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Emerging Treatments for Pediatric Leukodystrophies

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Abstract

The leukodystrophies are a heterogeneous group of inherited disorders with broad clinical manifestations and variable pathologic mechanisms. Improved diagnostic methods have allowed identification of the underlying etiology of these diseases, facilitating identification of the pathologic mechanisms associated with leukodystrophies. As such, clinicians and researchers are now able to prioritize treatment strategies and advance research in therapies for specific disorders. While only a handful of these disorders have well-established treatments or therapies readily available to the leukodystrophy population, a number are on the verge of Pilot or Phase I/II clinical trials, providing promising prospects for treatment of leukodystrophy patients. As clinical investigators are able to shift care from symptomatic management of individual disorders to targeted therapeutics, the unmet therapeutic needs could be much reduced for this patient population.

Keywords

leukodystrophy; genomics; therapy; symptomatic; disease-modifying; stem cell; gene therapy

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The leukodystrophies are a heterogeneous group of inherited disorders with broad clinical manifestations and variable pathologic mechanisms (Vanderver et al 1993; Vanderver et al 2012; Vanderver et al 2014). While these disorders are individually rare, an incidence of 1 in 7,000 suggests that these disorders are more collectively common than once thought (Bonkowsky et al 2010; Vanderver et al 2012; Brimley et al 2013; Nelson et al 2013). In many cases, patients with leukodystrophy remain in the diagnostic category of unsolved disorders, despite significant improvements in diagnostic approaches (Parikh et al 2014; Vanderver et al 2014). Even more important, only a handful of these disorders have well-established treatments or therapies readily available to the leukodystrophy population (Helman et al 2014). With this in mind, we provide an update on the emerging treatments available to leukodystrophy patients 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

While a comprehensive and disease-specific overview of clinical features of the leukodystrophies is beyond the scope of this chapter, important neurologic and extra-neurologic features are described below. The early clinical course for leukodystrophy patients is most commonly marked by motor symptoms, manifesting as delayed development of motor skills, a plateau in development, or regression in motor skills (Parikh et al 2014). While patients typically present with acute or subacute onset of neurologic symptoms, a few of these disorders have such a slowly progressive course that they appear more like a static encephalopathy until one looks at their course over a long span of time (Vanderver et al 2014). While marked spasticity and pyramidal motor symptoms are a prominent feature, leukodystrophies are often associated with rigidity, dystonia, ataxia, and bulbar symptoms.

While cognition may be relatively 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 due to 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 co-morbid psychiatric features (Parikh et al 2014).

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

A number of extra-neurologic features in a broad range of categories may be indicative of 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 dysgenesis are other common extra-neurologic manifestations of specific white matter disorders. These symptoms are well covered by the work of Parikh et al. (Parikh et al 2014).

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 (Van der Knaap 2005; Schiffmann and van der Knaap 2009; Steenweg et al 2010). Improved MRI technology is now able to explore abnormalities of myelin in these disorders without neuropathologic correlation (Pouwels et al 2014). Characterization of MRI patterns has facilitated diagnosis in patients who present on neuroimaging with abnormalities of the cerebral white matter suspicious for a leukodystrophy (Vanderver et al 1993; Van der Knaap 2005). 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 twenty percent (Vanderver et al 2014).

Several recent publications discuss the diagnostic approach in patients with abnormal white matter on neuroimaging (Parikh et al 2014; Vanderver et al 2014) which consists of detailed clinical and neurologic evaluations, review of the MRI to identify disease specific patterns followed by either target 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, supplementation with chenodeoxycholic acid in 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 (Shapiro et al 2000; Peters et al 2004; Miller et al 2011; Pilo-de-la-Fuente et al 2011).

Additionally, 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 can be found listed on clinicaltrials.gov, 16 of these are listed as a Phase I, II or III trial. Covering a broad spectrum of modalities, these studies include traditional pharmaceutical practices as well as the manipulation of stem cells, genes, and enzymes.

