

Practical Approaches and Knowledge Gaps in the Care for Children With Leukodystrophies

Journal of Child Neurology

2021, Vol. 36(1) 65-78

© The Author(s) 2020



Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/0883073820946154

journals.sagepub.com/home/jcn



Stephanie R. Keller, MD¹, Eric J. Mallack, MD² , Jennifer P. Rubin, MD³, Jennifer A. Accardo, MD, MSCE⁴, Jennifer A. Brault, MD⁵, Camille S. Corre, BS⁶, Camila Elizondo, MSN, RN⁷, Jennifer Garafola, MSN, RN⁵, April C. Jackson-Garcia, BA⁸, Jullie Rhee, MSN, RN⁹, Elisa Seeger, BS⁸, Kaprice C. Shullanberger, BESS⁸, Amanda Tourjee, MSN, RN⁶, Melissa K. Trovato, MD¹⁰, Amy T. Waldman, MD, MSCE¹¹, Jenna L. Wallace, BS⁸, Michael R. Wallace, BBA⁸, Klaus Werner, MD, PhD¹², Angela White, MSN, RN⁵, Kevin C. Ess, MD, PhD⁵, Catherine Becker, MSN, RN⁶, and Florian S. Eichler, MD⁶

Abstract

Leukodystrophies are a group of neurodegenerative genetic disorders that affect approximately 1 in 7500 individuals. Despite therapeutic progress in individual leukodystrophies, guidelines in neurologic care are sparse and consensus among physicians and caregivers remains a challenge. At patient advocacy meetings hosted by Hunter's Hope from 2016-2018, multidisciplinary experts and caregivers met to conduct a literature review, identify knowledge gaps and summarize best practices regarding neurologic care. Stages of severity in leukodystrophies guided recommendations to address different levels of need based on a newly defined system of disease severity. Four core neurologic domains prioritized by families were identified and became the focus of this guideline: sleep, pain, seizures/epilepsy, and language/cognition. Based on clinical severity, the following categories were used: presymptomatic, early symptomatic, intermediate symptomatic, and advanced symptomatic. Across the leukodystrophies, neurologic care should be tailored to stages of severity while accounting for unique aspects of every disease and multiple knowledge gaps present. Standardized tools and surveys can help guide treatment but should not overburden families.

Keywords

leukodystrophy, cognition, disability, genetics, pediatric, rehabilitation, seizures, sleep, spasticity

Received September 7, 2018. Received revised May 16, 2020. Accepted for publication June 3, 2020.

¹ Department of Pediatrics, Division of Pediatric Neurology, Emory University/Children's Healthcare of Atlanta, Atlanta, GA, USA

² Department of Pediatrics, Division of Child Neurology, Weill Cornell Medical College/New York-Presbyterian Hospital, New York, NY, USA

³ Department of Pediatric Neurology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

⁴ Department of Neurology, Children's Hospital of Richmond at VCU, Richmond, VA, USA

⁵ Department of Pediatrics, Division of Pediatric Neurology Vanderbilt University Medical Center, Nashville, TN, USA

⁶ Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

⁷ East Boston Neighborhood Health Center, East Boston, MA, USA

⁸ Hunter's Hope Foundation, Orchard Park, NY, USA

⁹ Children's National Health Systems, Washington, DC, USA

¹⁰ Department of Physical Medicine and Rehabilitation, Kennedy Krieger Institute and Johns Hopkins University, Baltimore, MD, USA

¹¹ Division of Neurology, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA

¹² Department of Pediatrics, Duke University, Durham, NC, USA

Corresponding Author:

Florian S. Eichler, MD, Department of Neurology, Massachusetts General Hospital, 175 Cambridge Street, Suite 340, Boston, MA 02114, USA.

Email: feichler@partners.org

Leukodystrophies are a heterogeneous group of genetic disorders that affect the white matter of the central nervous system with or without peripheral nervous system involvement. This does not include acquired central nervous system myelin disorders, such as multiple sclerosis and related acquired central nervous system demyelinating processes.¹ In 2015, Vanderver et al¹ classified more than 30 diseases as leukodystrophies and more than 61 as genetic leukoencephalopathies. This operational definition was used:

Leukodystrophies are heritable disorders affecting the white matter of the central nervous system with or without peripheral nervous system involvement. These disorders have in common glial cell or myelin sheath abnormalities. Where known, neuropathology is primarily characterized by the involvement of oligodendrocytes, astrocytes and other non-neuronal cell types, although in many disorders the mechanism of disease remains unknown, and in other cases is suspected to include significant axonal pathology.”¹

Approximately 1 in 7500 individuals²⁻⁴ are affected with leukodystrophies, many of which are neurodegenerative. While there are many differences between individual leukodystrophies, there are core commonalities in the neurologic care required for children affected by these diseases. A focus on these neurologic symptoms may improve quality of life and help direct future research for children and families living with a leukodystrophy.

A knowledgeable medical team can proactively anticipate potential complications, limit such complications when possible, and provide families with appropriate anticipatory guidance. Medical providers should partner with families as soon as feasible to provide family- and patient-centered care. While caring for a child with a leukodystrophy, one is challenged by the lack of scientific evidence available to guide clinical care for these complicated diseases. Preventative and symptomatic care guidelines for patients with leukodystrophies were first published in 2015 as an effort from the Global Leukodystrophy Initiative (GLIA) Consortium, and an updated consensus statement was published in 2018.^{5,6} The intent of the current guidelines are to focus more specifically on neurologic symptom management in leukodystrophies in relation to the stage of disease. We brought together a team of multidisciplinary experts and caregivers in the USA to identify best practices but also knowledge gaps that need to be addressed by future studies.

