

The Leukodystrophies

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Abstract

Keywords

- ▶ leukodystrophy
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- ▶ adrenoleukodystrophy
- ▶ metachromatic leukodystrophy
- ▶ bone marrow transplantation
- ▶ enzymatic replacement therapy
- ▶ hematopoietic stem cell transplantation

Leukodystrophies are a group of genetically determined disorders that affect development or maintenance of central nervous system myelin. Leukodystrophies have a reported incidence of 1 in 7500 live births, but fewer than half of patients receive a specific diagnosis. In this review, the authors discuss types of leukodystrophies: their prevalence, clinical presentation, symptoms, and diagnosis, as well as current and future treatments. Diagnosis is based on a combination of history, exam, radiological, and laboratory findings, including genetic testing. Leukodystrophies can present at any age from infancy to adulthood, with variability in disease progression and clinical presentation, ranging from developmental delay to seizures to spasticity. Although there are few cures, there are significant opportunities for care and improvements in patient well-being. Their high prevalence, combined with rapid advances in imaging, genetics, and potential treatments, makes an understanding of the leukodystrophies necessary for care providers in genetics and neurology.

Leukodystrophies are a group of genetically determined disorders that affect development or maintenance of central nervous system (CNS) myelin.^{1–4} Leukodystrophies have a reported incidence of 1 in 7500 live births, but fewer than half of patients receive a specific diagnosis.⁵ Diagnosis can be based on a combination of history, expected prevalence, physical and neurologic examination, radiological features, or laboratory findings, including genetic testing.^{5,6} Leukodystrophies can present at any age from infancy to adulthood, with variability in disease progression and clinical presentation ranging from developmental delay to seizures to spasticity. Although there are few cures, there are significant opportunities for care and improvements in patient well-being. Their high prevalence, combined with rapid advances in imaging, genetics, and potential treatments, makes an understanding of the leukodystrophies necessary for care providers in genetics, bone marrow transplantation, and neurology.

One confusing issue is the definition of the term “leukodystrophy.” For the purposes of this review, a leukodystrophy will refer to a presumed genetically determined abnormality in myelin development, maintenance, or turnover. In contrast, a “leukoencephalopathy” will be defined more broadly as any abnormality of the white matter, including not only leukodystrophies,² but also abnormalities of the white matter, such as caused by trauma, toxicity, or insult, for example, periventricular leukomalacia secondary to premature birth or white matter abnormalities caused by chemotherapy or meningitis.

Myelin Development

Myelin development begins during fetal life and continues through adulthood. It involves a complex developmental orchestration of genes, proteins, and different cell types. Production of myelin requires oligodendrocytes, the glial

cells that produce myelin and the myelin sheath, and interactions with other cell types, particularly neurons. Myelin is necessary for normal action potential propagation and nervous system function, maintenance of axonal health, and nutritional support of axons.⁷

Myelin is produced by oligodendrocytes (also known as oligodendroglia). Oligodendrocytes are generated during fetal and postnatal life by oligodendrocyte precursor cells (OPCs). Oligodendrocyte precursor cells can persist into adult life,⁸ and there is evidence that new oligodendrocytes formed during adult life generate new myelin.⁹ Each oligodendrocyte extends many myelin sheet-forming processes that envelope axonal projections. Different processes from a single oligodendrocyte typically envelope different axons.¹⁰ Thus, on any axon, different oligodendrocytes can be contributing to neighboring stretches of myelin. Myelin is composed of proteins (30%) and lipids (70%), and its production is highly energy-dependent. The most abundant protein components are myelin basic protein (MBP) and proteolipid protein (PLP). The lipid components of myelin are cholesterol, phospholipids, and glycolipids; glycosphingolipids, particularly galactocerebrosides, are the predominant glycolipids.^{11,12}

In addition to the oligodendrocyte-specific determinants of myelin formation, neuron-oligodendrocyte interactions are also necessary for normal myelination.¹³ Oligodendrocytes must migrate to the correct locations in the brain to effect axonal ensheathment by myelin,¹⁴ and the extent of myelination is affected by neuronal activity.¹⁵

During brain development, myelination proceeds in an inside-outside and caudal-to-rostral fashion, with myelination of deeper structures occurring first. Myelination begins by the fourth month of gestation. Essentially all areas of the brain are myelinated by the second year of life, although the total myelin content of the brain does not peak until the third decade of life.¹⁶

