHIES: CLINICAL BACKGROUND

Although a comprehensive and disease-specific overview of clinical features of the leukodystrophies is beyond the scope of this article, important neurologic and extra-neurologic features are described (**Table 1**). The early clinical course for patients with leukodystrophy is most commonly marked by motor symptoms, manifesting as delayed development of motor skills, a plateau in development, or regression in motor skills.⁶ Although patients typically present with acute or subacute onset of neurologic symptoms, a few of these disorders have such a slowly progressive course that they seem more like static encephalopathy until their course is considered over a long span of time.⁹ Although marked spasticity and pyramidal motor symptoms are prominent features, leukodystrophies are often associated with rigidity, dystonia, ataxia, and bulbar symptoms.

Although cognition may be spared in the early stages of disease, it is almost invariably affected in the more advanced stages of most leukodystrophies. The nature and severity of cognitive impairment is most likely based on the neural networks affected because of neuronal and axonal dysfunction secondary to myelin disturbances. In childhood this dysfunction is often initially categorized as developmental delay or intellectual disability, and may progress, in some patients, to dementia. However, testing cognitive skills by standard diagnostic tools becomes a challenge as the motor disease progresses and the level of patient cognitive function is often underestimated. In adult-onset leukodystrophies the dysfunction and decline commonly include signs and symptoms of dementia, sometimes accompanied by comorbid psychiatric features.⁶

Other neurologic features may also be present and can help streamline diagnostic efforts. These features include nystagmus, irritability, titubation, autonomic dysfunction, and encephalopathy (with or without autistic features). Macrocephalies and microcephalies are associated with a few leukodystrophies.

Several extraneurologic features in a broad range of categories may indicate specific disorders. These clinical features are particularly useful for guiding the diagnostic evaluation of patients who are initially found to have white matter disease. Endocrine dysfunction may be present as adrenal insufficiency (Addison disease), manifested by fatigue; hypotension; hyponatremia; cutaneous hyperpigmentation; and, sporadically, hypoglycemia. Hypothyroidism, hypogonadotropic hypogonadism, and growth failure are other prominent endocrine abnormalities associated with specific leukodystrophies. Ophthalmologic abnormalities are present in many disorders and may include congenital cataracts or cataract development, retinitis pigmentosa, retinal cherry red macula, optic atrophy, and retinal vascular defects. Dysmorphic physical features, bony abnormalities, hearing impairment, cutaneous abnormalities, and ovarian

Table 1
Common neurologic symptoms for pediatric leukodystrophies with existing and emerging therapies

Symptoms	Associated Diseases	Prevention/Treatment
Adrenal insufficiency	ALD	Annual ACTH screening; corticosteroids. Rare in women with ALD
Inflammatory cerebral demyelination	ALD	Sporadic onset. Highest risk (~40%) of onset occurs in ALD boys 3–12 y old. Also affects 25% of ALD men aged 12–50 y, although comorbid symptoms of AMN in adult men can complicate HSCT. Phenotype is rare among older men as well as women with ALD of any age. Surveillance MRI can detect early demyelination before symptoms appear, thereby enabling HSCT, which effectively halts demyelination, but only if initiated soon after lesion onset
Premature ovarian failure	VWM	None known
Episodic deterioration	VWM, mitochondrial, Pol-III	Avoidance of triggers (eg, head trauma, fevers, severe fright)
Cardiac dysfunction	Mitochondrial	Cardiac evaluation; pacemaker/defibrillator may be appropriate in some patients. Patients should be reevaluated at intervals according to their needs
Deafness	Mitochondrial and 18q ⁻ in early stages; many leukodystrophies in later stages	Auditory evaluation; treatments limited
Hypogonadotropic hypogonadism, growth hormone deficiency	Pol-III	Supplemental hormonal therapies
Dental anomalies	Pol-III, ODDD, Cockayne	Dental care to prevent caries, consultation with an orthodontist as necessary. General anesthesia should be used with caution if procedure is nonessential
Hypercholesterolemia xanthoma formation, cataracts, psychomotor decline	CTX	Daily supplementation with chenodeoxycholic acid normalizes cholestanol levels and may prevent and/or improve other disease manifestations, statins

This list is not exhaustive and the remaining leukodystrophies without current therapeutic options are covered elsewhere.

Abbreviations: ACTH, adrenocorticotropic hormone; ALD, adrenoleukodystrophy; AMN, advanced mucosal neoplasia; CTX, cerebrotendinous xanthomatosis; HSCT, hematopoietic stem cell transplant; ODDD, oculo-dento-digital dysplasia; VWM, vanishing white matter disease.