Methods

Hunters Hope (<https://www.huntershope.org/>) is a patient advocacy group representing families of various leukodystrophies. In partnership with other organizations, they created the Leukodystrophy Care Network. Part of the organization's goals were to link Leukodystrophy Centers across the USA and encourage the development of care guidelines for these centers but also serve as a reference for other medical practitioners caring for patients with leukodystrophies. At the 2016, 2017, and 2018 Hunter's Hope Annual Meetings, a group of 10-15 interdisciplinary care providers and 5 family advocates with personal experience in the leukodystrophies met. The medical providers involved were all members of leukodystrophy-focused programs at

major hospitals throughout the United States. The family advocates represented children with X-linked adrenoleukodystrophy (X-ALD), Krabbe disease, and metachromatic leukodystrophy. The group collaborated to focus on neurologic care to create the guidelines presented here. Patient/family surveys established a list of clinical symptoms of concern and from among these, chose 4 core neurologic symptoms of highest priority: sleep, pain, seizures/epilepsy, and language/cognition. We further defined stages of severity in leukodystrophies to guide appropriate recommendations at different levels of need and to find commonalities among a variety of genetic conditions.

The recommendations discussed in this section are based on established guidelines, a systematic literature review, and multidisciplinary expert and caretaker opinions. Our literature review was conducted using both PubMed and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), with search terms specific to each symptom category, as outlined below. Shortcomings and gaps in the literature were summarized (Table 1). No specific date range exclusions were used in our search, but the majority of our references were within the last 20 years, with the oldest article being from 1979.

For sleep symptoms, we used the key terms *leukodystrophy* and *sleep*, followed by *sleep* along with the individual names of more common leukodystrophies (X-linked adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe, Pelizaeus-Merzbacher disease, and Alexander disease). Many of the resulting articles focused on adult-onset leukodystrophies, but were included because of the lack of literature specific to pediatric populations.

For symptoms related to pain, we used the key terms *pain*, *assessment*, *pharmacological*, *nonpharmacological*, *interventions*, *management*, *chronic medical illness*, *cognitive/neurologic impairment*, *leukodystrophy*, *spasticity*, *gabapentin*, and *palliative care*.

For seizures/epilepsy in the leukodystrophies, we individually combined the search term *seizures* along with the individual names of more common leukodystrophies (X-linked adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe, Pelizaeus-Merzbacher disease, and Alexander disease).

For cognition and language impairment in the leukodystrophies, we used the key terms *leukodystrophy*, *cognition*, *language*, *neuropsychological evaluation*, and *development*. Most of the available literature reviewed for cognition and language impairment involved children with metachromatic leukodystrophy and X-linked adrenoleukodystrophy.

Recommendations based only on the personal experience of leukodystrophy family members have been included in some areas and are identified as such when they occur and are summarized in Table 2. Best practices were arrived at through multidisciplinary expert opinion and iterative group discussions. Where leukodystrophy-specific literature was lacking, published data from other neurologic diseases with similar symptomatology was adopted. This again prompted addition of items to a table on knowledge gaps in the field (Table 1). Before finalizing our guidelines, we presented our findings to a group of parents, caregivers, and other leukodystrophy medical providers, who reviewed our recommendations and added specific experiences and context.

Multidisciplinary Team

Children living with a leukodystrophy often have marked medical needs that require a multidisciplinary team. Multidisciplinary care is considered to be the gold standard model

Table 1. Summary of Knowledge Gaps for Neurologic Care in the Leukodystrophies Knowledge Gaps in Neurologic Care for the Leukodystrophies.

Lack of systematic research on treatment of neurologic symptoms
Potential floor effects of screening and assessment tools
Lack of literature specific to pediatric leukodystrophies
Relative lack of literature on leukodystrophy-specific symptomatology
Lack of data on multidisciplinary care in the leukodystrophies
Lack of data on reliability of proposed tools in this population

of care for many neuromuscular and neurodegenerative diseases such as Duchenne muscular dystrophy (DMD) and amyotrophic lateral sclerosis (ALS), particularly those that are progressive and profoundly debilitating.⁷⁻¹¹ Studies have shown that both quality of life and survival are better for these patients treated in multidisciplinary clinics than in isolated clinics. Because of the rare nature of these diseases, children usually do not have a leukodystrophy expert close to home. As a result, many children either have no leukodystrophy experts on their medical team or have to travel great distances to an academic medical center that house specialty clinics, for example. This is all in addition to their local team of medical providers. Children who require daily nursing, therapies, and accommodations in school have additional needs with further layers of providers and caregivers.

In order to enhance patient quality of life for as long as possible, we are recommending an early referral to a palliative care specialist, and in cases where one is not readily accessible, we advocate for clinical practice which is informed by principles of palliative care.¹² Palliative care is not only helpful for end-of-life care, but can also help facilitate discussions about medical issues and the goals of care, as well as support families. As parents and guardians are the chief sources of care on an everyday basis, we emphasize the importance of soliciting their understanding of symptomatic priorities in their child's health.¹² Similarly, we recommend close collaboration between Leukodystrophy Care Network-associated providers, who have specific expertise in the leukodystrophies, and a child's local primary medical providers, who are generally most knowledgeable about a child's overall health. Combining the individual strengths and expertise of parents/guardians, local medical providers, and Leukodystrophy Care Network center team members helps bring palliative care principles to the long-term management of children with a leukodystrophy.