It is apparent, then, that a large number of insults or processes, during development or in adulthood, could affect myelin development or the maintenance of myelin, and hence lead to a leukodystrophy. The biological complexity of myelin development requires both neurons and glia, and requires their interactions. Therefore, problems with any of these three could produce a leukodystrophy. In addition, leukodystrophies can arise from defects in intrinsic/biochemical pathways that are common to all cells, but that are magnified in glia due to their high energy requirements and extensive membrane turnover. For example, mutations in the intrinsic myelin protein *PLP1* lead to Pelizaeus-Merzbacher disease, and vanishing white matter disease (VWMD) is caused by mutations in the ubiquitously expressed translation initiation factor subunits *EIF2B1-5* that are required in all cells for protein production.

Despite improvements in our fundamental understanding of myelin development, there remain numerous confusing aspects to the pathogenesis of many of the leukodystrophies. Why can VWMD be asymptomatic until initiated by a sudden precipitant?¹⁷ Why can the same mutation in X-linked adrenoleukodystrophy be asymptomatic, or cause an adult-onset neuropathy, or lead to a fatal childhood cerebral

inflammatory demyelination?¹⁸ Research into these topics will lead to improved treatment for patients and significant insights into myelin biology.

Categories and Diseases

Significant confounders for discussing the different leukodystrophies are several. First, there is disagreement over the exact definition of a leukodystrophy.^{5,19} Second, only about half of all causes of leukodystrophies are known.^{5,20} Finally, limited understanding of the pathogenesis of the leukodystrophies makes classification difficult.

Currently, leukodystrophies appear to fall into three broad categories (– **Table 1**): (1) *hypomyelination*, in which there is absent or diminished myelin production; (2) *dysmyelination*, in which there is abnormal myelin development; and (3) *demyelination*, in which there is loss and/or destruction of previously established myelin. Although widely accepted (or perhaps tacitly assumed) that demyelinating inflammatory diseases such as multiple sclerosis or neuromyelitis optica constitute a different diagnostic category than demyelinating leukodystrophies,²¹ it will be interesting in the next decade to see if shared common elements of pathogenesis are discovered.²² This being said, trials of immune modulatory therapy for demyelinating leukodystrophies have not shown efficacy.²³

However, certain leukodystrophies do not fit clearly into the above categories. For example, Rett syndrome and Batten disease can have white matter changes and clinical features that would initially suggest a leukodystrophy before subsequent testing leads to their ultimate diagnosis. Or some patients have syndromic dysmorphic physical features, and are found to have chromosome microdeletions or microduplications, such as in the 18q- syndrome²⁴; yet the primary CNS pathology can consist of leukodystrophy.

An alternative method of classification is based on the primary site of action of the gene product implicated in the leukodystrophy. In this regard, leukodystrophies such as metachromatic leukodystrophy or Krabbe disease can be linked to defects in the lysosome, while X-linked adrenoleukodystrophy can be linked to defects in the peroxisome.⁴ A drawback to the site-of-action classification approach is the imperfect correlation between gene function and pathology of the leukodystrophy. For example, X-linked adrenoleukodystrophy is caused by mutation of the *ABCD1* gene producing a peroxisomal transporter protein, yet levels and presence of very-long chain fatty acids correlate with neither the development of disease nor the timing of disease onset.

Clinical Presentation

There are few reliable clinical indicators of leukodystrophies: The symptoms can be nonspecific, and the age of onset can vary from prenatal to adult. After history and examination, magnetic resonance imaging (MRI) is the key diagnostic test that should prompt evaluation for a specific leukodystrophy diagnosis.

Table 1 Categories, disease, and gene name abbreviations of representative leukodystrophies

