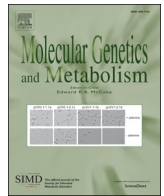




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Consensus statement on preventive and symptomatic care of leukodystrophy patients

Keith Van Haren^{a,*}, Joshua L. Bonkowsky^b, Genevieve Bernard^c, Jennifer L. Murphy^d, Amy Pizzino^d, Guy Helman^d, Dean Suhr^e, Jacque Waggoner^f, Don Hobson^g, Adeline Vanderver^{d,h,i}, Marc C. Patterson^j, on behalf of the GLIA Consortium

^a Department of Neurology, Lucile Packard Children's Hospital and Stanford University School of Medicine, Stanford, CA, USA

^b Department of Pediatrics and Neurology, University of Utah School of Medicine, Salt Lake City, UT, USA

^c Departments of Pediatrics, Neurology and Neurosurgery Montreal Children's Hospital/McGill University Health Center, Montreal, Canada

^d Department of Neurology, Children's National Medical Center, Washington DC, USA

^e MLD Foundation, USA

^f The Hunter's Hope Foundation, Buffalo, NY, USA

^g The PMD Foundation, USA

^h Department of Integrated Systems Biology, George Washington University School of Medicine, Washington DC, USA

ⁱ Center for Genetic Medicine Research, Children's National Health System, Washington DC, USA

^j Departments of Neurology, Pediatrics and Medical Genetics, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Leukodystrophies are inherited disorders whose primary pathophysiology consists of abnormal deposition or progressive disruption of brain myelin. Leukodystrophy patients manifest many of the same symptoms and medical complications despite the wide spectrum of genetic origins. Although no definitive cures exist, all of these conditions are treatable. This report provides the first expert consensus on the recognition and treatment of medical and psychosocial complications associated with leukodystrophies. We include a discussion of serious and potentially preventable medical complications and propose several preventive care strategies. We also outline the need for future research to prioritize clinical needs and subsequently develop, validate, and optimize specific care strategies.

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1. Introduction: lack of a cure should not result in a lack of care

Leukodystrophies are degenerative neurogenetic disorders whose primary pathophysiology involves abnormal deposition or disruption of brain myelin. These disorders are individually rare, but collectively common, affecting roughly 1 in 7500 individuals and covering the full spectrum of age, gender, and ethnicity [1].

Abbreviations: X-ALD, X-linked adrenoleukodystrophy; ADLD, Adult onset autosomal dominant leukodystrophy; AGS, Aicardi–Goutières syndrome; AxD, Alexander disease; CER, Comparative effectiveness research; CT, Computed tomography; CTX, Cerebrotendinous xanthomatosis; GLIA, Global Leukodystrophy Initiative; MLD, Metachromatic leukodystrophy; Pol III, Polymerase III; UTIs, Urinary tract infections; VWM, Vanishing white matter disease

* Corresponding author at: Department of Neurology, Stanford University School of Medicine, 750 Welch Rd, Suite 317, Palo Alto, CA 94304, USA.

E-mail address: kpv@stanford.edu (K. Van Haren).

Recently, a small number of genetic and stem cell therapies have finally achieved promising results in human trials for leukodystrophies [2–4]. Although tantalizing, in most cases these therapies are still many years away from widespread use and have limited relevance to patients suffering from debilitating symptoms in the present day. In this context, the more distant hope of technological “cures” may undermine the immediate relevance of routine and preventive care.

Improved medical care and quality of life for leukodystrophy patients need not, should not, and must not await the arrival of technological “cures”. Few other genetic disorders have exemplified this principle as dramatically as cystic fibrosis, where average life expectancy has rocketed from 30 days to 30 years without the benefit of a genetic “cure” [5]. Rather, these gains in longevity were derived from incremental improvements in the approach to “routine and preventive care” (e.g. aggressive physiotherapy, antibiotics) and the establishment of expert centers. These expert centers monitored outcomes and used the data to publish and refine management guidelines [5]. Clearly, this

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astounding progress requires us to consider the possibility that “low tech” solutions to routine care could offer advantages for other genetic disorders still awaiting their definitive “cures”.

2. The process of developing a consensus on preventive and symptomatic care

Impatience with the current state of care and a strong desire for progress in all its forms were part of the impetus that prompted a diverse group of leukodystrophy experts, patients, and patient advocates to convene in Washington DC in early 2013 to establish an international leukodystrophy consortium now called the Global Leukodystrophy Initiative or GLIA. The members of GLIA collectively identified four key areas in need of Consensus guidelines: (1) the definition and categories of leukodystrophies, (2) the diagnostic evaluation of suspected leukodystrophies, (3) the approach to leukodystrophy-specific therapies, and (4) the approach to preventive and symptomatic leukodystrophy care. This manuscript summarizes the latter. The remaining guidelines are available in this issue of *Molecular Genetics and Metabolism* [6–8].

The consensus process for symptomatic and preventive care began by designating a core team of seven leukodystrophy clinicians and patient advocates who generated a preliminary outline of care needs and treatment strategies. This outline was subsequently presented to the larger GLIA consortium for discussion and criticism. The consortium members made every effort to incorporate relevant evidence from the medical literature in devising the care guidelines. However, the paucity of research on clinical care strategies in leukodystrophies necessitated that many of our guidelines have been extrapolated from related fields or derived via consensus expert-opinion. The current manuscript represents the outcome of this consensus process and is the first of its kind to provide care recommendations for the full spectrum of leukodystrophy patients.

The basic principles underlying the current clinical guidelines are three-fold:

1. Although currently incurable, all leukodystrophies are treatable conditions.
2. Leukodystrophies share many of the same clinical symptoms, suggesting that a common approach to symptomatic and preventive treatment is reasonable.
3. The emotional vitality and the economic vitality of the caregiving family are important to the patient's health.