From Parikh S, Bernard G, Leventer R, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Mol Genet Metab* 2014. [pii:S1096-7192(14)00827-0]; with permission.

dysgenesis are other common extraneurologic manifestations of specific white matter disorders. These symptoms are well covered by the work of Parikh and colleagues.⁶

DIAGNOSTIC STRATEGY

Historically, characterization of leukodystrophies has been based on gross pathology and microscopy, identifying common glial cell or myelin sheath abnormalities. More recently, disease characterization has been supplemented by MRI pattern recognition.^{10–12} Improved MRI technology is now able to explore abnormalities of myelin in these disorders without neuropathologic correlation.¹³ Characterization of MRI patterns has facilitated diagnosis in patients who present on neuroimaging with abnormalities of the cerebral white matter suspicious for a leukodystrophy.^{3,12} More recently, diagnosis of patients with leukodystrophies has been successfully enhanced by next-generation sequencing technologies, decreasing the number of unsolved cases from nearly half to approximately 20%.²

Several recent publications discuss the diagnostic approach in patients with abnormal white matter on neuroimaging,^{2,6} which consists of detailed clinical and neurologic evaluations, review of the MRI to identify disease-specific patterns followed by either targeted genetic or biochemical testing, or, if no disease-specific MRI pattern is found, rapid advance to broad genetic testing strategies.

EXISTING AND EMERGING THERAPIES

A small number of therapies are established in the leukodystrophies. Hematopoietic stem cell therapy (HSCT) is a therapy currently in use for a restricted number of leukodystrophies including X-linked adrenoleukodystrophy (X-ALD) and Krabbe disease, and is still being evaluated as a viable therapy in the case of metachromatic leukodystrophy (MLD). For patients with cerebrotendinous xanthomatosis (CTX), supplementation with chenodeoxycholic acid may provide some neurologic benefits. In all cases, patients benefit most if intervention occurs early in the course of disease, making prompt recognition of the disorders of utmost importance.^{14–17}

In addition, an increased understanding of the mechanisms of disease in leukodystrophies has provided a molecular framework for developing potential therapeutic strategies. As such, there are a variety of promising, disease-specific therapies currently in or on the verge of human trials for several leukodystrophies, including Aicardi-Goutières syndrome (AGS), adult polyglucosan body disease (APBD), X-ALD, Krabbe disease, MLD, peroxisomal biogenesis disorders, and Pelizaeus-Merzbacher disease (PMD). Of the 29 active leukodystrophy studies that are listed on clinicaltrials.gov, 16 of these are listed as phase I, II, or III trials (**Table 2**). Covering a broad spectrum of modalities, these studies include traditional pharmaceutical practices as well as the manipulation of stem cells, genes, and enzymes.

Although improved therapeutic strategies and advanced research trials in specific disorders provide long-term hope to patients, clinicians must also attend to the more immediate goals of daily patient care. Leukodystrophies as a group of disorders are symptomatically treatable and require thorough management by the caregiver and responsible clinician to address the complex array of symptoms. As such, this article describes existing and emerging therapies for individual leukodystrophies and highlights several important complications associated with select leukodystrophies as a tool for clinicians encountering a patient with leukodystrophy.

X-ALD is the most common leukodystrophy with disease-specific management and therapeutic guidelines.¹⁸ X-ALD is caused by mutations in *ABCD1*, encoding the adrenoleukodystrophy protein (ALDP), and is an X-linked dominant disorder that results

Table 2
Current clinical trials for pediatric leukodystrophies

Associated Diseases	Study Title	Phase	Intervention
All leukodystrophies and genetic leukoencephalopathies	The Nosology and Etiology of Leukodystrophies of Unknown Causes NCT00889174	NA	Biorepository study
X-ALD; globoid cell leukodystrophy; MLD; PMD	UCB Transplant of Inherited Metabolic Diseases With Administration of Intrathecal UCB Derived Oligodendrocyte-Like Cells NCT02254863	Phase I	Biological: DUOC-01
Globoid cell leukodystrophy; MLD; X-ALD; PMD	Phase I/II Pilot Study of Mixed Chimerism to Treat Inherited Metabolic Disorders NCT01372228	Phase I	Biological: enriched HSCT/novel platform technology
X-ALD; MLD; globoid cell leukodystrophy	Human Placental-Derived Stem Cell Transplantation NCT01586455	Phase I	Drug: human placental-derived stem cell
X-ALD; MLD; globoid cell leukodystrophy	HSCT for High Risk Inherited Inborn Errors NCT00383448	Phase II	Drug: clofarabine Procedure: total body irradiation Drug: melphalan Biological: HSCT Drug: alemtuzumab Drug: mycophenolate mofetil Device: cyclosporine A Drug: hydroxyurea
X-ALD; peroxisomal biogenesis disorders; globoid cell leukodystrophy; MLD; fucosidosis	MT2013-31:Allo BMT for Metabolic Disorders, Osteopetrosis and Males With Rett Syndrome NCT02171104	Phase II	Procedure: blood stem cell transplant Drug: rabbit antithymocyte globulin Drug: fludarabine Drug: busulfan Drug: cyclophosphamide Drug: cyclosporine A Drug: methylprednisolone Drug: mycophenolate mofetil Drug: granulocyte colony-stimulating factor Drug: granulocyte-macrophage colony-stimulating factor Drug: <i>N</i> -acetylcysteine Drug: celecoxib Drug: vitamin E Drug: alpha lipoic acid