Stages of Leukodystrophies

For the purpose of these guidelines, we defined leukodystrophies with 4 stages of disease progression, rather than by their individual phenotypes. Based on clinical severity, we use the following categories: presymptomatic, early symptomatic, intermediate symptomatic, and advanced symptomatic. Inspired by similar models used in muscular dystrophy to separate guidelines by stages of mobility, we recognize that

symptoms will vary in age of onset across leukodystrophies but recommendations can be generalized for shared symptoms at the different severity stages of disease.¹³ In this model, presymptomatic includes children who have a genetically confirmed leukodystrophy but currently no symptoms. Early symptomatic refers to children with mild neurologic symptoms that do not interfere with any activities of daily living (eg, bathing, dressing, feeding, toileting) for his or her developmental age. Intermediate symptomatic indicates children with neurologic symptom(s) impacting at least 1 activity of daily living. Finally, advanced symptomatic describes children with neurologic symptoms that severely impact almost all activities of daily living, making a child dependent on others for care far beyond what would be expected for his or her developmental age. It should be noted that not all leukodystrophies will progress through all stages. For example, children with early onset forms of Aicardi Goutières or Pelizaeus-Merzbacher disease may not have a presymptomatic stage,¹⁴ whereas children with Megalencephalic Leukodystrophy with subcortical cysts improving type (MLC2B) do not progress to the advanced symptomatic stage.¹⁵ In the sections below, we discuss appropriate symptom-specific methods of screening, assessment, and treatment for our 4 neurologic symptom domains: sleep, pain, seizures/epilepsy, and language/cognition.

Sleep

The neurobiology of sleep is a complex interplay between neurochemical systems responsible for wakefulness, as well as the hypothalamic regions responsible for rapid eye movement (REM), non-rapid eye movement (NREM) sleep, and maintenance of overall sleep architecture.¹⁶ These systems are further modulated by behavior and by comorbid medical conditions.¹⁶ Sleep pathology is common in pediatric disorders. Although the exact incidence of sleep disorders in children with a leukodystrophy is not known, clinical experience and parental reports suggest that it is quite high. Recommendations for screening, assessment, and management of sleep disturbances are listed in Table 3.

The available literature suggests that leukodystrophies disrupt many of the neurobiological mechanisms involved in sleep.^{20,23,28,29} Damage to fibers in the white matter of the brain stem from the subceruleus nucleus in the dorsal pontine tegmentum or adjacent structures including the ventrolateral periaqueductal gray, preceruleus, locus ceruleus, pedunculo-pontine nucleus, and laterodorsal tegmental nucleus may lead to REM sleep behavior disorders, as seen in adult-onset autosomal dominant leukodystrophy.²⁸ Additionally, adults and children with blindness and/or vocal cord/upper respiratory compromise secondary to a leukodystrophy have been diagnosed with comorbid sleep disorders.^{20,22,29,30} Comorbid manifestations such as seizures and muscle spasms are also common among the leukodystrophies,⁶ and may secondarily impact sleep quality.

Table 2. Summary of Leukodystrophy Patient Caregiver Recommendations for Nonpharmacologic Sleep and Pain Management.^a

Pain management	
Rocking, repositioning, music, lighting, warm water, and vibration can all be helpful particularly for children with spasticity and in the intermediate and advanced stages of the disease.	
Aquatherapy provides the opportunity for a child in an advanced symptomatic stage to be temporarily free of constant support—whether from wheelchair positioning or being held—and experience the freedom of motion in the water.	
Pain from feeding intolerance and constipation may be alleviated by adjusting a child's feeding schedule, venting gastrostomy tubes, or through enemas or light abdominal massage.	
Monitor discomfort by tracking vital signs, such as with a home pulse oximeter device	
Sleep	
Weighted blankets and the use of aromatherapy pillows to position small children in bed.	
Memory foam mattress topper to be used as an easily portable and adaptable support to prevent pressure sores and maintain comfortable positioning while away from home	

^aThese recommendations have not been scientifically validated.

Screening: Sleep Habits Questionnaire

Poor sleep is associated with increased complaints of pain, anxiety, inattention, and overall poor quality of life in the general population.³¹⁻³⁴ Lack of sleep is particularly detrimental for children with epilepsy, as it lowers a child's seizure threshold.^{33,35} Therefore, it is prudent for clinicians to screen children with advanced brain diseases, such as those affected by a leukodystrophy, for sleep quality at every neurologic visit. Regardless of disease stage, all children can be screened using the Children's Sleep Habits Questionnaire (CSHQ).¹⁷ This tool can be helpful in assessing frequency of behaviors associated with sleep disturbances. Polysomnography remains the gold standard for the diagnosis of sleep disorders.¹⁸

Assessment: Common Etiologies of Sleep Disturbance, Evaluative Tools

In children with an asymptomatic leukodystrophy, sleep disturbance is not an expected symptom. These children should still be evaluated for sleep difficulties seen in children of their developmental age: restless leg syndrome, sleep apnea, and environmental factors affecting sleep hygiene.^{18,19}

In symptomatic patients, special attention should be paid to contributing medical factors such as gastrointestinal dysmotility, pain, spasticity, and dysautonomia. Environmental factors such as nighttime nursing care, feedings, suctioning, and medications are other possible factors contributing to sleep disturbance.