3. Establishing a diagnosis is only the first step

Although a genetic diagnosis is not always achievable, a rigorous diagnostic evaluation is important because of its implications for treatment, prognosis, and family planning. Consensus guidelines on defining and diagnosing leukodystrophies are covered separately [7,8]. Delivering the news of a confirmed genetic diagnosis to a family is an important milestone that should include the input of an experienced genetic counselor. The diagnostic disclosure should occur promptly after confirmation and should include the following four topics: diagnosis, prognosis, recurrence risk/reproductive options, and treatment plan. The absence of a genetic diagnosis should not delay the delivery of symptomatic and preventive care.

4. An effective treatment plan requires well-coordinated, multi-disciplinary care

The long-term care goals for leukodystrophy patients do not differ from the general population: to enhance the quality and prolong the duration of life. The strategies required to achieve these goals, however, are substantially more complex and require hefty doses of preventive, chronic, and acute care that must evolve as the disease progresses. Leukodystrophy patients invariably require the care of multiple specialists

in addition to their primary care physician. In some cases, a dedicated specialist (e.g. geneticist, neurologist or hospital-based pediatrician) may function as the de facto primary care provider or “medical home” for these complex patients. Effective multidisciplinary care delivery requires a strong leader, clear communication, continual reprioritization, and a strong commitment from the patient and family.

An effective treatment plan should address acute, chronic, preventive, and psychosocial needs as outlined herein. However, it is often impractical to devise a complete treatment plan in a single visit. Rather, a thorough treatment plan may take several visits to properly develop and will inevitably evolve as the disease progresses. In order to keep up with these changes, medical visits with the primary care physician should be scheduled at least every 6-months. At each visit, care needs should be reassessed and reprioritized.

Soliciting the patient's and/or caregiver's subjective sense of symptomatic priorities is an invaluable means for identifying treatment strategies in need of refinement. These visit-specific priorities should complement, but not overshadow, the treating physician's assessment of care needs. Consultation with a dedicated leukodystrophy clinic may offer both the referring physician and the family valuable nuances on individualized care strategies and/or clinical trial availability. Lastly, the treatment plan should include a discussion of the family's preferred approach to end-of-life care.

5. Disease-modifying and disease-specific therapies exist for a subset of leukodystrophies

Several leukodystrophies have important disease specific therapies available, most of which require prompt triage and initiation in order to take full effect, adding a level of urgency to an accurate diagnosis and therapeutic knowledge. These disease-specific therapies are covered in a separate GLIA consensus statement [6].

6. Many symptoms and treatments are shared across the spectrum of leukodystrophies

Because all leukodystrophies, by definition, affect brain myelin, these disorders commonly manifest a wide range of overlapping symptoms that allow a degree of uniformity in the approach to care in many cases. Below we highlight several treatable symptoms that appear across the leukodystrophy spectrum and include a brief description of treatment strategies, summarized in Table 1, and common medications, summarized in Table 2.

6.1. Autonomic dysfunction

Autonomic dysfunction or dysautonomia is a frequent source of secondary morbidity in leukodystrophy patients. Clinical manifestations are protean and often subtle, but can be readily uncovered during a comprehensive history and review of systems. Symptoms may affect bowel (e.g. constipation or incontinence), bladder (e.g. retention or incontinence), cardiac (e.g. arrhythmias), vascular (e.g. postural hypotension), and thermoregulation (e.g. diminished sweating). For patients with the adolescent or adult onset phenotypes of Alexander disease, metachromatic leukodystrophy, and adult-onset autosomal dominant leukodystrophy (ADLD), dysautonomia is a prominent feature [9,10]. Although well documented among adult-onset leukodystrophy patients, dysautonomia can also affect younger patients, particularly during the more advanced stages of neurologic progression.

6.2. Cognitive dysfunction and decline

Although some leukodystrophy patients begin life with normal cognitive function, most will eventually manifest some level of cognitive decline. The nature and the severity of cognitive dysfunction are determined by the neural networks affected as well as by the degree of injury.

Table 1

Common symptoms inherent to many leukodystrophies and recommended treatment goals. Abbreviations: adaptive and augmentative communication (AAC), individualized educational plan (IEP), occupational therapy (OT), speech therapy (SPT).

Symptom	Treatment goals	Comments
Cognitive delay and deterioration	Maximize developmental potential and quality of life	IEPs are appropriate for most patients and should include a focus on life enrichment. OT is appropriate for some patients.
Constipation	Identify and alleviate this under-recognized source of pain and distress	Etiologies include dehydration, improper diet, inactivity, and autonomic dysfunction. Stool softener, fibers, laxative, and/or modified nutrition and hydration should be considered as needed.
Dystonia	Maximize mobility for necessary function with minimal side effects; alleviate pain	Several therapeutic options exist including trihexyphenidyl and tetrabenazine; consider neurology movement disorder consultation.
Hearing impairment	Maintain awareness of auditory function to enable modification of education and communication strategies	Auditory evaluation should be obtained at baseline and as needed thereafter.
Language impairment	Facilitate verbal, non-verbal, and adaptive communication between patients and caregivers	Adequate communication can improve care, reduce distress, and enrich life. SPT is appropriate for many patients; AAC strategies should be considered for non-verbal patients.
Motor milestone delay and deterioration	Maximize mobility and independence; prevent falls	Physical therapy and/or orthotic evaluation are often appropriate.
Scoliosis	Prevent secondary pulmonary, cardiac, and neurologic morbidity	Screening should occur in the form of a brief exam of the spine during routine clinic visits. A pediatric orthopedic consultation should be sought if scoliosis is suspected. Treatment varies depending on the severity and progression of the deformity.
Seizures	Minimize seizure frequency and unnecessary hospitalizations; maximize quality of life and cognitive potential	Establish a clear plan of care for seizure exacerbations with the goal of minimizing unnecessary emergency room visits and radiologic studies. A written plan of care to present at outside ERs may be helpful.
Sialorrhea	Prevent aspiration pneumonia; balance cosmetic/social concerns with risks of medical intervention	Botox injection may offer safety and efficacy profile. Glycopyrrolate should be used with caution; adverse effects may outweigh benefits. Multidisciplinary consult can be helpful when available.
Sleep disturbance	Identify and alleviate an under-recognized source of distress for patients and families; maintain circadian rhythms conducive to social and educational enrichment	Etiologies include pain, improper sleep hygiene, and primary CNS disturbance. If pain and sleep hygiene have been excluded consider a step-wise approach starting with melatonin and other agents that lack the potential for respiratory depression and hypersalivation or are already in the patients' medication regimen (e.g. clobazam for epilepsy or gabapentin for neuropathic pain).
Spasticity	Maximize mobility for necessary function with minimal sedation; alleviate pain	Several therapeutic options exist including baclofen (also administered intrathecally by pump), dorsal rhizotomy, and diazepam.
Visual impairment	Maintain awareness of visual function such that education and communication can be modified accordingly	Ophthalmologic evaluation should be obtained at baseline and on interval basis thereafter. Support services for the visually impaired may be appropriate.