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Table 2
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Associated Diseases	Study Title	Phase	Intervention
X-ALD; MLD; globoid cell leukodystrophy; peroxisomal biogenesis disorders	Allogeneic Bone Marrow Transplant for Inherited Metabolic Disorders NCT01043640	Phase II	Drug: campath-1H Drug: cyclophosphamide Drug: busulfan Procedure: allogeneic stem cell transplantation Drug: cyclosporine A Drug: mycophenolate mofetil
X-ALD	Exercise Study of Function and Pathology for Women With X-linked Adrenoleukodystrophy NCT01594853	NA	Behavioral: exercise training
	Expanded Access for Lorenzo's Oil (GTO/GTE) in Adrenoleukodystrophy NCT02233257	NA	Drug: Lorenzo's oil
	Safety and Pharmacodynamic Study of Sobetirome in X-ALD NCT01787578	Phase I	Drug: sobetirome
	A Phase 2/3 Study of the Efficacy and Safety of Hematopoietic Stem Cells Transduced With Lenti-D Lentiviral Vector for the Treatment of Childhood Cerebral Adrenoleukodystrophy NCT01896102	Phase II/III	Genetic: Lenti-D drug product Drug: busulfan Drug: cyclophosphamide Drug: filgrastim
APBD	Triheptanoin Treatment Trial for Patients With Adult Polyglucosan Body Disease NCT01971957	Phase II	Drug: triheptanoin Dietary supplement: vegetable oil
Canavan disease	Oral GTA in Newborns With Canavan NCT00724802	NA	Dietary supplement: GTA Drug: GTA
CTX	Evaluation of Carotid IMT and Atherogenic Risk Factors in Patients With Cerebrotendinous Xanthomatosis NCT01613898	NA	Biological: blood tests
	Phase II Study of Cholesterol- and Cholestanol-Free Diet, Lovastatin, and Chenodeoxycholic Acid for Cerebrotendinous Xanthomatosis NCT00004346	Phase II	Drug: chenodeoxycholic acid Drug: lovastatin

Krabbe disease	The Natural History of Infantile Globoid Cell Leukodystrophy NCT00983879	NA	NA
	Biomarker for Krabbe Disease NCT01425489	NA	NA
	Lysosomal Storage Disease: Health, Development, and Functional Outcome Surveillance in Preschool Children NCT01938014	NA	NA
MLD	Biomarker for Metachromatic Leukodystrophy NCT01536327	NA	NA
	Imaging Study of the White Matter Lesions in Children With Metachromatic Leukodystrophy NCT01325025	NA	High-field MRI
	Natural History Study of Children With Metachromatic Leukodystrophy NCT01963650	NA	Natural history study
	The Natural History of Infantile Metachromatic Leukodystrophy NCT00639132	NA	—
	Intracerebral Gene Therapy for Children With Early Onset Forms of Metachromatic Leukodystrophy NCT01801709	Phase I/II	Genetic: intracerebral administration of AAVrh.10cuARSA
	Gene Therapy for Metachromatic Leukodystrophy NCT01560182	Phase I/II	Genetic: autologous CD34+ stem cells transduced with ARSA encoding lentiviral vector
	Multicenter Study of HGT-1110 Administered Intrathecally in Children With MLD NCT01510028	Phase I/II	Biological: recombinant human arylsulfatase A
Peroxisomal biogenesis disorders	Open-Label Extension Study Evaluating Safety and Efficacy of -1110 in Patients With Metachromatic Leukodystrophy NCT01887938	Phase I/II	Biological: recombinant human arylsulfatase A
	Betaine and Peroxisome Biogenesis Disorders NCT01838941	Phase III	Drug: betaine
Sjögren-Larsson syndrome	Sjögren-Larsson Syndrome: Natural History, Clinical Variation and Evaluation of Biochemical Markers NCT01971957	Phase III	NA
18q deletion syndrome	Growth Hormone and Chromosome 18q ⁻ and Abnormal Growth NCT00134420	Phase III	Drug: Nutropin AQ Procedure: arginine and clonidine stimulation testing Procedure: growth factors laboratory testing Procedure: neuropsychological testing