While 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, below we describe existing and emerging therapies for individual leukodystrophies and highlight several important complications associated with select leukodystrophies as a tool for clinicians encountering a leukodystrophy patient.

X-ALD is the most common leukodystrophy with disease-specific management and therapeutic guidelines (Engelen et al 2012). X-ALD is caused by mutations in *ABCD1*, encoding the adrenoleukodystrophy protein (ALDP). This is an X-linked dominant disorder that results 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 X-ALD patients, 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. Unfortunately, all men and most women who carry an aberrant copy of the X-ALD gene will 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 X-ALD males should be screened via cortisol stimulation testing every 6-9 months for adrenal insufficiency. Endocrinology follow-up and a corticosteroid regime should be considered in patients who exhibit 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 relatively small. Unfortunately, HSCT has no therapeutic effect if administered in the later stages of disease (Shapiro et al 2000; Peters et al 2004; Miller et al 2011), 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 (Peters et al 2004). In general, lower levels of pre-transplant neurologic morbidity (i.e. low MRI severity score (Thibert et al 2012), low degree of neurologic disability, and a high neuropsychometric measures)

predict favorable HSCT outcomes (Peters et al 2004; Miller et al 2011). The therapeutic benefits of HSCT in X-ALD patients are believed 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 (Cartier et al 2009).

Newborn screening for X-ALD is being implemented in a growing number of US states. X-ALD males, aged 3-12 years identified through newborn screening or as relatives of a proband, should undergo gadolinium-enhanced magnetic resonance imaging (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, (Figure 1). Among X-ALD men over 50 years and X-ALD women (heterozygotes) of any age, the onset of the cerebral and/or adrenal insufficiency phenotypes are uncommon, suggesting that routine surveillance screening for these individuals is probably unnecessary.

The risk of developing cerebral X-ALD, the most feared phenotype, may be mitigated somewhat by daily consumption of Lorenzo's Oil, a mixture of oleic and erucic acid, in combination with dietary restriction of very long chain fatty acids (Moser et al 2005). The oil acts as a competitive inhibitor enzymes involved in endogenous production of very long chain fatty acids (Sassa et al 2014). Use of Lorenzo's Oil does not impact the progression of cerebral X-ALD once the disease course has begun (Moser et al 2005) nor does it have been proven to mitigate the onset or progression of adrenomyeloneuropathy. Its consumption carries health risks (Semmler et al 2008) and its availability in the US is currently restricted to X-ALD boys aged 3-10 under an expanded access trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02233257), NCT02233257). A pilot phase trial using thyromimetics, synthetic structural analogs of thyroid hormone that mimic tissue-restricted thyroid hormone actions (Hirano and Kagechika 2010) is in 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 β agonist (Scanlan 2010) has had promising results in cholesterol metabolism. It is thought that sobetirome can also activate the production of ATP-binding cassette, sub-family D (ALD), member 2 (ABCD2), closely related to ATP-binding cassette, sub-family D (ALD), member 1 (ABCD1) protein. The work of Weber et al. has shown that ABCD2 can compensate for defective ABCD1 providing support for its targeting in therapeutic measures (Weber et al 2014). Lentiviral-based gene therapy has shown early promise in X-ALD (Biffi et al 2013). This technology relies on ex vivo transduction of autologous HSCs encoding wild type ABCD1 cDNA by a human immunodeficiency virus type 1-derived vector which targets microglial precursors. The therapy performed in two young males resulted in polyclonal hematopoietic repopulation and stable lentivirally encoded ALD protein expression (Cartier et al 2009). 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 four recognized phenotypes, each has its own distinct management strategies (Engelen et al 2012). Adrenal insufficiency is life-threatening

in most cases of X-ALD but can be treatable if identified in a timely fashion. While symptoms may not be present, extenuating circumstances such as an affected relative may allow for early diagnosis of the X-ALD genotype.