Table 2

Common symptomatic medications. "Start low and go slow" is a good rule of thumb for avoiding overmedication and undesirable off-target effects. All anti-cholinergic agents should be used with caution in patients with autonomic dysfunction as they may exacerbate existing co-morbidities (e.g. constipation, urinary retention). Many anti-epileptics carry a small but important risk of Stevens–Johnson syndrome (SJS), a life-threatening rash.

Medication	Indication(s)	Mechanism	Side effects/comments
Amitriptyline	Chronic pain; depression	Anti-cholinergic	Off-target effects can be both helpful (e.g. reduce sialorrhea) and harmful (e.g. exacerbate constipation, urinary retention, hypotension).
Baclofen	Spasticity	GABA-agonist	Off-target effects include sedation, sialorrhea, and constipation. Axial hypotonia may limit dose. Intrathecal administration may reduce systemic side effects but requires implanted hardware which carries some risks.
Botulinum toxin	Spasticity; dystonia; sialorrhea	Enzymatic cleavage of specific vesicular proteins	First-line therapy for focal dystonia. Administered via intramuscular injection every few months. Highly effective with minimal to no systemic side effects if properly administered. Requires an experienced provider.
Carbamazepine and oxcarbazepine	Epilepsy	Sodium channel modulation	May exacerbate some seizure types. Risk of life threatening rash and blood dyscrasias. Risk of hyponatremia with oxcarbazepine.
Clobazam	Epilepsy	Selective GABA-agonist	Expensive in the US, but may result in fewer off-target effects (e.g. sedation, sialorrhea) when compared to other GABA-agonist anti-seizure agents (e.g. phenobarbital).
Diazepam	Spasticity	GABA-agonist	Off-target effects include sedation, increase and/or thickened salivation, and constipation. May have some effect on reducing anxiety.
Gabapentin	Chronic pain/epilepsy	Calcium channel modulation	Minimal drug interaction and low toxicity. The most limiting side effect is usually dose-dependent sedation.
Glycopyrrolate	Sialorrhea	Anti-cholinergic	Anti-cholinergic agent. Thickened secretions are often dose limiting. Off-target effects can be problematic and may outweigh benefits in patients with pre-existing sedation, constipation, cardiovascular instability.
Lamotrigine	Epilepsy	Sodium channel modulation	Effective and non-sedating, but requires unusually slow titration and close observation to mitigate risk of SJS.
Levetiracetam	Epilepsy	Not well-established	Common first line agent. Minimal drug interaction. Risk of psychiatric disturbance (e.g. irritability, depression) requires monitoring, but may be attenuated by pyridoxine supplementation.
Tetrabenazine	Dystonia	Presynaptic dopamine depletion	Sedation, anxiety, insomnia, and sialorrhea are fairly common. All patients should be monitored for depression, suicidality, parkinsonism, liver injury, and QT prolongation.
Trihexyphenidyl	Dystonia	Anti-cholinergic	Peripheral anticholinergic side effects such as constipation can limit dose escalation. Beneficial effect may be delayed for several weeks. Sedation as well as disturbances in memory and concentration may occur with dose escalation, although children may be more tolerant of these cognitive side effects than adults.
Valproic acid	Epilepsy	Multiple mechanisms	Broad efficacy with limited sedation. Mild platelet dysfunction, nausea, weight gain, and tremor may occur. Hepatotoxicity pancreatitis and Stevens–Johnson occur more frequently than with most other anti-seizure medications. Check liver function prior to initiation. Avoid in patients with mitochondrial or liver disease.

Although this progressive dysfunction can rarely be slowed (with the possible exceptions of cerebrotendinous xanthomatosis (CTX) and X-ALD, as described in a separate consensus statement [6]) it can and should be addressed proactively.

In childhood, this dysfunction is often initially categorized as “developmental delay”, “learning disability”, or “intellectual disability”. Proactive management requires a multi-disciplinary needs assessment followed by implementation of an individualized educational plan, whose goal is to maximize developmental progress and quality of life. The physician's input is often required in order for educators and therapists to properly anticipate future needs as the disease progresses. For example, specifying the expectation of increasing (rather than static or decreasing) educational needs may help the parents and educational team consider the utility of more frequent educational needs reassessments. Similarly, framing the neurologic origins of behavioral problems (e.g. in the setting of frontal lobe pathology) can help therapists and teachers develop more specific management strategies that eliminate punitive behavioral modification methods.