Category	Gene	Diagnosis	MRI Features
Hypomyelinating			
Pelizaeus-Merzbacher disease	PLP1	G	
Pelizaeus-Merzbacher-like disease	GJA12	G	
4H syndrome	POLR3A, POLR3B	G	Cerebellar atrophy
Salla disease/sialuria	SLC17A5	Urine sialic acid	
Fucosidosis	FUCA1	Urine oligosaccharides, LLE	
HABC/Other	TUBB4A	G	Atrophy of basal ganglia, cerebellum
Dysmyelination/demyelination ^a			
Metachromatic leukodystrophy	ARSA	Urine sulfatides, LLE	Frontal onset, symmetric
MLD-like	PSAP	Urine sulfatides, G	frontal onset, symmetric
	SUMF1	Urine mucopolysaccharides	Frontal onset, symmetric
Krabbe (Globoid cell leukodystrophy)	GALC1	LLE	Optic nerve enlargement, DGM
Canavan disease	ASPA	Urine NAA, G	Macrocephaly, increased NAA on MRS
Alexander disease	GFAP	G	Frontal onset, megalencephaly, contrast enhancement, BG, T, BS
Aicardi-Goutieres syndrome	TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR	CSF pleocytosis, CSF IFN- α , G	Calcifications, temporal cysts
Megalencephalic leukodystrophy with cysts	MLC1, HEPACAM	G	Megalencephaly, cysts
X-linked adrenoleukodystrophy	ABCD1	Plasma VLCFA	Contrast Enhancement, parieto-occipital onset
Mitochondrial diseases	various	Lactate (serum, CSF), G	BG, BS, DGM
Vanishing white matter disease (VWMD)	EIF2B, subunits 1–5	G	Stranding in white matter, white matter isointense with CSF
VWMD-like disease	LMNB1	G	Stranding in white matter, white matter isointense with CSF

Abbreviations: BG, basal ganglia involvement; BS, brainstem involvement; CSF, cerebrospinal fluid; DGM, involvement of deep gray matter; G, gene test; LLE, leukocyte lysosomal enzymes; MRS, magnetic resonance spectroscopy; T, thalamus involvement; VLCFA, serum very-long chain fatty acids. Note. "Diagnosis" indicates the primary initial method for diagnosis; "MRI features" indicate any particularly unique and/or distinguishing features observed on MRI associated with the disease.

^aDysmyelination and demyelination disorders are included together, as many of these diseases may have both characteristics at different points in their natural history.

A few leukodystrophies can have classic presentations, and a specific diagnosis should be considered. In a child with acute deterioration of neurologic status, mitochondrial disease or VWMD should be considered. Infants with Pelizaeus-Merzbacher disease often present with nystagmus and/or head titubation. Macrocephaly is a common feature in Canavan disease and Alexander disease, whereas microcephaly is a

feature of Aicardi-Goutieres disease. Skin color changes and/or adrenal insufficiency (e.g., Addison disease) in a school-age boy should lead to evaluation for X-linked adrenoleukodystrophy.

In neonates and infants, presenting symptoms can include encephalopathy or developmental delay. In children, teens, and adults, symptoms can be more insidious, ranging from behavioral or psychiatric changes, loss of formerly achieved

milestones or deterioration in skills, vision changes, ataxia, or gait problems (often from spasticity). Although not necessarily a presenting symptom, seizures are much more common than previously realized in children with leukodystrophies, and affect up to 49% of children.⁵

Incidence and Prevalence

The most recent population-based estimate for leukodystrophies shows an incidence of 1 in 7,663 live births, although this was felt to be an underestimate, with a “true” incidence closer to 1:7,500.⁵ A population-based determination for X-linked adrenoleukodystrophy in Norway revealed a birth prevalence of 1.6 in 100,000.²⁵ In Poland, the birth prevalence of metachromatic leukodystrophy has been estimated at 4.1 in 100,000.²⁶ To date, there have been few large studies from Africa, the Middle East, or Asia to examine relative incidences or prevalences of the different leukodystrophies, and it will be important and interesting to learn the disease distribution from these regions.

The prevalence of different leukodystrophies has also been difficult to determine; furthermore, in most studies almost half of all patients remain without a definitive diagnosis.^{5,20} In the Utah cohort, the most common diagnoses (in descending order of prevalence) were metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, mitochondrial diseases, X-linked adrenoleukodystrophy, and VWMD.⁵ Most studies have not compared incidences of different leukodystrophies. For many years, leukodystrophy-specific incidences were estimated based on case determinations at tertiary referral centers. Given the referral bias in case ascertainment, these estimates must be interpreted with caution. That being said, and using a restrictive definition of leukodystrophy, an incidence of 2 in 100,000 live births was determined from referral centers in Germany.²⁷ X-linked adrenoleukodystrophy has been estimated at 1 in 100,000 in France, 1.6 in 100,000 in Australasia, and 1 in 30,000 in Japan.^{28–30}