Aicardi–Goutières syndrome (AGS) is an inherited leukodystrophy characterized by a calcifying microangiopathy and elevated cerebral spinal fluid (CSF) α -interferon (IFN α) 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 appear to result in the irregular accumulation of RNA: DNA (ribonucleic acid: deoxyribonucleic acid) hybrids and other immunogenic nucleic acid structures within the cell (Crow et al 2006; Crow et al 2006; Rice et al 2009; Rice et al 2012). Experiments in the murine model of AGS have demonstrated this over-accumulation of endogenous retro elements (Stetson et al 2008; Stetson 2012) while SAM domain and HD 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 (Zhao et al 2013). Within the murine model of AGS, the use of reverse transcriptase inhibitors presumably targeting production of endogenous retroelements has been studied with promising results (Beck-Engeser et al 2011). 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 AGS patients.

AGS patients are susceptible to autoimmune complications as a result of possible accumulated immunogenic nucleic acids. Elevated cerebral spinal fluid α -interferon 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 exhibited 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 (Chahwan and Chahwan 2012).

Previously symptom management has involved corticosteroid and other immunosuppressive regimens but definite improvements in neurologic symptoms have not been observed (Chahwan and Chahwan 2012). AGS patients require monitoring for chilblains and other skin inflammation, arthritis, inflammatory bowel disease, hematologic complications, and cardiomyopathy (Crow YC and Chase In Press). Additionally, AGS patients may manifest other autoimmune, thyroid and other 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 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 (GFAP) that can result in obstruction of CSF pathways and hydrocephalus (Prust et al 2011). 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. Late onset (older child or adult), Type II AxD patients may exhibit symptoms such as obstructive sleep apnea, which if untreated can result in encephalopathy, as well as significant bulbar dysfunction may occur, with the characteristic dysphonia and palatal myoclonus (Prust et al 2011).

Adult onset polyglucosan body disease (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. Mutated *GBE1* causes deficient glycogen brancher enzyme activity and in combination with accumulated polyglucosan bodies are hypothesized to lead to an energy deficient state subsequent to deficient glycogen degradation. The implementation of triheptanoin, a 7-carbon triglyceride, is suspected to be an efficient substrate to the citric acid cycle to correct the resultant energy deficit (Roe et al 2010). 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-acetyl aspartic acid (NAA) metabolism in the brain (Matalon et al 1988). 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 (Leone et al 2000). Subsequent Phase I/II clinical trials used intraparenchymal gene delivery and a recombinant adeno-associated virus serotype 2 (AAV2) vector. Magnetic Resonance Spectroscopy (MRS) 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 (Leone et al 2012).

Cerebrotendinoxanthomatosis (CTX) patients 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 exhibit symptoms of cataracts and diarrhea in early childhood, progressing to psychomotor decline, and tendon xanthomas in late adulthood. Daily oral supplementation with 750mg of chenodeoxycholic acid, a bile salt, typically corrects the biochemical abnormalities and may reverse some clinical symptoms (Berginer et al 1984; Tokimura et al 1992). Earlier treatment initiation may lead to better outcomes; reversibility of existing neurologic injury is limited (Pilo-de-la-Fuente et al 2011). 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. Krabbe disease patients suffer from severe neurological symptoms due to mutations in *GALC*, the gene encoding galactosylceramidase. 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 (Krivit et al 1999; Krivit 2004; Escolar et al 2005). It should be noted however, that a number of cases have experienced progressive motor difficulties despite early intervention. Clinical staging criteria have been proposed for Krabbe disease (Escolar et al 2006) and are useful in evaluating potential outcomes of HSCT (Escolar et al 2009). 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 and adult onset cases, although it has not been well studied (Krivit et al 1999; Krivit 2004).