In adult-onset leukodystrophies the dysfunction and decline commonly include signs and symptoms of dementia sometimes accompanied by co-morbid psychiatric features. Patients and families should be advised to seek professional advice on disability and financial planning in order to mitigate the social and fiscal challenges of future loss of employability. These are difficult conversations that should be conducted separately from the discussion of diagnosis and prognosis; they are best addressed in one or more subsequent clinic visits explicitly dedicated to this topic. Although the prognosis should be clearly outlined by a knowledgeable physician, a social worker is often best suited to connect the family with the most appropriate social services. A financial planner can advise on financial decisions. Advocacy groups can provide unique support for patients and families.

Lastly, it is also important to counsel families about the widely variable rate of neurological decline that can occur across the leukodystrophy spectrum and even within the same family or genotype. For example, the cognitive decline associated with the cerebral form of X-ALD or the lysosomal storage leukodystrophies are often rapid, but may show significant variability even within the same family. For most leukodystrophies, a later age of symptomatic onset often portends a slower rate of clinical progression as exemplified by the difference in survival among individuals with infantile versus adult-onset phenotypes of MLD [11].

6.3. Constipation

Impaired bowel motility is a common problem in both children and adults with neurologic impairment. This complication is an easily treated, but frequently overlooked, source of chronic pain that can seriously impair quality of life and lead to more serious secondary complications. Failure to stool for more than three days should be considered abnormal. Diagnosis is aided by the history, examination, and a plain abdominal X-ray. Treatment of acute constipation may require disimpaction in combination with oral and/or rectal medications. Treatment strategies for chronic constipation should begin with simple dietary changes, increased hydration, and supplemental dietary fiber, but also may require the use of stool softener (e.g. docusate) and/or laxatives (e.g. polyethylene glycol). The treatment regimen should be titrated to achieve one daily soft stool. Refractory cases should be managed by a gastroenterologist.

6.4. Dystonia

Dystonia is characterized by involuntary, sustained muscle contractions involving opposing muscle groups (e.g. flexors and extensors at a joint) manifesting as repetitive movements, torsion, or abnormal postures. Voluntary movements, emotions, and physical discomfort are common exacerbating features. Dystonia's most important secondary morbidities include orthopedic injury, functional motor limitations,

social stigma, and pain. Treatment goals for all dystonia therapies should involve alleviation of one or more of these symptoms.

The severity and extent of involvement should guide the dystonia treatment plan [12]. Dystonia may be focal, multifocal, segmental, or generalized, the latter of which is most common among leukodystrophy patients. Trihexyphenidyl or tetrabenazine may be effective in treating generalized dystonia. Unfortunately, these medications have a variety of limitations (Table 2), including a paucity of controlled trials and a narrow therapeutic window [12]. Baclofen may be useful when treating a combination of spasticity and dystonia. Deep brain stimulation therapy has not yet been described in leukodystrophy patients, but may be an option for carefully selected cases. For focal or segmental dystonia, botulinum toxin injections can be effective and carry a much lower risk of systemic toxicity.

6.5. Hearing and language impairment

Hearing impairment not only is common in the later stages of leukodystrophy progression, but also may be seen early in the course of disease in selected leukoencephalopathies. Loss of hearing has a dramatic impact on quality of life. Audiometric testing should be considered in any leukodystrophy patient who demonstrates impairment in communication. If a hearing impairment is confirmed, the patient should be referred for further evaluation by a speech pathologist who can provide caregiver education and assist in devising a communication plan. The evaluation should include a formal opinion on the suitability of an augmentative communication device.

6.6. Scoliosis and hip dislocation

Although scoliosis has not been systematically studied in leukodystrophy patients, experience suggests that it is relatively common, particularly among patients with advanced disease. Scoliosis among leukodystrophy patients may be progressive and can seriously impact health and quality of life, posing particular risks to pulmonary and cardiac function. Treatment goals should focus on the prevention of secondary medical morbidity. Scoliosis management guidelines for other neurodegenerative disorders recommend brief spinal exam by clinical observation at each clinic visit [13,14]. If scoliosis is suspected, anterior–posterior and lateral spine X-rays should be obtained, and the patient should be referred to an orthopedic surgeon. Various braces and external frames may be appropriate in milder cases. Spinal surgery is often considered if the curve exceeds a Cobb angle of 40° or 50°.

6.7. Seizures

Seizures are a frequent and disruptive symptom for many leukodystrophy patients, particularly in more advanced stages. In a few leukodystrophies, such as Alexander disease, seizures may be a presenting symptom. A standard approach that balances seizure reduction, safety, side effects, and quality of life is generally appropriate [15,16]. Polypharmacy can be minimized through efficient use of higher-dose monotherapy and by selecting medications capable of simultaneously treating seizures along with other comorbid symptoms (e.g. gabapentin for seizures and neuropathic pain). Goals of therapy should include prevention of seizure-related co-morbidities including trauma, encephalopathy, aspiration, and hospitalization. A formal written document addressing seizure care in the emergency room setting may be helpful to the patient and family in promoting safe and efficient treatment and in preventing unnecessary procedures.

6.8. Sialorrhea

Excessive oral secretions are a common problem in leukodystrophy patients, where it may result from injury to brain regions controlling

oropharyngeal strength or coordination. Nonetheless, non-neurologic etiologies should be carefully excluded before establishing a treatment plan. These etiologies include medication side effects, oropharyngeal injury or abscess, gastroesophageal reflux, and constipation. If no alternate cause is identified medical intervention should be considered in appropriate cases, with the goal of reducing aspiration risk and/or social stigma, and improving hygiene. Sublingual botox injection is a reasonable first-line treatment based on its efficacy and relatively safety, but requires an experienced practitioner. Oral anti-cholinergic therapies are modestly effective and can be gradually titrated but may be limited by a wide range of side effects. They should be avoided in patients with autonomic dysfunction, constipation, urinary retention, or cardiac dysfunction. When used, careful attention to dental hygiene and regular visits with a dental specialist should be considered. Evaluation by an otolaryngologist and/or speech pathologist can be helpful in complex cases [17].