Magnetic Resonance Imaging and Neuroimaging

Magnetic resonance imaging is the current gold standard for diagnosis of a leukodystrophy. Although computed tomography (CT) can indicate abnormal signal density in the white matter, MRI is necessary for the determination of signal characteristics that can provide potentially diagnostic information. A large amount of careful work has been performed on the use of MRI and features that can be used for diagnosis.^{6,31–33} Key features on MRI include the presence of contrast enhancement; the presence of cysts, calcifications, or more subtle structural abnormalities (such as periventricular garlands in Alexander disease)³⁴; hypomyelination versus high T2-signal abnormality; and the relative T1-signal hyper- or hypointensity.⁶ However, even though MRI algorithms are helpful for diagnosis,⁶ they are not able to provide a final diagnosis for many patients because of the need for skilled radiological interpretation and experience and limitations of their sensitivity and specificity.³¹

Complications and limitations to the use of MRI include the appearance and characteristics of myelin change with normal development,³⁵ and this can be confounding for the interpretation of what is normal or abnormal on MRI. In particular, until the age of 2 years children are normally relatively hypomyelinated compared with adults. Further, there is a range (or bell curve) of normal development of myelin appearance on MRI, and at age 2 years some children will not be fully myelinated. Also, hypomyelination can be a result or complication of developmental delay or other systemic disorders or illnesses.^{36,37} Another complicating feature is that the T1 and T2 signal characteristics of myelin shift between birth and 1 year; in infants, myelin is bright on T1 and dark on T2. By 1 year of life, myelin is dark on T1 and bright on T2. Despite caveats, it is important to broadly recognize leukodystrophies by certain key features on MRI, and to differentiate these from potential leukodystrophy mimics (►Fig. 1; ►Table 1).

Diagnosis

How does one diagnose a new patient with a leukodystrophy? This continues to be a vexing problem for the clinician. High costs of genetic testing, combined with the likelihood that many causes of leukodystrophy have not yet been discovered, continue to limit the ability to make diagnoses. There is no universally accepted algorithm, and no estimation of costs or sensitivity and specificity for different approaches to diagnosis.

Currently, the most sensible approach appears to combine three elements: (1) testing for treatable diseases, (2) testing based on MRI features, and (3) using relative prevalence to guide testing (►Fig. 2). We propose an algorithm for leukodystrophy diagnosis that is rational and cost effective, with a tiered approach to testing. There is utility in making an expedient diagnosis by excluding treatable forms of leukodystrophies, curtailing other expensive and lengthy testing, and providing valuable reassurance and prognostic information to the patient and their family.

Steady advances in next-generation sequencing technologies are making whole exome sequencing a first-tier option for diagnosis of complex genetic disorders, with reported yields of 25%.³⁸ Unbiased genome-wide approaches exemplified by whole exome or whole genome sequencing provide the potential for diagnosis of known diseases without stepwise ordering of multiple individual tests. Further, genome-wide sequencing can contribute to the ongoing discovery of novel disease genes.

Next-generation sequencing technologies provide the potential for unbiased diagnosis of known diseases without individual ordering of multiple individual tests, and will contribute to the discovery of novel disease genes. However, continued limitations and problems associated with this technology include (1) substantial cost—up to \$15,000 to \$20,000—although these numbers are rapidly decreasing; (2) potential for identifying unanticipated disease variants unrelated to the test indication; (3) potential false-negatives due to imperfect exome coverage; and (4) methodological