More than 60% of Krabbe patients have missense mutations in *GALC*. These mutations are predicted to generate misfolded proteins (Wenger et al 1997) that can be mislocalized, prematurely degraded, accumulate intracellularly, or trigger an unfolded protein response (Herczenik and Gebbink 2008; Bueter et al 2009; D'Antonio et al 2009). The neurologic consequences of this disorder are hypothesized to be potentially avoidable with even just 10% of normal galactosylceramidase (GALC) function (Conzelmann and Sandhoff 1983). Orally administered pharmacological chaperones, can rescue function of mutant proteins by directing proper folding or cellular localization, or protecting them from degradation (Chaudhuri and Paul 2006; Valenzano et al 2011; Boyd et al 2013). α -Lobeline and 3',4',7-trihydroxyisoflavone are two pharmacological are currently being studied for their utility in improving the function of GALC after initial misfolding (Ribbens et al 2013; Berardi et al 2014).

Hypomyelination with Brain Stem and Spinal cord abnormalities and leg spasticity (HBSL) is the result of mutations in *DARS*, a cytoplasmic tRNA synthetase gene for aspartate. HBSL patients present with a broad phenotypic spectrum characterized by focal cerebral white matter abnormalities and spinal cord signal abnormalities (Wolf et al 2014). Interestingly, responsiveness to steroids in a number of HBSL patients with subacute disease onset suggests that steroids may be an appropriate treatment modifying approach in mutation positive patients (Wolf et al 2014). Certain tRNA synthetases have non-canonical functions in biological processes such as angiogenesis, regulation of gene transcription, and RNA splicing (Yao et al 2014). These non-canonical tRNA synthetase functions are conserved across the complete phylogeny of animals, and are now established as playing key roles in a number of pathophysiological processes (Yao et al 2014). *DARS* specifically, is one of nine cytoplasmic tRNA synthetases that make up the multi-synthetase complex (MSC) which facilitates gene-specific translational silencing of inflammation-related mRNAs. While these mechanisms and functions must be studied further to elucidate why individuals appear responsive to steroids and what their clinical response is, it provides an interesting basis for compassionate care treatment in these patients.

Metochromatic Leukodystrophy (MLD) patients have been treated with HSCT (Malm et al 1996; Krivit et al 1999; Bredius et al 2007; Duffner et al 2009), although its use has been widely debated within the MLD community. Due to the phenotypic variability seen, the use of HSCT has proven particularly complex. The post-transplant 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. (Peters et al 2004). 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 (Krivit et al 1995; Krivit et al 1999; Peters et al 2004; Weinberg 2005). Bone marrow transplantation has been shown to halt demyelination in asymptomatic patients diagnosed because of family history of late infantile onset, minimally symptomatic patients with juvenile or adult MLD (Sevin et al 2007).

While there is still disagreement about the viability of transplant for some forms of MLD, morbidity rates for HSCT have fallen and treatment regimens have been notably improved (Peters et al 2004). 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. Patient with the minimally symptomatic juvenile disease form have reported the most favorable outcomes although there is still substantial variability with regards to clinical status, MRI severity score, peripheral nerve disease and neurologic examination (Pierson et al 2008; Cable et al 2011; Martin et al 2013; van Egmond et al 2013).

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 (Duffner et al 2009; Kohlschutter 2013; Martin et al 2013). The decision to pursue transplant 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.

As therapy with HSCT has resulted in variable outcomes, enzyme replacement therapy (ERT) is currently in study internationally. ERT replaces the deficient or missing enzyme with an active enzyme through a recombinant human protein produced by gene activation technology. While data is currently being collected, therapeutic efficacy of ERT appears to be dependent 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 (rhASA) used in previous clinical trials had limited efficacy in permeating the blood-brain barrier (Matthes et al 2012), 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, MLD patients saw above-normal enzyme activity in the central nervous system and arrested disease progression in three presymptomatic patients 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) (Biffi et al 2013).

In MLD patients, 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 while gallbladder complications

preceding neurologic symptom onset may provide an opportunity for early detection and management to stall the neurologic consequences associated with MLD (Agarwal and Shipman 2013).