Abbreviations: APBD, adult polyglucosan body disease; ARSA, arylsulfatase A; BMT, bone marrow transplantation; DUOC, UCB-derived oligodendrocyte-like cells; GTA, glyceryl triacetate; HGT, horizontal genet transfer; IMT, intima-media thickness; MLD, metachromatic leukodystrophy; NA, not applicable; PMD, Pelizaeus-Merzbacher disease; UCB, umbilical cord blood; X-ALD, X-linked adrenoleukodystrophy.

from a deficient very-long-chain fatty acid transport protein on the surface of the peroxisome. Four primary phenotypes (asymptomatic, adrenal insufficiency, cerebral ALD, and adrenomyeloneuropathy) have been identified in patients with X-ALD, which may overlap during the lifespan. All patients begin life asymptomatic and, in rare cases, may remain asymptomatic into the fourth decade in the case of men or the sixth decade in the case of women. However, all men and most women who carry an aberrant copy of the X-ALD gene eventually manifest the spastic paraparesis and sphincter dysfunction that is characteristic of adrenomyeloneuropathy. Women are generally spared from adrenal insufficiency and cerebral ALD, which are the most dangerous forms of ALD. The adrenal insufficiency phenotype is life threatening if undiagnosed, but is also easily treatable with a daily, oral corticosteroid supplementation. Diagnosis is made via clinical history and cortisol stimulation testing. All men with X-ALD should be screened via cortisol stimulation testing every 6 to 9 months for adrenal insufficiency. Endocrinology follow-up and a corticosteroid regime should be considered in patients who show an inadequate response to cortisol stimulation testing.

As for the cerebral ALD phenotype, HSCT is highly effective at arresting the otherwise relentless progression of the brain lesion if administered during the early stages of cerebral demyelination when the lesion is still small. However, HSCT has no therapeutic effect if administered in the later stages of disease,^{14,15,17} highlighting the importance of early diagnosis. Surveillance MRI studies can help identify early brain lesions, before clinical symptoms appear and in time for HSCT. When a suspicious brain lesion is identified in an individual with X-ALD, it is imperative that they be promptly evaluated using established clinical and radiologic criteria that have been established for triaging candidates for HSCT.¹⁵ In general, lower levels of pretransplant neurologic morbidity (ie, low MRI severity score,¹⁹ low degree of neurologic disability, and a high neuropsychometric measures) predict favorable HSCT outcomes.^{14,15} The therapeutic benefits of HSCT in patients with X-ALD are thought to arise, at least in part, through the replacement of the patient's genetically deficient brain microglia with genetically competent microglial progenitor cells arising from the donor blood.²⁰

Newborn screening for X-ALD is being implemented in a growing number of US states. Boys with X-ALD, aged 3 to 12 years, identified through newborn screening or as relatives of a proband, should undergo gadolinium-enhanced MRI of the brain every 6 months to screen for early signs of cerebral demyelination in order to establish the need for early intervention. Annual MRI studies should be considered for adolescent boys and adults, who are at slightly lower risk for developing the cerebral ALD phenotype (**Fig. 1**). Among men with X-ALD more than 50 years of age and women with X-ALD (heterozygotes) of any age, the onset of the cerebral and/or adrenal insufficiency phenotypes is uncommon, suggesting that routine surveillance screening for these individuals is probably unnecessary.

The risk of developing cerebral X-ALD, the most serious phenotype, may be mitigated by daily consumption of Lorenzo's oil, which is a mixture of oleic and erucic acid, in combination with dietary restriction of very-long-chain fatty acids.²¹ The oil acts as a competitive inhibitor of enzymes involved in endogenous production of very-long-chain fatty acids.²² Use of Lorenzo's oil does not affect the progression of cerebral X-ALD once the disease course has begun,²¹ and it has not been proved to mitigate the onset or progression of adrenomyeloneuropathy. Its consumption carries health risks²³ and its availability in the United States is currently restricted to boys with X-ALD aged 3 to 10 years under an expanded access trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02233257), NCT02233257). A pilot phase trial using thyromimetics, synthetic structural analogues of thyroid hormone that mimic tissue-restricted thyroid hormone actions,²⁴ is in