6.9. Sleep disturbance

Sleep disorders are a frequent, but under-recognized cause of morbidity for neurologically impaired patients as well as their caregivers. A general diagnosis can often be made based on the clinical history, although a polysomnogram can provide a precise diagnosis and help stratify the many potential etiologies and thus help devise an appropriate treatment strategy. Etiologies include pain, behavioral disturbance, medication side effects, and obstructive airway disturbances, and organic brain dysfunction. Regardless of etiology, most sleep plans begin with behavioral and environmental modifications. Melatonin is a safe, well-tolerated, and moderately effective medication in this population that may also be considered as part of a first-line treatment regimen [18]. Sedative medications such as zolpidem and temazepam may also be effective at inducing and/or maintaining sleep but should be used judiciously due to the possibility of undesired effects, including exacerbation of daytime sleepiness, increased airway obstruction, and increased oral secretions.

6.10. Spasticity

Spasticity is clinically defined as velocity-dependent hypertonia that is usually accompanied by weakness and hyperreflexia. It occurs as the result of injury to the myelin and/or axons of the primary motor pathways (i.e. corticospinal tracts) of the central nervous system and is, therefore, one of the most common symptoms among leukodystrophy patients. Treatment is indicated if the spasticity causes significant pain or if it impairs functional activities such as ambulation or, in more severe cases, puts the patient at increased risk of joint dislocation. In milder cases, oral medications such as baclofen or diazepam in combination with physical therapy and daily stretching routines are usually sufficient steps in management. Intramuscular injections of botulinum toxin can be useful to target focal areas of spasticity that impedes functional tasks (e.g. gastrocnemius spasticity impairing ambulation). If these are not effective or oral medications are not tolerated, consideration should be given to surgical approaches such as intrathecal baclofen or selective dorsal rhizotomy. In more severe cases, surgical interventions to severe tendons or nerve pathways may be necessary to allow meaningful mobility or to prevent joint deformity, contractures and/or fractures.

6.11. Visual impairment

Among leukodystrophy patients, visual impairment typically results from injury to the cortical visual pathways, but retinal abnormalities, cataracts and glaucoma may occur with some disorders. Chronic corneal injury can occur among patients who are unable to close their eyes. Comprehensive care for the leukodystrophy patient should include regular evaluations by a qualified ophthalmologist. Awareness of the

problem is essential to maintaining appropriate educational and communication strategies. Services for the visually impaired are available in most communities.

7. Many serious medical complications are potentially preventable

In addition to the diagnosis and treatment of some of the “inevitable” symptoms associated with leukodystrophy progression, we have outlined a subset of medical conditions that are both serious and potentially amenable to preventive strategies. The conditions, risk factors, and suggested strategies are described below and summarized in Table 3. Although the guidelines below are drawn from the collective experience of leukodystrophy experts, future research is essential to further refine our ability to predict and prevent these complications.

7.1. Anxiety/depression

Mood disorders are well-established co-morbidities of chronic illness, particularly among neurologic disorders [19,20]. Psychiatric disturbances are characteristic features of several leukodystrophies, particularly during adult onset (e.g. hereditary diffuse leukoencephalopathy with axonal spheroids, MLD [21]), but are probably also under-recognized as comorbid features among the larger leukodystrophy populations. Important risk factors that should prompt further evaluation include social isolation, loss of communication, chronic pain, sleep deprivation, and hopelessness. To the extent that these factors can be addressed through social (e.g. increased peer or caregiver interaction), technologic (e.g. augmentative communication devices), or pharmacologic (e.g. sertraline) modifications, these disorders are theoretically preventable. If and when a mood disorder is diagnosed, effective treatment strategies do exist and are outlined in clinical guidelines for other degenerative disorders (e.g. multiple sclerosis) that may be applicable to leukodystrophy patients [22]. Potential risks of pharmacologic treatment in leukodystrophy patients include sedation, insomnia, and mania; close observation for these symptoms is warranted.

7.2. Chronic pain

Pain severely impairs quality of life. Extrapolation from experience as well as the cerebral palsy literature suggests that chronic pain is probably under-recognized among leukodystrophy patients and may develop through a wide range of etiologies, many of which are readily treatable [23]. Critical diagnoses that should not be missed include (but are not limited to) joint dislocation, spasticity, bone fractures, constipation, bowel obstruction, appendicitis, gastroesophageal reflux, and dental injury. Patients with impaired communication may be at particularly high risk for under-diagnosis and may require a particularly meticulous approach to diagnosis and treatment. Although challenging, every effort should be made to recognize pain and to work rigorously to determine its etiology before resigning the patient to a course of non-specific analgesic management. Primary neurogenic irritability is a cardinal feature among a small subset of leukodystrophies, most notably Krabbe disease and Aicardi–Goutières syndrome and may respond to benzodiazepines.

7.3. Iatrogenic sedation/polypharmacy

Sedation is a common side effect of psychoactive medications. It can lead to increased risk of aspiration and other adverse events and should thus be carefully monitored as medications are increased in response to symptoms. It is difficult to avoid polypharmacy in medically complex patients, however, a regular review of medications can be used to reconsider each medication necessity and dose, thereby preventing adverse effects. Hamdy et al. [24] have proposed the following five questions aimed at simplifying medication regimens:

Table 3
Serious and potentially preventable medical complications that may occur in leukodystrophy patients.