Peroxisomal Biogenesis Disorders or Zellweger Spectrum Disorders (ZSD) result from mutations in at least 13 peroxisomal (*PEX*) genes that aid in peroxisome assembly (Braverman et al 2013) and is inherited in autosomal recessive fashion. The resulting defects result in a heterogeneous clinical picture with peroxisomal enzyme deficiencies due to a diminished number of peroxisomes, enlarged peroxisomes for those that are formed and loss of enzyme import functions. While there is multisystem involvement in almost all patients, those with mutations that entirely annul *PEX* protein function cause Zellweger syndrome, the most severe form of the disorder. Zellweger syndrome patients are born with neuronal migration defects, and typically do not survive past 1-2 years of age. In contrast, the majority of ZSD patients do not exhibit similar migration defects. MRI may initially be normal, but patients are at risk of developing white matter changes over time. About 30% of patients exhibit a *PEX1*-Gly843Asp common mutation, due to a founder effect in persons of European ancestry (Collins and Gould 1999). The resultant protein is misfolded and open to degradation but was notably receptive to stabilizing cell-level interventions (Walter et al 2001). Zhang et al. 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 (Zhang et al 2010). This work has been ongoing in a Phase III clinical trial, based on the nonspecific chemical chaperone betaine, to determine if there is improvement in key peroxisome functions and patient growth/development ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT01838941) Identifier: NCT01838941).

Pelizaeus-Merzbacher Disease results from mutations in *PLP1*. *PLP1* encodes proteolipid protein, which comprises a large percentage of myelin sheath proteins and promotes stability within the sheath, yet also plays a role in oligodendrocyte development, and axonal survival (Appikarla et al 2014). The resultant phenotype is a devastating hypomyelinating leukodystrophy characterized by early onset nystagmus, hypotonia, and cognitive impairment progressing to ataxia and spasticity. The congenital form is notably more severe with onset within the first two weeks of life and symptoms commonly including seizures and stridor. Pre-clinical studies with Human Central Nervous System Stem Cell (HuCNS-SC) showed that transplantation in hypomyelinated *shiverer* mice generated new oligodendrocytes with myelin production (Uchida et al 2012). Phase I safety studies have been pursued in the use of HuCNS-SC transplant for patients with the congenital form of PMD. The Phase I trial at UCSF in conjunction with StemCells, Inc. (Newark, CA), transplanted HuCNS-SC directly into subcortical white matter tracts of four children with congenital PMD. MRI studies showed evidence for qualitative changes on T₁- and T₂-weighted imaging and progressive increases in fractional anisotropy on diffusion tensor imaging (DTI) (Trepanier et al 2010). 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 (e.g., oligodendrocyte precursors), through direct transplantation into the brain (Gupta et al 2012).

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 and 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 is important for *all* leukodystrophy patients as 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 leukodystrophy patients.

Conclusion

Current treatment for most leukodystrophy patients is based on symptomatic management and supportive care. Leukodystrophies are complex, devastating 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 leukodystrophy patients, who after a long diagnostic journey frequently find themselves encountering a disorder with limited treatment prospects. While there is still much work to be done, the growth of clinical research networks in the field of leukodystrophies and likewise the alliance of these consortiums with patient advocacy groups is an important step for the advancement and prioritization of care for leukodystrophy patients.

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Key Points

- Although leukodystrophies remain incurable, they are uniformly treatable disorders
- Next-Generation Sequencing technologies have enhanced our ability to detect the underlying cause of disease and permitted identification of pathologic mechanisms in many disorders
- A number of Pilot, Phase I, II, or III clinical trials are currently in progress for leukodystrophy patients covering a number of disorders
- Awareness and early-recognition of the signs and symptoms of leukodystrophy patients is of utmost importance for the small number with existing therapies

Figure 1. X-ALD Outpatient Care Management Flow Diagram

Note emphasis on identification of a treatable disorder if recognized early in the clinical course. Routine evaluations for any clinical changes are of utmost importance.