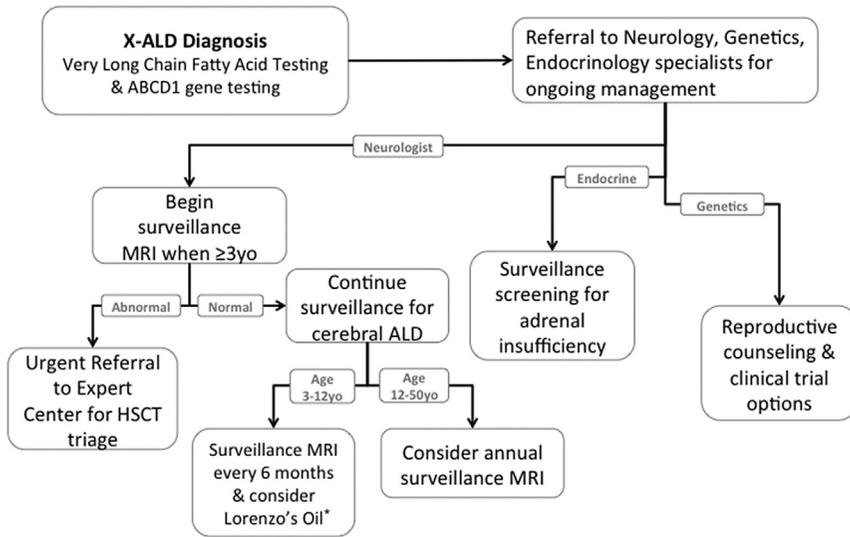


Fig. 1. X-ALD outpatient care management flow diagram. Note the emphasis on identification of a treatable disorder if recognized early in the clinical course. Routine evaluations for any clinical changes are of utmost importance. The asterisk designates therapies in clinical trial stages. (Adapted from Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis* 2012;7:51.)

preparatory phases using soberitome ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01787578) identifier NCT01787578). They can distinctly regulate subsets of thyroid hormone-responsive genes by mimicking subtype-selective thyroid hormone receptor agonists. Sobetirome, a thyroid hormone receptor beta agonist,²⁵ has had promising results in cholesterol metabolism. It is thought that sobetirome can also activate the production of ATP-binding cassette, subfamily D (ALD), member 2 (ABCD2), closely related to ATP-binding cassette, subfamily D (ALD), member 1 (ABCD1) protein. The work of Weber and colleagues²⁶ has shown that ABCD2 can compensate for defective ABCD1, providing support for its targeting in therapeutic measures.

Lentiviral-based gene therapy has shown early promise in X-ALD.²⁷ This technology relies on ex vivo transduction of autologous hematopoietic stem cells encoding wild-type ABCD1 complementary DNA by a human immunodeficiency virus type 1-derived vector that targets microglial precursors. The therapy performed in 2 young male patients resulted in polyclonal hematopoietic repopulation and stable lentivirally encoded ALD protein expression.²⁰ In addition, stabilization of cerebral demyelination was noted on MRI after reinfusion of the genetically modified cells. To date, there have been no reported cases of insertional mutagenesis or malignancy. This treatment is now entering phase II/III clinical trials ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01896102) identifier NCT01896102).

Despite the potential for overlap between the 4 recognized phenotypes, each has its own distinct management strategies.¹⁸ Adrenal insufficiency is life threatening in most cases of X-ALD but can be treatable if identified in a timely fashion. Although symptoms may not be present, extenuating circumstances, such as an affected relative, may allow early diagnosis of the X-ALD genotype.

AGS is an inherited leukodystrophy characterized by a calcifying microangiopathy and increased cerebrospinal fluid (CSF) interferon alpha levels. There are now 7 known AGS causative genes (*TREX1*, *RNASEH2A/B/C*, *SAMHD1*, *ADAR1*, and *IFIH1*), all of

which are associated with genome surveillance, integrity, damage repair, and DNA sensing. Mutations in these genes seem to result in the irregular accumulation of RNA/DNA hybrids and other immunogenic nucleic acid structures within the cell.^{28–31} Experiments in the murine model of AGS have shown this overaccumulation of endogenous retroelements,^{32,33} whereas sterile alpha motif (SAM) domain and histidine-aspartic domain-containing protein 1 (SAMHD1) has been shown to be a dominant suppressor of long interspersed element 1 (LINE-1). AGS-related mutations compromise the potency of SAMHD1 against LINE-1 retrotransposition.³⁴ Within the murine model of AGS, the use of reverse transcriptase inhibitors presumably targeting production of endogenous retroelements has been studied with promising results.³⁵ Significant work is still necessary to better understand the mechanisms of this disorder but efforts are underway to test the use of antiretroviral therapy in patients with AGS.

Patients with AGS are susceptible to autoimmune complications as a result of possible accumulated immunogenic nucleic acids. Increased CSF interferon alfa level has been an important marker in patient diagnosis as well as prompting investigation into these autoimmune complications. Patients may manifest features that overlap with those shown by patients affected by systemic lupus erythematosus (SLE), and rare cases of SLE have been found to be associated with *TREX1* mutations. Patients with AGS have persistent induced immune system activation with autoinflammation and cytokine production causing an accumulation of cytokines.³⁶ Symptom management has involved corticosteroid and other immunosuppressive regimens but definite improvements in neurologic symptoms have not been observed.³⁶ Patients with AGS require monitoring for chilblains and other skin inflammation, arthritis, inflammatory bowel disease, hematologic complications, and cardiomyopathy.³⁷ In addition, patients with AGS may manifest other autoimmune, thyroid, and endocrine conditions, and should be screened and treated appropriately. For patients with mutations in *SAMHD1* causative of AGS, a potential life-threatening complication is large vessel vasculitis, which requires screening.