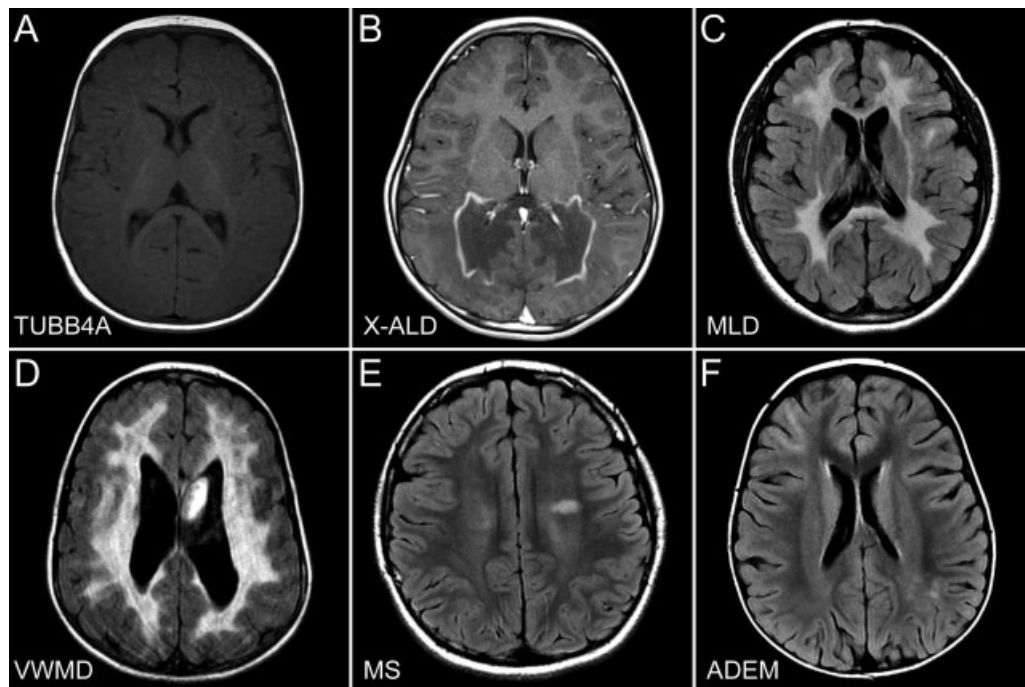


Fig. 1 Illustrative examples of magnetic resonance images of different leukodystrophies, and of leukodystrophy mimics. Images are axial slices. (A) T1 Image of a hypomyelinating leukodystrophy, TUBB4A. (B) T1 Image with contrast of a demyelinating leukodystrophy, X-linked adrenoleukodystrophy (X-ALD). (C) T2 Fluid-attenuated inversion-recovery (FLAIR) image of metachromatic leukodystrophy (MLD). (D) T2 FLAIR image of vanishing white matter disease (VWMD). (E) T2 FLAIR image of multiple sclerosis (MS). (F) T2 FLAIR image of acute disseminated encephalomyelitis (ADEM).