Complication	Risk factors	Prevention/treatment strategies	Comments
Anxiety/ depression	Impaired communication; pain; witness to more advanced disease states in similarly affected siblings	Treatment guidelines for other neurodegenerative disorders do exist [24] and include both behavioral and pharmacologic interventions.	Consider unrecognized pain syndrome and/or painful medical complication. Consider consulting a psychologist and/or a psychiatrist. Augmentative communication strategies may be beneficial.
Chronic pain	Impaired communication; peripheral neuropathy; decreased mobility	Prevention may include augmentative communication strategies. MD and caregiver must be vigilant for early signs of pain and distress.	Essential to rule-out unrecognized medical complications including: constipation, hip fracture, GI reflux, neuropathy, headache, urinary retention, and dental pain.
Iatrogenic sedation/polypharmacy	Polypharmacy; multi-organ dysfunction	Regularly reassess the need for pharmacologic therapy; see guidelines from Hamdy et al. [24].	Sedation may be an acceptable side effect in some circumstances (e.g. chronic anxiety). Consider possibility of other causes of encephalopathy (e.g. UTI).
Joint dislocation/fracture	Spasticity; seizures; prior occurrence of dislocation/fracture	Maintain adequate control of nutrition, seizures, and spasticity. If diagnosed, consider evaluation for osteoporosis, nutritional deficiency, and endocrine dysfunction.	Consider diagnosis in settings of severe pain. The possibility of abuse should not be overlooked.
Malnutrition	Impaired speech, swallow, and/or inability to self-feed	Feeding and nutritional needs should be evaluated by a GI and/or a nutritional consultant.	Feeding difficulties can be an under-recognized burden for families. Associated aspiration events are a major cause of morbidity.
Pneumonia – community acquired	Severe weakness; respiratory impairment; bed-bound	Hand-washing; influenza and pneumococcal vaccination; avoidance of sick contacts.	Severe or prolonged illness can result in permanent loss of neurological skills in some patients.
Pneumonia – aspiration acquired	Oropharyngeal weakness and/or incoordination	Caregivers and MDs must be vigilant. Refer to a GI or a pulmonary specialist at the earliest sign of dysfunction. G-tube/PEG-tube +/- fundoplication can reduce aspiration risk; radiologic swallow studies help triage appropriate candidates.	Aspiration may be silent, yet it is a major cause of morbidity/mortality. Early signs of oromotor dysfunction include altered speech, impaired cough/gag/feeding, and/or reduced clearance of oral secretions.
Pressure sores/wound infection	Severe weakness; sensory impairment/neuropathy; communication impairment	Frequent position changes and daily skin surveys should be considered for severely weak/dependent patients.	A serious but easily preventable complication; its occurrence should raise concern for the possibility of caregiver neglect. Caregiver depression and fatigue should also be considered.
Urinary tract infection	Female gender; infrequent diaper changes; urodynamic dysfunction	Strategies vary depending on etiology. Recommend urology consultation after 1st UTI in males or 2nd UTI in females. Urodynamic studies as needed.	Symptoms are protean and may include altered mental status and irritability; fever may be absent. Urine obtained via catheter can ensure accurate diagnosis.

1. Is the indication for which the medication was originally prescribed still present?
2. Are there duplications in drug therapy (e.g. the same class) that might allow a simpler regimen?
3. Does the regimen include drugs prescribed for an adverse reaction? Can the drug be withdrawn?
4. Is the present dosage likely to be subtherapeutic or toxic due to the patients' comorbidities (e.g. renal function)?
5. Are any significant drug–drug or drug–illness interactions present?

7.4. Joint dislocation and fracture

At least anecdotally, dislocations of the hip and other joints are common among leukodystrophy patients, occurring as a result of hypotonia, spasticity, seizures, and/or bone demineralization. The decision for surgical reduction or repair may not always be indicated (e.g. radial head dislocation), but should be individualized based on associated pain, prognosis, and risk/benefits of surgery. Although treatable, dislocation and fracture are also potentially preventable to the extent that their predisposing conditions are also amenable to treatment. Proactive management of spasticity and dystonia may help prevent subluxation and dislocation. Calcium and vitamin D supplements can help preserve bone mineralization. Some leukodystrophies result in ovarian failure or hypogonadotropic hypogonadism (e.g. vanishing white matter disease, AARS2-related disorder and Pol-III related leukodystrophy), which may result in an increased risk of osteoporosis. The use of hormonal therapy should be considered on a case by case basis.

7.5. Malnutrition/dehydration

Chronic malnutrition can have wide ranging adverse effects on growth, brain development, and immune function. Patients at highest risk include those with impaired communication, impaired mobility, and/or dysphagia [25]. An anticipatory consultation with a nutritionist or a gastroenterologist should be considered in all patients with one or more of these risk factors. In all patients, growth parameters should be used in conjunction with history and exam findings to monitor and promptly address early signs of malnutrition. Acute and anticipatory interventions are similar and include dietary modification, supplementation, and feeding tube placement. Any discussion to install a feeding tube must include a discussion of the patient and family's end of life wishes and long term care goals.

7.6. Pneumonia and respiratory insufficiency

Respiratory complications are the most frequent cause of serious comorbidity and death among individuals with neurodegenerative disorders [26,27]. Among leukodystrophy patients, aspiration pneumonia and community-acquired pneumonia are both theoretically amenable to preventive strategies.

Dysphagia, resulting from weakness, incoordination or both, is the most important risk factor for aspiration pneumonia [28]. A swallowing assessment by an occupational or speech therapist, combined with a radiologic swallowing study (e.g. barium swallow), is the most appropriate evaluation for evaluating aspiration risk. These studies should be considered in all patients with clinical signs of oropharyngeal weakness, incoordination, or sialorrhea or in those who have a clinical history of pneumonia or coughing during meals. If negative, the study may need to be repeated at a future date if neurologic symptoms progress or if new symptoms appear. If aspiration is identified, common preventive strategies include thickened oral feeds and/or placement of a permanent feeding tube.

Even in the absence of aspiration pneumonia, many leukodystrophy patients eventually develop motor weakness and impaired physical mobility that leave them at increased risk of serious morbidity in the setting of community-acquired pneumonia. Preventive strategies should

include avoidance of sick contacts, caregiver hand washing, and annual influenza vaccinations.