Alexander disease (AxD) is a leukodystrophy with distinct early-onset and late-onset forms, named type I and type II, respectively. Patients present with common leukodystrophy symptoms, such as motor deficits and, in type I AxD, seizures. More specific to type I AxD is the accumulation of mutated glial fibrillary acidic protein, which can result in obstruction of CSF pathways and hydrocephalus.³⁸ Patients require routine monitoring for this complication and attention to complaints of headache, changes in vision, or abrupt changes in behavior should help detect this complication. Consultation and intervention by neurosurgical teams maybe warranted depending on severity. Patients with late-onset (older child or adult), type II AxD may show symptoms such as obstructive sleep apnea, which if untreated can result in encephalopathy, as well as significant bulbar dysfunction, with the characteristic dysphonia and palatal myoclonus.³⁸

APBD is an adult-onset leukodystrophy manifesting with peripheral neuropathy and progressive spasticity. It is thought that these symptoms arise from neuronal damage and dysfunction caused by accumulated intracellular polyglucosan bodies throughout the peripheral nerves and central nervous system (CNS). Mutated *GBE1* causes deficient glycogen brancher enzyme activity and, in combination with accumulated polyglucosan bodies, is hypothesized to lead to an energy-deficient state after deficient glycogen degradation. The implementation of triheptanoin, a 7-carbon triglyceride, is suspected to provide an efficient substrate to the citric acid cycle to correct the resultant energy deficit.³⁹ The use of triheptanoin in anaplerotic therapy may prove beneficial in slowing the clinical course of these patients ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00947960) identifier NCT00947960).

Canavan disease is caused by a deficiency of the aspartoacylase, which is required for *N*-acetylaspartic acid (NAA) metabolism in the brain.⁴⁰ Onset is usually in the first year of life and neuropathology is characterized by progressive spongiform degeneration of the brain. Initial results from the first gene therapy trial showed that intraventricular delivery of liposome-encapsulated plasmid DNA produced a transient decrease in NAA accumulation, with neuroimaging suggestive of new myelination in 50% of patients.⁴¹ Subsequent phase I/II clinical trials used intraparenchymal gene delivery and a recombinant adeno-associated virus serotype 2 vector. Magnetic resonance spectroscopy revealed decreased brain NAA concentrations and MRI changes suggesting more normal myelination and stabilization of brain atrophy with reduced disease symptoms on long-term follow-up.⁴²

Patients with CTX may benefit from chenodeoxycholic acid therapy by oral supplementation. CTX is an autosomal recessive inherited lipid storage disorder that results from a genetic mutation causing a deficiency in 27-hydroxylase. This mitochondrial enzyme is responsible for an early step in bile acid synthesis. High levels of serum cholestanol and bile acids deposit in the brain, lens, and tendons as features of this disorder. Patients show symptoms of cataracts and diarrhea in early childhood, progressing to psychomotor decline and tendon xanthomas in late adulthood. Daily oral supplementation with 750 mg of chenodeoxycholic acid, a bile salt, typically corrects the biochemical abnormalities and may reverse some clinical symptoms.^{43,44} Earlier treatment initiation may lead to better outcomes; reversibility of existing neurologic injury is limited.¹⁶ Oral statins are often included in the CTX treatment regimen, although their clinical benefit is unknown.

Krabbe or globoid cell leukodystrophy results in deficiency in galactosylceramidase (GALC). Patients with Krabbe disease have severe neurologic symptoms caused by mutations in *GALC*, the gene encoding GALC. Patients have had beneficial results from HSCT, in particular in the presymptomatic infantile-onset forms. HSCT can arrest CNS deterioration and cognitive ability has been well preserved based on clinical follow-up.^{45–47} However, several patients have experienced progressive motor difficulties despite early intervention. Clinical staging criteria have been proposed for Krabbe disease⁴⁸ and are useful in evaluating potential outcomes of HSCT.⁴⁹ Newborn screening for Krabbe disease is also available in a select number of US states, providing a basis for presymptomatic treatment. HSCT may also prove beneficial to patients with later disease onset, such as late-infantile, juvenile-onset, and adult-onset cases, although it has not been well studied.^{46,47}