Patients with vocal cord dysfunction, upper respiratory compromise, or gastroesophageal reflux have been described as having specific sleep disturbances.^{22,29,30} These patients, along with those experiencing symptoms of nighttime choking and

coughing, should be assessed for sleep apnea. Referral to a sleep specialist for evaluation and sleep study is warranted. Similarly, children with known blindness should be evaluated for circadian rhythm disorders. Such disorders, defined by the inability to maintain normal periods of sleep and wakefulness, are most commonly due to blindness secondary to the disease process.²⁰

In patients with central nervous system pathology, myoclonic jerks, which are nonepileptic and part of the normal movements of sleep, can be exaggerated.³⁶ Such jerks can wake the patient from sleep,²¹ resulting in excessive daytime sleepiness. These jerks, especially if worsening, should be evaluated for an epileptic etiology using electroencephalography (EEG).

There are important consequences of sleep disruption. As mentioned above, lack of sleep is particularly detrimental for children with epilepsy because of its effect on seizure threshold. Aside from seizure activity, sleep disruption also has the potential to adversely affect pain, spasticity, and cognition, all of which should be considered when assessing sleep quality.³⁷⁻³⁹

In consideration and evaluation of the above-mentioned common etiologies of sleep disturbance in the leukodystrophies, we recommend a tailored approach involving the use of sleep diaries to identify patterns of poor sleep, sleep studies, testing ferritin levels to assess for restless leg syndrome, or referral to a gastrointestinal specialist for evaluation of dysmotility, as appropriate.

Treatment: Sleep Hygiene and Pharmacologic Interventions

There is no literature on the treatment of sleep disturbance specific to children with a leukodystrophy. Based on literature available in pediatric sleep disorders, recommendations include sleep hygiene counseling, followed by the use of melatonin, and finally, use of prescription medications.^{25,26,34,40-42}

General sleep interventions include the implementation of nightly bedtime routines, the graduated extinction techniques (delaying response time to child's night waking), and the maintenance of a dark room during sleep (by removing electronics and sources of light stimuli).²⁴ In addition to finding benefit to traditional sleep hygiene techniques, parents of children with leukodystrophy in the Hunter's Hope Consortium also reported benefit from weighted blankets and the use of aromatherapy pillows to position small children in bed. One family reported benefits from downsizing a memory foam mattress topper to be used as an easily portable and adaptable support to prevent pressure sores and maintain comfortable positioning while away from home (Table 2). These techniques were used in children with moderate to advanced leukodystrophies.

Insomnia has been shown to improve with cognitive behavioral therapy.^{41,43,44} Likewise, there has been success in alleviating sleep disturbances in other disease processes through treatment of comorbid mood, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), or other neuropsychiatric comorbidities. However, the pharmacologic agents commonly used, including stimulants and selective serotonin reuptake inhibitors, are associated with disruption of

REM sleep.⁴² Therefore, to maximize treatment while preserving sleep, patients may benefit from morning and afternoon dosing schedules, with weekend medication “holidays.”

When sleep hygiene methods are insufficient, another consideration should be the use of melatonin. This approach has been studied in children with multiple neurologic conditions including autism, ADHD, epilepsy, headaches, and intellectual disability.^{25,26} It has been shown to be safe, with varying levels of effectiveness.

Finally, as a step beyond the above interventions, certain prescription medications may aid in the management of sleep disturbance. In many cases, it is possible to take advantage of the sedating side effects of medications indicated for other symptoms, by giving the medications in the evening. Specifically, clonazepam can be considered for patients with persistent nonepileptic nighttime myoclonic jerks.²⁷ Similarly, valproic acid has been used in advanced symptomatic leukodystrophy patients with epilepsy and myoclonic jerks. Sedation from gabapentin may aid in sleep as well as irritability and neuropathic pain.

Pain

Pain is a common problem in many of the leukodystrophies secondary to other symptoms such as spasticity and dystonia,⁶ particularly in the intermediate and advanced symptomatic phases. Unfortunately, pain in children with a leukodystrophy is often under recognized and undertreated. Barriers to adequate pain treatment may include uncertainty in identifying pain as well as limited experience with medications for pain treatment.⁴⁵ Optimal pain management in pediatric populations requires anticipatory guidance, routine screening, thorough assessment, and both pharmacologic and nonpharmacologic interventions.⁴⁶ Limited evidence exists in the literature on pain management of pediatric leukodystrophy patients. The recommendations discussed in this section are based on established guidelines, systematic literature reviews, and multidisciplinary expert opinions.

Screening: Pediatric Pain Intensity Scales

Pain is a subjective experience best assessed by self-report, taking into account patient age, cognitive and communication abilities, and contextual factors.⁴⁷ When screening for pain, providers must account for disease stage. For presymptomatic to early symptomatic stages of a leukodystrophy, pictorial pain scales and numeric scales are generally appropriate self-report measures. See Table 4 for the age-appropriate scales.⁴⁷⁻⁵⁰

Preverbal children and children in intermediate and advanced disease stages, experiencing cognitive impairments and/or communication limitations, should be assessed using observational pain scales. When screening for pain in children with cognitive impairment, the revised-FLACC tool has significant evidence supporting its validity and reliability.⁵¹ The revised-FLACC was developed to incorporate pain descriptors commonly exhibited in children with cognitive impairment including verbal outbursts, tremors, increased spasticity,

jerking movements, and respiratory changes.⁶⁴ The use of various rating scales involves reviewing symptoms with parents and caregivers, including skilled nursing care, to determine child’s baseline behaviors and deviations from that baseline when pain occurs.^{45,52}

Assessment: Common Etiologies of Pain, Evaluative Tools

Any indication of pain revealed by screening with appropriate pain scales requires further evaluation. Detailed pain history from both patient and caregiver, complete physical examination, and potential diagnosis of the cause of pain should be considered.⁴⁶ Leukodystrophy pain profiles vary greatly as patients progress through symptomatic stages (Table 4).