Primary respiratory failure may also occur in the late stages of some leukodystrophies, particularly those with peripheral nerve dysfunction (e.g. infantile MLD). Mechanical ventilation strategies can prolong life, however, as opposed to other neurodegenerative conditions (e.g. amyotrophic lateral sclerosis; Duchenne's muscular dystrophy) the arrival of primary respiratory failure in leukodystrophy patients almost always occurs in the setting of severe cognitive impairment such that the ability to ensure a meaningful quality of life on mechanical ventilation is uncertain. Anticipatory discussions of mechanical ventilation (i.e. before the acute need arises) should be the goal.

7.7. Pressure sores and wound infections

Skin infections can result in serious morbidity yet they are readily amenable to prevention strategies. Patients at highest risk include those who are bed-bound with severe weakness, those wearing orthotics or similar hardware, and those with peripheral neuropathies that can dull sensation. Daily skin surveys by the primary caregiver are a simple and practical means of prevention. Red or indurated skin may be a sign of an emerging skin abrasion and should prompt an immediate change in hardware, bed care, or behavioral strategies.

7.8. Urinary tract infections

Injury to the central nervous system can disrupt the pathways that control bladder function, increasing the risk of urinary tract infections (UTIs) [29]. UTIs are a famously protean "forme fruste" of symptomatic exacerbation in a broad range of neurologic disorders [27]. For this reason, the possibility of a UTI could be reasonably considered as a cause of any acute exacerbation of neurologic symptoms (e.g. seizures, irritability). Evaluation should include a urinalysis with and urine culture, where isolation of more than 100,000 colonies per milliliter is a reasonable threshold to rule-in clinically significant bacteriuria [30]. Preventive strategies for UTIs do exist; we suggest consultation with a urologist for female patients with two or more UTIs annually and male patients with one or more UTIs. The decision to initiate a prophylactic anti-microbial agent should be performed on an individual basis under the guidance of a urologist or an infectious disease specialist. Nephrolithiasis may occur in association with some anticonvulsants and should be considered in patients with persistent urinary symptoms.

8. The health of the patient and that of the family are intertwined

An accumulating body of evidence suggests that clinical outcomes of children with chronic illnesses are closely intertwined with the family's psychosocial dynamics [31–33]. Unfortunately, the psychosocial aspects of care are not well addressed in current health care models. The available data suggests that we ignore these psychosocial aspects of care at the peril of patients and their families. In Table 4, we have summarized some of the key psychosocial complications and suggested management strategies.

8.1. Patient health impacts family health

Chronic diseases extract a heavy psychosocial, emotional, and economic toll on the caregiving family. The role of primary caregiver is uniquely stressful and is associated with a daunting list of adverse health risks for the caregiver, including a lower quality of life [34], higher risk of depression [35], and higher overall mortality [36–38]. In light of this, caregivers must make a special effort to maintain their own physical, social, and emotional health in order to ensure the health of the affected individual. Respite care, family support, and sustained social connectivity are all essential in this regard. Patient advocacy groups (see Supplemental Table 1) can connect caregivers to similarly affected

Table 4
Common psychosocial complications and suggested treatment and prevention strategies for families affected by leukodystrophies. Leukodystrophy patients are often completely dependent on the health and function of the primary caregiver and/or family unit; yet these complications are often overlooked.

Complication	Signs and symptoms	Treatment and prevention strategies	Comments
Parental guilt	Parental depression, anger, marital stress	Open discussion and genetic counseling should be aspects of care for all leukodystrophy patients; referral to psychotherapy should be considered where appropriate. Referral to family/couple counseling. Referral to support groups (see Supplemental materials).	Can have myriad effects on parents' mental health, family dynamics, and, subsequently, optimal care delivery. The transition to a single parent home places the family at a resource disadvantage in caring for a medically complex child.
Parental relationship stress and divorce	Family tension/anger at visit		
Caregiver fatigue, depression, illness	Missed/canceled appointments; poor care of patient; disheveled/exhausted appearance of caregiver	Referral to psychotherapy and/or family counseling. Referral to support groups (see Supplemental materials). Respite care.	Medical and psychiatric illnesses affecting the caregiver will have a direct effect on patient care as well as MD–family relationship. Single-parent givers are at high risk. Probably an under-recognized problem.
Sibling neglect	Sibling depression, withdrawal, acting-out, attention seeking behavior	Recognition of problem. Referral to family therapy as needed.	
Financial hardship	Missed/canceled appointments	Minimize burden by streamlining care and procedures (see Table 3). Referral to medical social worker.	Medical social workers are best equipped to help.
Administration of unwanted medical care	Incomplete physician–family communication; cultural barriers; language barriers; unconscious avoidance of challenging conversations	Clear communication between patients, caregivers, and MDs is the essential ingredient for preventing this common complication. Establish goals of care with family early in the course and after disclosure of the prognosis. Revisit goals of care at least annually. Encourage advance directives. Include family/patient values and priorities in care decisions.	Perhaps the most easily preventable complication, yet easily overlooked.
Medical exhaustion, therapeutic burden	Multi-organ dysfunction; multiple medical providers; polypharmacy; incomplete physician–family communication	MD visits: strong care coordination is essential. Consolidate and coordinate appointments around a single 1–2 day period to save the patient and family valuable time, money, and missed work/school. “complex care clinics” or “leukodystrophy clinics” are designed to address these problems; consider referral where available. Med/therapy: annually review the medical necessity and frequency of appointments and interventions.	Medical social workers are well equipped to assess these needs; they are an essential part of high quality, efficient, patient-centered care delivery for complex patients.

families. Caregivers routinely describe these connections as unique and meaningful, enabling the exchange of practical advice and emotional support.