More than 60% of patients with Krabbe have missense mutations in *GALC*. These mutations are predicted to generate misfolded proteins⁵⁰ that can be mislocalized, prematurely degraded, accumulate intracellularly, or trigger an unfolded protein response.^{51–53} The neurologic consequences of this disorder are hypothesized to be potentially avoidable with even 10% of normal *GALC* function.⁵⁴ Orally administered pharmacologic chaperones can rescue the function of mutant proteins by directing proper folding or cellular localization, or protecting them from degradation.^{55–57} α -Lobeline and 3',4',7-trihydroxyisoflavone are two pharmacologic agents that are currently being studied for their utility in improving the function of *GALC* after initial misfolding.^{58,59}

Hypomyelination with brain stem and spinal cord abnormalities and leg spasticity (HBSL) is the result of mutations in *DARS*, a cytoplasmic transfer RNA (tRNA) synthetase gene for aspartate. Patients with HBSL present with a broad phenotypic spectrum characterized by focal cerebral white matter abnormalities and spinal cord signal abnormalities.⁶⁰ Responsiveness to steroids in several patients with HBSL with subacute disease onset suggests that steroids may be an appropriate treatment modifying

approach in mutation-positive patients.⁶⁰ Certain tRNA synthetases have noncanonical functions in biological processes such as angiogenesis, regulation of gene transcription, and RNA splicing.⁶¹ These noncanonical tRNA synthetase functions are conserved across the complete phylogeny of animals, and are now established as playing key roles in several pathophysiologic processes.⁶¹ Aspartyl-tRNA synthetase (DARS) is one of 9 cytoplasmic tRNA synthetases that make up the multisynthetase complex, which facilitates gene-specific translational silencing of inflammation-related mRNAs. Although these mechanisms and functions must be studied further to elucidate why individuals seem responsive to steroids and what their clinical response is, it provides an interesting basis for compassionate care treatment in these patients.

Metachromatic leukodystrophy (MLD) has been treated with HSCT,^{47,62–64} although its use has been widely debated within the MLD community. Because of the phenotypic variability seen, the use of HSCT has proved particularly complex. The posttransplant patients with late-infantile-onset forms have been found to have poor motor skills and variable cognitive outcomes, resulting in some doubt over the utility of transplant.¹⁵ Other factors, such as transplant-refractory peripheral neuropathy, significant morbidity and mortality risks, and a lack of long-term outcome data have hindered its use. Symptomatic children with the late-infantile form of MLD are poor candidates for these therapies, as are individuals with later onset forms of the disease who have already accrued cognitive morbidity.^{15,47,65,66} Bone marrow transplantation has been shown to halt demyelination in asymptomatic patients diagnosed because of family history of late-infantile-onset disease, and in minimally symptomatic patients with juvenile or adult MLD.⁶⁷

Although there is still disagreement about the viability of transplants for some forms of MLD, morbidity rates for HSCT have decreased and treatment regimens have been improved.¹⁵ Patient outcomes of minimally symptomatic patients with late-infantile and juvenile MLD have also been improved by the use of umbilical cord blood, which has decreased the time between diagnosis and transplantation. Patients with the minimally symptomatic juvenile disease form have reported the most favorable outcomes, although there is still substantial variability with regard to clinical status, MRI severity score, peripheral nerve disease, and neurologic examination.^{68–71}

Treatment recommendations are based on the limited long-term longitudinal outcome data currently available, as is the case of allogeneic HSCT for Krabbe and MLD.^{63,69,72} The decision to pursue transplantation among patients with these disorders can be complex and as a result must be evaluated on an individual basis by a specialized and experienced center, prepared to provide the most up-to-date information and support patients with complex neurologic and systemic manifestations.

Because therapy with HSCT has resulted in variable outcomes, enzyme replacement therapy (ERT) is currently being studied internationally. ERT replaces the deficient or missing enzyme with an active enzyme through a recombinant human protein produced by gene activation technology. Although data are currently being collected, therapeutic efficacy of ERT seems to depend on factors such as enzyme dose, frequency, and the disease stage at which treatment is initiated. A regular repeated intravenous delivery of recombinant human arylsulfatase A used in previous clinical trials had limited efficacy in permeating the blood-brain barrier,⁷³ thus current phase I/II studies use an intrathecal delivery and a different enzyme doses ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01510028) identifier NCT01510028).

As a result of lentiviral gene therapy, there was greater than normal enzyme activity in the CNS and arrested disease progression in 3 presymptomatic patients with MLD as part of a phase I/II clinical trial. There are efforts ongoing to prepare for phase II/III studies ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01560182) identifier NCT01560182).²⁷

In patients with MLD, deficient arylsulfatase A results in accumulated sulfatides, with significant complications. The gallbladder is especially affected, and patients may present with enlarged gallbladder, cholecystitis, sludge, gallstone, papillomatosis, wall thickening, and more rarely polyposis. Special monitoring is required for these patients whereas gallbladder complications preceding neurologic symptom onset may provide an opportunity for early detection and management to stall the neurologic consequences associated with MLD.⁷⁴