Presymptomatic patients. Pain reported prior to disease onset should be evaluated and treated according to common causes of pediatric pain, such as acute injury, infection, migraine, and teething/oral discomfort/dental pain.^{12,52} If this evaluation is unable to identify an external source of the pain, providers should consider whether the pain is an early manifestation of the underlying leukodystrophy.

Early symptomatic patients. In this early disease phase, children with a leukodystrophy involving peripheral nerve involvement (commonly metachromatic leukodystrophy and Krabbe) may experience neuropathic pain.^{53,54} Metachromatic leukodystrophy is also known for associated gallbladder pathologies which in rare cases can precede neurologic symptoms.⁵⁵ Therefore, patients with metachromatic leukodystrophy presenting with significant abdominal pain should be evaluated for gallstones, papillomatosis, or cholecystitis as sources of pain.⁶³ In children with infantile Krabbe disease, inconsolable irritability may indicate discomfort from gastrointestinal reflux, an early clinical indicator of the disease.⁵⁶

Intermediate symptomatic patients. Pain related to neuropathy, dystonia, and spasticity is typically observed across the leukodystrophies.^{5,54,57} Patients may begin to experience gastrointestinal symptoms including gastroesophageal reflux and chronic constipation resulting from autonomic dysfunction. Pain resulting from feeding intolerance is common as dysphagia develops during the course of the disease.^{59,60} Dysautonomia can also disrupt bladder function, leading to urinary retention and pain associated with urinary tract infections as patients approach more advanced stages of the disease.⁶

Advanced symptomatic patients. In the advanced stages, intractable crying can persist despite maximal management.⁴⁵ Chronic spasticity can lead to painful complications including contractures, scoliosis, joint dislocation, and overall positional discomfort.⁶ Pathologic fractures occur in patients as they become unable to bear weight, and also as side effects of long-term glucocorticoid replacement (eg, patients with adrenoleukodystrophy) and possible demineralization.⁵⁸ Furthermore, patients are at increased risk for skin wounds and pressure injuries as they lose the ability to

Table 3. Recommendations for Screening, Assessment, and Management of Sleep Disturbances in Children With a Leukodystrophy.

	Presymptomatic	Early Symptomatic	Intermediate Symptomatic	Advanced Symptomatic
Screening	Children's Sleep Habits Questionnaire (CSHQ) ¹⁷			
Assessment Common etiologies to consider	<ul style="list-style-type: none"> • Poor sleep hygiene¹⁸ • Restless leg syndrome¹⁹ • Sleep apnea¹⁸ 		In addition to presymptomatic etiologies: <ul style="list-style-type: none"> • Gastrointestinal dysmotility⁵ • Pain and spasticity⁶ • Dysautonomia⁵ • Circadian rhythm disorders²⁰ • Exaggerated myoclonic jerks^{6,21} • Environmental factors: nighttime nursing care, feedings, and suctioning²² 	
Tools	<ul style="list-style-type: none"> • Sleep journal/diary¹⁸ • Test ferritin levels¹⁹ • Sleep study²³ 		In addition to presymptomatic tools: <ul style="list-style-type: none"> • Consider gastrointestinal consult 	
Management	<ul style="list-style-type: none"> • Sleep hygiene counseling²⁴ • Treat any contributing medical/environmental factors¹⁸ • Behavioral interventions to improve sleep¹⁸ • Consider medication/supplements: melatonin first, avoid polypharmacy when possible^{25,26} • Take advantage of sedating side effects of medications indicated for other symptoms²⁷ 			

ambulate, require the use of orthotics, or lose sensation due to neuropathy.⁶ Particularly in advanced symptomatic, non-verbal children, parents reported the benefits of monitoring discomfort by tracking vital signs, such as with a home pulse oximeter device (Table 3). In cases where intractable pain persists despite a cause being unidentifiable, it is appropriate to escalate pharmacologic interventions, while carefully considering the relative risks and potential benefits of doing so.

Treatment: Nonpharmacologic and Pharmacologic Interventions for Pain

Parents of children with chronic illnesses report one of their major aims in caregiving is controlling symptoms.⁶⁵ Effective pediatric pain management requires diligent communication of the prescribed regimen to home caregivers as well as continued assessment of therapeutic effect. In order to determine the benefit of a pain regimen, caregivers need tools to accurately assess pain. Consistent usage of an identified pain scale at home will supply health care providers with objective information of the pain trends of the child, allowing providers to tailor treatment accordingly.

Nonpharmacologic. In order to limit polypharmacology, non-pharmacologic approaches should be optimized. Interventions such as biofeedback, guided imagery, therapeutic massage, application of heat or cold, Reiki and physical/occupational therapies are commonly used in palliative care settings.⁶¹ Families and caregivers report having found the following interventions helpful: rocking, repositioning, music, lighting, warm water, and vibration can all be helpful particularly for children with spasticity and in the intermediate and advanced stages of the disease. In particular, aquatherapy poses the unique opportunity for a child in an advanced symptomatic stage to be

temporarily free of constant support—whether from wheelchair positioning or being held—and experience the freedom of motion in the water. Pain from feeding intolerance and constipation may be alleviated by adjusting a child's feeding schedule, venting gastrostomy-tubes, or through enemas or light abdominal massage (Table 3). Although there is limited evidence to support these interventions, they typically have minimal to no side effects and are thus reasonable interventions to consider.