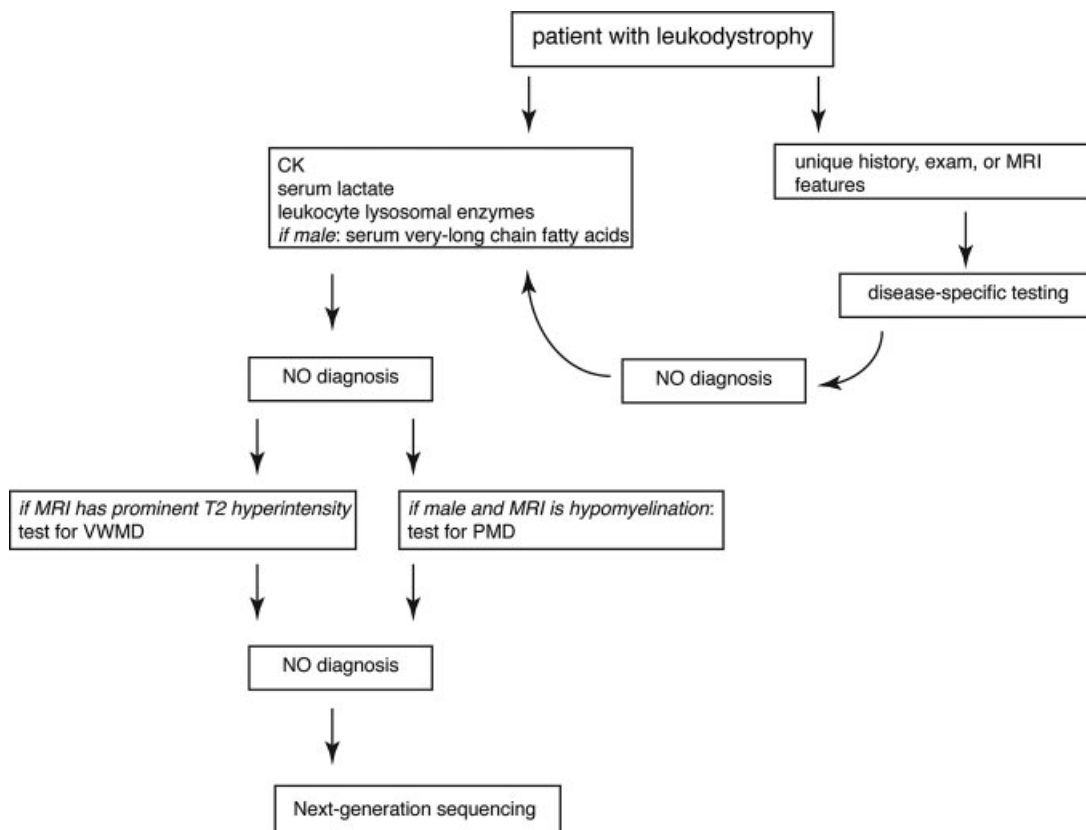


Fig. 2 A proposed diagnostic algorithm for testing of leukodystrophies. CK, creatine kinase; MRI, magnetic resonance imaging; PMD, Pelizaeus-Merzbacher disease; VWMD, vanishing white matter disease.

limitations in the interpretation phase if a clear disease-associated variant is not identified. This last problem is significant due to the large number of deleterious gene variants in all humans that could plausibly be related to a phenotype (especially in the CNS), which could yield false-positive associations.

Whole-exome sequencing continues to become more accessible, and may become the method of choice for the diagnosis of leukodystrophies. A rational, cost-effective algorithm for leukodystrophy diagnosis could be developed, with a tiered approach to testing. For example, first-tier testing could include assessment for treatable leukodystrophies: leukocyte lysosomal enzyme testing for metachromatic leukodystrophy, and in males, serum very-long chain fatty acids, for adrenoleukodystrophy. The second tier could be whole-exome sequencing. However, without sufficient data on the sensitivity of whole-exome sequencing for leukodystrophies, and of the false-negative rate for missing gene deletions or duplications (such as for Pelizaeus-Merzbacher or VWMD), this approach is not yet indicated.

Newborn screening for leukodystrophies is being developed in several states.^{39,40} Screening has been piloted in New York for Krabbe disease,^{41,42} but is now also being considered in other states, including California and Minnesota. However, because of variability in disease course, variability in penetrance and disease progression, as well as limited treatment options, there continues to be debate about how widely, and for what diseases, newborn screening should be considered.⁴³⁻⁴⁵

Treatments

Treatment options for leukodystrophies are disappointingly sparse at the current time. Essentially, the only curative treatment option is bone marrow transplant (BMT)/hematopoietic stem cell transplantation (HSCT). Bone marrow transplant is only available for a subset of leukodystrophies, chiefly X-linked adrenoleukodystrophy, metachromatic leukodystrophy, and Krabbe disease,⁴⁶⁻⁴⁸ and is only helpful if transplantation is performed prior to substantial disease progression. Patients who have BMT are at high risk for disease progression; first, because there is a time lag between transplant and effective “rescue,” and second, because the BMT process itself appears to accelerate disease progression in some patients. Bone marrow transplant is not always successful, and carries a substantial mortality risk, approaching 20%. Donor sources for BMT include cord blood, bone marrow, or peripheral blood stem cells.^{49,50}

Enzyme replacement therapy (ERT) is an option for some of the lysosomal disorders (Gaucher disease; Fabry disease; mucopolysaccharidosis types I, II, and VI; and Pompe disease), which can have leukodystrophy as a component.⁵¹ Enzyme replacement therapy has shown some efficacy in animal models in other leukodystrophies.⁵² Clinical trials are being pursued, but convincing effectiveness has not yet been shown.

Lorenzo’s oil is a treatment that has been proposed to reduce progression of X-linked adrenoleukodystrophy in its cerebral form.⁵³ A 4:1 mixture of glyceryl trioleate and

glyceryl trierucate, Lorenzo’s oil can normalize levels of very-long chain fatty acids in plasma, although as previously noted, these do not show a correlation with disease progression, and current published data do not demonstrate efficacy for inhibiting disease progression or altering outcomes.⁵⁴⁻⁵⁶ In the United States, Lorenzo’s oil is available only in clinical trials.