Peroxisomal biogenesis disorders or Zellweger spectrum disorders (ZSDs) result from mutations in at least 13 peroxisomal (*PEX*) genes that aid in peroxisome assembly⁷⁵ and is inherited in autosomal recessive fashion. The resulting defects result in a heterogeneous clinical picture with peroxisomal enzyme deficiencies caused by a diminished number of peroxisomes, enlarged peroxisomes for those that are formed, and loss of enzyme import functions. Although there is multisystem involvement in almost all patients, those with mutations that entirely annul *PEX* protein function cause Zellweger syndrome, which is the most severe form of the disorder. Patients with Zellweger syndrome are born with neuronal migration defects, and typically do not survive past 1 to 2 years of age. In contrast, most patients with ZSD do not show similar migration defects. MRI may initially be normal, but patients are at risk of developing white matter changes over time. About 30% of patients have a *PEX1*-Gly843Asp common mutation, caused by a founder effect in persons of European ancestry.⁷⁶ The resultant protein is misfolded and open to degradation but was notably receptive to stabilizing cell-level interventions.⁷⁷ Zhang and colleagues⁷⁸ used a phenotype-based assay with *PEX1*-Gly843Asp cell lines expressing a GFP-PTS1 reporter to test the utility of chaperone compounds in recovering peroxisome enzyme import as part of a drug library screen. This work has been ongoing in a phase III clinical trial, based on the nonspecific chemical chaperone betaine, to determine whether there is improvement in key peroxisome functions and patient growth/development ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01838941) identifier NCT01838941).

PMD results from mutations in *PLP1*. *PLP1* encodes proteolipid protein, which comprises a large percentage of myelin sheath proteins and promotes stability within the sheath, but also plays a role in oligodendrocyte development and axonal survival.⁷⁹ The resultant phenotype is a severe hypomyelinating leukodystrophy characterized by early-onset nystagmus, hypotonia, and cognitive impairment progressing to ataxia and spasticity. The connatal form is more severe, with onset within the first 2 weeks of life and symptoms commonly including seizures and stridor. Preclinical studies with human CNS stem cell (HuCNS-SC) showed that transplantation in hypomyelinated *shiverer* mice generated new oligodendrocytes with myelin production.⁸⁰ Phase I safety studies have been pursued in the use of HuCNS-SC transplant for patients with the connatal form of PMD. The phase I trial at the University of California, San Francisco, in conjunction with StemCells, Inc (Newark, CA), transplanted HuCNS-SC directly into subcortical white matter tracts of 4 children with connatal PMD. MRI studies showed evidence for qualitative changes on T₁-weighted and T₂-weighted imaging and progressive increases in fractional anisotropy on diffusion tensor imaging (DTI).⁸¹ Moreover, such DTI signal changes persisted after stopping immunosuppressive therapies. This approach has established a potentially safe methodology for other leukodystrophies and leukoencephalopathies that may benefit from the application of HuCNS-SCs, or other CNS cell types (eg, oligodendrocyte precursors), through direct transplantation into the brain.⁸²

Polymerase III-related leukodystrophies typically present with some sort of hormonal deficiency, most notably hypogonadotropic hypogonadism, which presents as delayed puberty, requiring input and follow-up with an endocrinologist. Treatment of

hormonal deficiency should be evaluated on a case-by-case basis, weighing the risk of disease against potential treatment benefits with the input of the clinician and family. Other manifestations commonly seen are growth hormone failure and/or hypothyroidism, which should be screened for in routine follow-up.

Dental anomalies are also common manifestations of polymerase III-related leukodystrophies, and are also a common finding in other hypomyelinating leukodystrophies, such as Cockayne syndrome, and oculodentodigital dysplasia. For patients with any of these conditions, dental care is of utmost importance and regular visits to the dentist are recommended. Regular dental care and hygiene are important for all patients with leukodystrophy because cavities and abscesses may go unnoticed in routine medical care and can result in severe medical morbidity. Thus, regular dental visits are recommended for all patients with leukodystrophy.

SUMMARY

Current treatment of most patients with leukodystrophy is based on symptomatic management and supportive care. Leukodystrophies are complex, serious disorders that provide challenges for families and clinicians alike. The severe complications that can arise for these patients should be addressed proactively and follow a plan that is well communicated between the clinician and the family with the ultimate goals of maximizing patient quality of life and prevention of other serious complications. With this in mind, the number of disorders on the verge of phase I/II clinical trials is especially promising for treatment of patients with leukodystrophy, who after a long diagnostic journey frequently encounter a disorder with limited treatment prospects. Although there is still much work to be done, the growth of clinical research networks in leukodystrophies and the alliance of these consortiums with patient advocacy groups is an important step for the advancement and prioritization of care for patients with leukodystrophy.

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