Pharmacologic. Table 3 lists the management of common pain etiologies seen through various stages of leukodystrophies. Chronic nociceptive pain management that is resistant to treatment should follow the 2-step strategy established by the World Health Organization.⁴⁶ Key elements include dosing at regular intervals, using appropriate routes of administration, and adapting treatment to the individual child. Pain management according to the 2-step approach is dependent on the assessed level of pain severity. The first step is intended for children reporting mild pain, requiring nonsteroidal anti-inflammatory drugs (eg, ibuprofen, acetaminophen) for adequate management. Of note, acetaminophen should be used only in cases where the underlying leukodystrophy does not involve liver impairment. The second step should be applied in patients experiencing moderate to severe pain, requiring morphine, oxycodone, hydromorphone, fentanyl, or methadone.⁴⁶ For persistent distress in patients with neurologic impairments, pain management should target neuropathic pain, visceral hyperalgesia, and autonomic dysfunction.

Neuropathic pain may be attributed to peripheral nerve dysfunction and increased responsiveness to pain (peripheral neuropathic pain) or related to central nervous system involvement in the thalamus or spinothalamic tracts (central neuropathic pain). Neuropathic pain is typically described as burning, shooting, or needle-like pain.¹² For the management of

neuropathic pain, gabapentin and pregabalin are commonly used.⁶¹ Gabapentin appears to be an effective treatment, as suggested by a retrospective analysis performed with data from 22 children with symptoms similar to those seen in the leukodystrophies: severe impairment of the central nervous system and recurrent pain behaviors, including intermittent changes in muscle tone.⁶² In cases where muscle spasms or heightened spasticity are eliciting pain, the prudent use of benzodiazepines and other antispasmodics is indicated.

Visceral hyperalgesia refers to an altered threshold for pain in response to gastrointestinal stimulus, believed to be related to injury or inflammation in the gastrointestinal tract.¹² Information that suggests visceral hyperalgesia includes pain associated with gastrostomy or jejunostomy tube feeds, bowel gas, or pain associated with a bowel movement. Pharmacologic treatment of visceral hyperalgesia includes medications used for neuropathic pain, including gabapentin.⁶⁶

Children with leukodystrophies may also experience autonomic dysfunction. Features suggesting autonomic dysfunction may include diaphoresis, elevated heart rate or temperature, pallor or flushing, and increased salivation. Medications for the treatment of autonomic dysfunction include clonidine and benzodiazepines, although none have been specifically studied in children with leukodystrophies.

Pain in patients with cognitive impairments. In children with severe neurologic deficits, often including at least some degree of cognitive impairment, there is a higher incidence of pain compared with healthy children.⁶⁷ Common causes of pain not discussed above but seen in children with cognitive impairment include oral sores, headaches, trauma, infection, and menses.⁶⁸ Untreated pain can bear long-term consequences, in many cases leading to sensitization to pain. In patients with severe cognitive impairment, pain behaviors have shown to increase with number of pain experiences.⁶⁷ This knowledge should guide providers in providing clustered care, validating the necessity of painful procedures with provisions for adequate pain treatment.

Seizures and Epilepsy

Seizures tend to occur more frequently in the earlier-onset (infantile) leukodystrophies but can also be seen in juvenile- and adult-onset forms. Seizures can occur at any stage of the disease but tend to be more refractory in advanced stages, and they can start months to years after the initial onset of neurologic symptoms.⁶⁹⁻⁷¹ Specifically, seizures are the first symptom in fewer than 5% of adrenoleukodystrophy patients,⁷² while for infantile Krabbe and late-infantile metachromatic leukodystrophy, seizures can be more frequent and at times intractable. Interestingly, seizures are a common first presentation of Alexander disease.⁷³ In many of the more recently characterized leukodystrophies, the occurrence of seizures has not yet been well-documented.

A challenge among the leukodystrophies is that white matter disease leads to frequent behavioral changes/staring spells/myoclonus that are not necessarily epileptic.^{74,75} Seizure

management is further challenged by behavioral issues themselves: these issues could be seizure manifestations or could instead have been exacerbated by recent seizures⁷⁶ or by anti-seizure medication side effects. For these reasons, we propose that seizure management in children with a leukodystrophy follow general guidelines for otherwise healthy children (Table 5), while respecting the vulnerabilities of advanced disease (Table 5) and unique features of specific leukodystrophies (Table 6).

Screening: Clinical Suspicion

EEG studies in children with leukodystrophy should only be performed when there is reasonable clinical suspicion for a seizure. Children with leukodystrophies very often have abnormal EEGs, most commonly manifesting as excessive slow waves for age.^{76,80,81} Such findings in and of themselves should not lead to initiation of antiseizure medications. In general, we encourage parents to make use of smartphone technology to record photos and videos of their children during any abnormal or concerning events, so that these instances may be shared with medical providers to enhance understanding and provide feedback.

Assessment: Common Etiologies of Seizures and EEG as an Evaluative Tool

As with other neurologic conditions, etiologies for seizures may be identified using a combination of clinical history, EEG, and brain imaging. When fever is present, the typical considerations and evaluations should be employed based on the patient's age and associated symptoms, including infection or febrile seizure (particularly in the presymptomatic stage). If staring spells are present, workup should include the possibility of slower processing speed or the presence of clinical vs sub-clinical seizure activity.

As an assessment tool, we recommend that EEGs be ordered only with clear clinical concern for seizures. Considerations here follow general guidelines and are not specific to the leukodystrophies. Beyond slowing, EEGs can show epileptiform discharges, including single and multifocal spikes and paroxysmal activity, including high-voltage spike and wave discharges.^{80,81} Overall, a sleep-deprived EEG is higher yield but the ability to capture sleep will depend on the individual child.⁸² In rare instances, where no epileptiform activity on routine or sleep-deprived EEG is found despite recurring clinical events, a continuous video EEG (at least overnight and ideally 24 hours) may be indicated. As in other conditions not invariably causing seizures, we do not recommend routine follow-up EEGs if clinical response adequately guides anti-seizure medication treatment. However, if there has been a change in seizure semiology or following institution of anti-seizure medications, a repeat EEG may be helpful. Generally, any change in seizure semiology or syndrome will dictate management more than the specific leukodystrophy.