Adapted from Engelen M, Kemp S, de Visser M, et al (2012) X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet journal of rare diseases* 7: 51; with permission.

*Designates therapies in clinical trial stages.

Table 1

Common Neurologic Symptoms For Pediatric Leukodystrophies with Existing and Emerging Therapies.

Symptom	Associated Disease(s)	Prevention/Treatment
Adrenal insufficiency	ALD	Annual ACTH screening; corticosteroids. Rare in ALD women.
Inflammatory cerebral demyelination	ALD	Sporadic onset. Highest risk (~40%) of onset occurs in ALD boys between 3-12 years. Can also affects 25% of ALD men aged 12-50 years, although comorbid symptoms of AMN in adult men can complicate HSCT. Phenotype is rare among older men as well as ALD women of any age. Surveillance MRIs can detect early demyelination before symptoms appear, thereby enabling HSCT, which is 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 (e.g. head trauma, fevers, severe fright)
Cardiac dysfunction	Mitochondrial	Cardiac evaluation; pacemaker/defibrillator may be appropriate in some patients. Patients should be re-evaluated 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 employed with caution if procedure is non-essential.
Hypercholestanolemia xanthoma formation, cataracts, psychomotor decline	CTX	Daily supplementation with chenodeoxycholic acid normalizes cholestanol levels and may prevent and/or improve other disease manifestations, statins

Below we provide a brief synopsis of common neurologic symptoms for leukodystrophies with in-practice and indevelopment therapies. This list is by no means exhaustive and the remaining leukodystrophies without current therapeutic options are covered elsewhere

From Parikh S, Bernard G, Leventer R, et al (2014) A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Molecular Genetics and Metabolism*. *In press*; with permission.

Table 2

Current Clinical Trials for Pediatric Leukodystrophies

Associated Disease(s)	Study Title	Phase	Intervention
All Leukodystrophies and Genetic Leukoencephalopathies	The Nosology and Etiology of Leukodystrophies of Unknown Causes <i>NCT00889174</i>	N/A	Biorepository Study
X-ALD; Globoid Cell Leukodystrophy; MLD; PMD	UCB Transplant of Inherited Metabolic Diseases With Administration of Intrathecal UCB Derived Oligodendrocyte-Like Cells <i>NCT02254863</i>	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 <i>NCT01372228</i>	Phase I	Biological: Enriched Hematopoietic Stem Cell Transplantation/novel platform technology
X-ALD; MLD; Globoid Cell Leukodystrophy;	Human Placental-Derived Stem Cell Transplantation <i>NCT01586455</i>	Phase I	Drug: Human Placental Derived Stem Cell
X-ALD; MLD; Globoid Cell Leukodystrophy;	HSCT for High Risk Inherited Inborn Errors <i>NCT00383448</i>	Phase II	Drug: Clofarabine; Procedure: Total body Irradiation; Drug: Melphalan; Biological: Hematopoietic Stem Cell Transplantation; Drug: Alemtuzumab; Drug: mycophenylate 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 <i>NCT02171104</i>	Phase II	Procedure: blood stem cell transplant; Drug: Rabbit Anti-Thymocyte Globulin (ATG); Drug: Fludarabine; Drug: Busulfan; Drug: Cyclophosphamide; Drug: Cyclosporine A (CSA); Drug: Methyprednisolone; Drug: Mycophenolate Mofetil (MMF); Drug: Granulocyte-Colony Stimulating Factor (G-CSF); Drug: Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF); Drug: N-acetylcysteine; Drug: Celecoxib; Drug: Vitamin E; Drug: Alpha Lipoic Acid
X-ALD; MLD; Globoid Cell Leukodystrophy; Peroxisomal Biogenesis Disorders	Allogeneic Bone Marrow Transplant for Inherited Metabolic Disorders <i>NCT01043640</i>	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 <i>NCT01594853</i> Expanded Access for Lorenzo's Oil (GTO/GTE) in Adrenoleukodystrophy <i>NCT02233257</i>	N/A N/A	Behavioral: Exercise training Drug: Lorenzo's Oil