Beyond the primary caregiver, other family members may also be adversely affected. Crucial family dynamics are disrupted by the consumption of caregiver time and attention in caring for the affected child. This can increase the risk for mood and behavior disturbances in healthy siblings [39] and may increase the divorce rates among parents [40,41]. Hence, it is important to emphasize the need for parents to maintain healthy relationships with their unaffected children as well as with their spouse. An experienced family therapist may be able to offer help in this regard.

The heritable nature of leukodystrophies carries major implications for family members. The discovery of a heritable condition commonly arouses feelings of guilt, shame, blame, and anger among those who carry the “responsible” genetic variants. A skilled genetic counselor is essential in addressing the genetic implications, the need for additional family screening, and grief counseling.

The financial cost of chronic illness can be substantial and often takes a heavy toll on the affected family and caregiver. Unfortunately, the financial hardship associated with chronic illness is often overlooked by both health providers and policy makers [42]. The input of a social worker and financial planner may be helpful in addressing these stressors.

8.2. Family health impacts patient health

As discussed above, the health of the patient impacts the health of the family; however, the reverse is also true. Nowhere is the impact of a patient's psychosocial environment more pronounced than among fully dependent patients who require the attention of a full-time caregiver. Among chronic childhood diseases such as leukodystrophies,

this intensive role is typically filled by a parent. Indeed, a parent who is caring for a chronically ill child may still face health concerns of their own. This may affect the ability of the parent to care for the child which in turn will affect the health of the child. Difficulties may include, transportation to medical appointments, potential passing of communicable diseases, and lack of attention to or awareness of new or concerning symptoms.

8.3. New care strategies are needed to address psychosocial aspects of care

Multi-disciplinary care teams are frequently employed to address the multi-faceted needs of patients with complex illnesses and, indeed, many studies suggest that these teams offer a measurable benefit [43,44]. These teams, however, are resource intensive and may not be widely available – or reimbursed by insurance carriers. Future research should focus on precisely how these teams improve outcomes and whether such improved outcomes can be delivered more efficiently. Despite these gaps in knowledge, the available data clearly suggest that a truly comprehensive care strategy for leukodystrophy patients must include careful attention to the patient's psychosocial context.

9. Systematic research is essential to improve care strategies

Due to a lack of leukodystrophy-specific clinical research, the consensus guidelines outlined in this report are extrapolated primarily from the expert opinion of leukodystrophy experts as well as the clinical study of other chronic neurological disorders. There is a pressing need for research to identify optimal care strategies for leukodystrophy patients.

A few recent publications offer some clues as to where these efforts might begin. Leukodystrophies include both “high cost” and “low cost” disease types, with very different rates of hospitalization [45]. High

cost patients have higher infection rates and more frequent intensive care unit admissions. These findings suggest that strategies to address infection rates and admissions could significantly impact and improve care for leukodystrophy patients. Further, hospital admissions and the cost of care for leukodystrophy patients have a 5-fold variation across children's hospitals [46]. The wide variation in admissions and costs suggests that essentially the same level of care is being provided with different efficiencies at different hospitals.

Ultimately, the best approaches and care models must be identified and shared to benefit patients and their families. This will require improved knowledge of natural history, well-defined clinical outcome metrics, and broad collaboration between institutions, patients, and patient advocacy groups.

9.1. The role of patients and patient advocacy groups

Patient advocacy groups have long played a central role in the dissemination of knowledge, comfort, and support and offer an essential venue for sharing first-hand experience about disease progression, treatment, and optimizing quality of life (see Supplemental Table 1). In recent years, patients and their advocates have played an increasing role in identifying, prioritizing, and validating the most valuable clinical outcomes, such as perceived quality of life. The recent emergence of patient social networks (e.g. patientslikeme.com; crohnology.org) is offering patients powerful new platforms for a wide range of patient-generated data and initiatives. Although promising, there are inevitable challenges ahead for these networks as they continue to resolve the thorny issues of privacy, data ownership, and conflicts of interest. Whether this emerging paradigm will amount to a patient-powered revolution in rapid healthcare advances or a more modest tweak to current protocols still remains to be seen, but there is reason to hope for great things ahead.

9.2. The role of clinical investigators

Judging from the paucity of evidence and the wealth of outstanding questions surrounding routine leukodystrophy care, it seems clear that the bulk of the work for investigators still lies ahead. The consensus guidelines outlined here are primarily intended to help guide and standardize leukodystrophy care. However, these guidelines should also serve as a blueprint for identifying gaps in our current clinical care strategies as we push for broader advances in the current standard of care. Meanwhile, leukodystrophy patients are poised as never before to help us effectively prioritize clinical goals and speed us along in achieving them.

10. Conclusion: all leukodystrophies are treatable

Although incurable, leukodystrophies are uniformly treatable conditions. The first step in management typically involves identifying and prioritizing a complex array of symptoms. The treatment goals should be designed to enhance both quality and duration of life. This can be accomplished through judicious use of acute, chronic, and preventive care strategies combined with close, multi-disciplinary attention to the practical and personal challenges faced by patients, caregivers, and families. In order to successfully improve and prolong the life of leukodystrophy patients, future research must engage patients, families, investigators, and patient advocates in defining, prioritizing, and advancing clinical care strategies.

Conflicts of interest

KV, JLB, GB, AP, JLP, AV, and MCP are all members of GLIA and, as such, participate in clinical and research programs dedicated to the care of leukodystrophy patients. DS is a member of GLIA and is the President and Chair of the Board at the MLD Foundation. DH is a

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Authorship and contributions

KVH, JLB, GB, GH, DS, MCP and AV wrote the manuscript. KVH, JLB, GB, AP, DS, MCP, JLP, and AV contributed to the consensus building process. KVH, JLB, GB, AV, and MCP provided expert consultation. DS represented the voice of patient advocacy groups in this consensus process. KVH, GH, and AV provided critical review and coordinated the manuscript.

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