Table 4. Recommendations for Screening, Assessment, and Management of Pain in Children With a Leukodystrophy.

	Presymptomatic	Early Symptomatic	Intermediate Symptomatic	Advanced Symptomatic
Screening ⁴⁷⁻⁵⁰	<ul style="list-style-type: none"> • Birth to 3 y: FLACC (Faces, Legs, Activity, Cry, and Consolability) • 4-12 y: FPS-R (Faces Pain Scale-Revised) and WBFPRS (Wong-Baker Faces Pain Rating Scale) • 8 y and older: NRS (numeric rating scale) 		r-FLACC (Revised Faces, Legs, Activity, Cry, and Consolability) ⁵¹	
Assessment Common etiologies to consider	<ul style="list-style-type: none"> • Acute injury • Infection • Migraine • Teething/oral discomfort/dental pain^{12, 52} 	Disease-specific etiologies: <ul style="list-style-type: none"> • Neuropathy in metachromatic leukodystrophy, Krabbe^{53,54} • Gallbladder pathologies in metachromatic leukodystrophy⁵⁵ • Reflux in infantile Krabbe⁵⁶ 	<ul style="list-style-type: none"> • Reflux⁵⁶ • Spasticity, dystonia^{5,54,57} • Contractures⁶ • Scoliosis⁶ • Joint dislocation⁶ • Pressure injuries⁶ • Compression fractures⁵⁸ • Constipation, feeding intolerance⁶⁰ • Urinary retention⁶ • Urinary tract infections⁶ • Corneal abrasions⁵ 	
Tools	History and physical exam consistent with applicable common etiologies, diagnostic workup as appropriate			
Management	<ul style="list-style-type: none"> • Targeted treatment of underlying pain causes • Targeted treatment of underlying pain causes 			
Nonpharmacologic	<ul style="list-style-type: none"> • Play/music therapy⁶¹ • Guided imagery⁶¹ • Cognitive behavioral therapy 		<ul style="list-style-type: none"> • Therapeutic massage, application of heat or cold, Reiki⁶¹ • Physical/occupational therapies⁶¹ • Rocking, repositioning, music, lighting, warm water, vibration 	
Pharmacologic	NSAIDs and acetaminophen ⁴⁶		<ul style="list-style-type: none"> • NSAIDs and acetaminophen⁴⁶ • Gabapentin⁶² • Consideration of opioids⁴⁶ • Spasticity management (eg, benzodiazepines, antispasmodics)⁶ 	

Treatment: Management of Triggers and Pharmacologic Intervention

Prevention of seizure triggers such as sleep deprivation, constipation, illness, gastrointestinal symptoms, and other stressors constitute best practice in seizure management. As seizures do not occur in all leukodystrophy patients,^{76,81,83} we do not as a rule recommend prophylactic medication. If seizures are evident by clinical presentation and/or epileptiform activity on EEG, antiseizure medications are recommended. Often, considerations of overlapping symptoms, coinciding treatment such as stem cell transplant, muscle spasms, or behavioral exacerbation may guide the choice of medications.^{77,79} Titration and further management will be guided by side effects such as sedation and other symptoms, as well as seizure control after beginning treatment. Future research is needed to help determine if specific epilepsy medications and treatments are more or less effective in leukodystrophies.

In general, polypharmacy should be avoided, given that many patients do not have intractable seizures. However, for intractable patients, consideration should be given to other treatment modalities, including ketogenic diet and vagus nerve stimulation (VNS). Here, the unique features of each leukodystrophy, with their metabolic and genetic underpinnings, such as likely

contraindication of the ketogenic diet in X-linked adrenoleukodystrophy due to increased very long chain fatty acids with the diet,⁷⁸ guide the choice of such experimental treatments. These considerations play a greater role in the management of patients with very advanced disease or with specific leukodystrophies that have polymicrogyria or other brain malformations.

Language and Cognition

Cognitive impairment, although variable in nature and severity, is a symptom shared among most leukodystrophies.⁶ Irritability is a common initial symptom of early onset Krabbe disease.⁵⁴ For leukodystrophies with onset in the late childhood to juvenile period, cognitive decline may be the presenting symptom and may precede motor dysfunction. For example, in boys with cerebral adrenoleukodystrophy, cognitive complaints at symptom onset may be as subtle as difficulties in attention and concentration.⁸⁴ Typically, a later age of disease onset correlates with a slower rate of progression, as seen among children with late-infantile versus juvenile metachromatic leukodystrophy.⁸⁵ However, it should be noted that neurologic impairment and/or decline can vary widely across the spectrum of leukodystrophies and even among members of the same family or genotype.⁸⁶ Cognition is also affected in hypomyelinating conditions. A recent paper on megalencephalic

Table 5. Recommendations for Screening, Assessment, and Management of Seizures in Children With a Leukodystrophy.