Associated Disease(s)	Study Title	Phase	Intervention
APBD	Safety and Pharmacodynamic Study of Sobetirome in X-Linked Adrenoleukodystrophy (X-ALD) <i>NCT01787578</i>	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 (CCALD) <i>NCT01896102</i>	Phase II/III	Genetic: Lenti-D Drug Product; Drug: Busulfan; Drug: Cyclophosphamide; Drug: Filgrastim
	Triheptanoin Treatment Trial for Patients With Adult Polyglucosan Body Disease <i>NCT01971957</i>	Phase II	Drug: Triheptanoin; Dietary Supplement: Vegetable Oil
Canavan Disease	Oral Glyceryl Triacetate (GTA) in Newborns With Canavan <i>NCT00724802</i>	N/A	Dietary Supplement: GTA (Glyceryl triacetate); Drug: GTA glyceryl triacetate
CTX	Evaluation of Carotid IMT and Atherogenic Risk Factors in Patients With Cerebrotendinous Xanthomatosis <i>NCT01613898</i>	N/A	Biological: Blood Tests
Krabbe Disease	Phase II Study of Cholesterol- and Cholesterol-Free Diet, Lovastatin, and Chenodeoxycholic Acid for Cerebrotendinous Xanthomatosis <i>NCT00004346</i>	Phase II	Drug: chenodeoxycholic acid; Drug: lovastatin
	The Natural History of Infantile Globoid Cell Leukodystrophy <i>NCT00983879</i>	N/A	N/A
	Biomarker for Krabbe Disease <i>NCT01425489</i>	N/A	N/A
MLD	Lysosomal Storage Disease: Health, Development, and Functional Outcome Surveillance in Preschool Children <i>NCT01938014</i>	N/A	N/A
	Biomarker for Metachromatic Leukodystrophy <i>NCT01536327</i>	N/A	N/A
	Imaging Study of the White Matter Lesions in Children With Metachromatic Leukodystrophy <i>NCT01325025</i>	N/A	High-field Magnetic Resonance Imaging
	Natural History Study of Children With Metachromatic Leukodystrophy <i>NCT01963650</i>	N/A	Natural History Study
	The Natural History of Infantile Metachromatic Leukodystrophy <i>NCT00639132</i>	N/A	N/A
Peroxisomal Biogenesis Disorders Sjögren -Larsson Syndrome	Intracerebral Gene Therapy for Children With Early Onset Forms of Metachromatic Leukodystrophy <i>NCT01801709</i>	Phase I/II	Genetic: intracerebral administration of AAVrh.10cuARSA
	Gene Therapy for Metachromatic Leukodystrophy <i>NCT01560182</i>	Phase I/II	Genetic: Autologous CD34+ stem cells transduced with ARSA encoding lentiviral vector
	Multicenter Study of HGT-1110 Administered Intrathecally in Children With Metachromatic Leukodystrophy (MLD) <i>NCT01510028</i>	Phase I/II	Biological: Recombinant human arylsulfatase A
	Open-Label Extension Study Evaluating Safety and Efficacy of HGT-1110 in Patients With Metachromatic Leukodystrophy <i>NCT01887938</i>	Phase I/II	Biological: Recombinant human arylsulfatase A
	Betaine and Peroxisome Biogenesis Disorders <i>NCT01838941</i>	Phase III	Drug: Betaine
	Sjögren -Larsson Syndrome: Natural History, Clinical Variation and Evaluation of Biochemical Markers <i>NCT01971957</i>	Phase III	N/A

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Associated Disease(s)	Study Title	Phase	Intervention
18q - Syndrome	Growth Hormone and Chromosome 18q- and Abnormal Growth NC700134420	Phase III	Drug: Nutropin AQ; Procedure: Arginine and Clonidine Stimulation Testing; Procedure: Growth Factors Laboratory Testing; Procedure: Neuropsychological Testing