Care for Patients

Although we have seen that treatment options for leukodystrophies are limited, there are tremendous opportunities for improving the care for patients.⁵⁷ This patient-centric approach should lead to discussions between the clinician, patient, and family about what care and treatment is most important and most helpful. As has been demonstrated for other currently incurable genetic conditions (e.g., cystic fibrosis), the strategies of routine symptomatic care can have a profound impact on both the quality and the duration of a patient’s life.⁵⁸ Nationally and internationally, there are no standardized guidelines for care or treatment of leukodystrophy patients, which results in wide variability in care and costs: > sevenfold difference in costs across children’s hospitals in the United States.⁵⁹

Complications of disease, even if the disease itself is not progressive, can lead to progressive disability requiring assistance for mobility and activities of daily living, and even surgery.^{60,61} Leukodystrophy patients can have significant health care requirements and costs, driven largely by inpatient admissions.^{5,62} A relatively small subset of leukodystrophy patients (15%) have much greater health care problems, suggesting that potential interventions for these patients could have a proportionately greater impact. As expected, patients who undergo BMT have much higher costs. However, even taking into account BMT, patients with infections and patients needing mechanical ventilation have higher costs and health care needs.⁶²

Building from this analysis of health care utilization, a recent study showed that infection rates in leukodystrophy patients correlate with potentially modifiable risk factors⁶³: for example, failure to vaccinate against seasonal flu significantly increases the risk for hospitalization with influenza, and urinary tract infections are associated with the presence of indwelling urinary catheters. Although these are common sense issues, they also outline a path for potential clinical care guidelines that could be implemented at this time to reduce hospitalizations and improve care.

Future Directions

The development of new treatments is and should be a primary goal. In this regard, studies in model organisms are leading to a better understanding of the molecular underpinnings of the leukodystrophies, which will provide foundations for new therapeutic options. The best examples include X-linked adrenoleukodystrophy and Alexander disease. Adrenoleukodystrophy has been studied in mouse knockout models⁶⁴⁻⁶⁷ although failing to recapitulate CNS

degeneration, mouse knockout models have proven useful for the testing of anti-inflammatory therapies.⁶⁷ Interestingly, a powerful genetic model of adrenoleukodystrophy is the *Drosophila* *bubblegum* mutant, which manifests two key hallmarks of the human disease: age-dependent CNS degeneration and very-long chain fatty acid accumulation.⁶⁸ For Alexander disease, both *Drosophila* and mice harboring the mutated isoform of human GFAP (glial fibrillary acidic protein) as a transgene exhibit Rosenthal fiber formation and neurodegeneration, which has been shown to originate from glia.^{69,70} Additional models are likely to emerge in the near future. It is also important to note that although animal models recapitulate key diagnostic aspects of diseases, they also have the potential to mimic the incomplete penetrance and variable expressivities that characterize human conditions. Thus, animal models will provide a platform to explore the environmental and genetic interactions that make each case presentation so unique.

From the perspective of existing therapies, two significant hurdles to their implementation are the absence of efficient delivery to the CNS, an organ system largely protected by the blood–brain barrier, and the lack of robust methodologies to deliver gene replacement in affected oligodendrocytes or neurons. In addition, significant pathology may happen early in development, in the first year of life, or even before birth. There is significant interest in using stem cells or modified induced pluripotent stem cells (iPSCs) for the leukodystrophies.⁷¹ Although their use has great potential, their practical use still does not seem imminent. Gene therapy is also under active investigation, but with only a few examples and considerable technical challenges, it remains experimental.^{72,73} A limitation of some of the gene therapy approaches is that they use BMT to provide the source of the enzyme, which thus introduces all of the potential morbidities of BMT. Novel drug discovery, or repurposing of known drugs, is another promising avenue of current therapies for several leukodystrophies.^{56,67,74}

A corollary to the need for improved treatments is the need for faster, definitive diagnosis. Whole exome or whole genome sequencing appears to be on the threshold of becoming the diagnostic method of choice, as it can avoid the “diagnostic odyssey” faced by many patients.^{75,76} Sequencing is as cost effective as a brain MRI, and with improved data analysis will become as rapid. However, there are unanswered questions about the disconnect between the underlying gene or biochemical defect, as in X-linked adrenoleukodystrophy or Krabbe disease, and actually developing the disease.^{39,77} Further, unresolved ethical questions surround the implementation of whole genome sequencing as a screening or general diagnostic tool.^{78,79}

Conclusions

The field of knowledge encompassing leukodystrophies is rapidly expanding. Within this decade new methods of diagnosis, such as next-generation sequencing, as well as new therapies will revolutionize patient care. Though exciting, we can still improve our care and improve the lives of

patients today by increased attention to preventable and modifiable features of the leukodystrophy diseases.

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