	Presymptomatic	Early Symptomatic	Intermediate Symptomatic	Advanced Symptomatic
Screening	<ul style="list-style-type: none"> Review seizure types Anticipatory guidance Seizure “first aid” Address parental anxiety relating to seizure presentations 	Anticipatory guidance relating to expected changes in seizure types/ presentations <i>First seizure</i> <ul style="list-style-type: none"> Description of seizure event Review of possible/subtle seizure presentations to determine true incidence 		
Assessment		<i>Recurrent seizures / epilepsy</i> Determine seizure types, frequency, and syndromes Consider common etiologies: <ul style="list-style-type: none"> Seizures with fever Infection Recent medication change Staring spells Electroencephalographs (EEGs) only when there is reasonable clinical suspicion for a seizure When considering repeat brain imaging, consider need for sedation and weigh risk against possible insights to be gained Seizure syndrome (or change in semiology) may dictate management more than the specific leukodystrophy 		
Management		<i>First seizure</i> <ul style="list-style-type: none"> EEG (consider sleep-deprived EEG if child tolerates) <i>Recurrent seizures / epilepsy</i> <ul style="list-style-type: none"> Prolonged EEG Antiseizure drug levels Seizure syndrome (or change in semiology) may dictate management more than the specific leukodystrophy Avoid polypharmacy when seizures are not intractable Consider the use of clonazepam or lorazepam for “bridges” only in the setting of illness, to avoid long-term/chronic drug use Consider adding gabapentin when sedative effects are preferable Weigh risks and benefits of potentially invasive interventions 		
		<i>First seizure</i> <ul style="list-style-type: none"> Prevent triggers Consider antiseizure medications <i>Recurrent seizures / epilepsy</i> <ul style="list-style-type: none"> Prevent triggers Consider antiseizure medications Consider ketogenic diet <i>Intractable seizures / epilepsy</i> <ul style="list-style-type: none"> Prevent triggers Consider antiseizure medications Consider ketogenic diet Consider surgical interventions (eg, vagus nerve stimulation) 		

leukoencephalopathy with subcortical cysts reported autistic features and cognitive decline.⁸⁷ Providers should support therapists and educators in anticipating increasing needs as the disease progresses. An individualized educational plan (IEP) with educational accommodations and therapies can help maximize developmental progress and quality of life.⁸⁶

Receptive and expressive language impairment is also a common symptom inherent to most leukodystrophies. Early in the course of disease, children may lose their ability to form complete sentences.^{85,88} Eventually, those children may become completely nonverbal. Still, most nonverbal children may be able to retain some communication using nonverbal techniques in the form of signs and gestures, low tech

strategies such as picture exchange, and with an appropriate augmentative/alternative communication (AAC) device (see Table 7).⁶

Screening: Developmental Inventories

As children affected by a leukodystrophy are at risk for regression, a neurologic exam with developmental surveillance should be performed and documented at every neurologic visit (Table 7). A review of prior milestones should be completed to look for areas of regression as well as continued development. If concerns are identified, patients should be screened with a comprehensive tool. Language screening is recommended for

Table 6. Seizure Considerations for Patients With Specific Leukodystrophies.

Disease	Special considerations
Alexander disease	Seizures are often an early symptom in infantile Alexander Disease ⁷³ ; the absence of seizures does not exclude other types of Alexander disease
Krabbe disease	Irritability is a common symptom of Krabbe Disease; consider pairing levetiracetam with vitamin B ₆ (pyridoxine) supplement to alleviate behavioral side effects of levetiracetam ⁷⁷
Vanishing white matter disease	Consider aggressively treating fevers, because both disease progression and seizure activity are known to occur in the setting of fevers
X-linked adrenoleukodystrophy	Ketogenic diet is likely contraindicated due to effect on very long chain fatty acid levels ⁷⁸
Zellweger syndrome (and others associated with polymicrogyria)	Consider proactive seizure treatment
All leukodystrophy patients undergoing hematopoietic stem cell transplant	Consider seizure prophylaxis with levetiracetam ⁷⁹ ; avoid valproic acid or felbamate due to possible bone marrow suppression

all children by the American Academy of Pediatrics at 9, 18, and 24 or 30 months of age.⁸⁶ This applies to children with leukodystrophies as well. Parental screening instruments, such as the Communicative Developmental Inventory (CDI) and Infant-Toddler checklist (ITC), have displayed consistently acceptable levels of sensitivity and specificity at each age level.⁸⁶ These instruments can also be easily administered and interpreted by staff in a primary care physician office without significant difficulty, time burden, or training.⁸⁶ A professionally administered developmental screening tool such as the Bayley Scales of Infant and Toddler Development may be administered in children at ages 1 to 42 months.⁸⁶

Assessment: Common Etiologies, Neuropsychological Testing as an Evaluative Tool

If developmental delay or regression is identified during screening, further evaluations are indicated. Potential contributing causes of regression beyond disease progression should be considered, such as illness, changes in sleep, increased pain, medication side effects, hormonal/metabolic imbalances, and seizures (Table 7).

Though there is a paucity of literature documenting neuropsychological testing outcomes in all leukodystrophies, based on expert opinion we recommend that formal neuropsychological testing begin at age 4-5 years and that it be continued every 1-2 years in the presymptomatic, early symptomatic, and intermediate symptomatic stages of disease (Table 7). This testing should emphasize evaluation of skills relying on white matter integrity, such as attention and executive skills, processing speed, and visual motor skills.⁸⁹ Testing may include but not be limited to the Wechsler Intelligence scales including verbal IQ and performance IQ, Vineland Adaptive Behavioral Scale, and visuomotor and executive function assessments.^{84,85}

In the later stages of disease, neuropsychological testing may no longer be feasible. The necessity and potential for benefit to the patient must be weighed against the time and travel burden on the patient and family.

Treatment: Speech Therapy and Communication Devices

Children with any form of symptomatic leukodystrophy may benefit from physical, occupational, and/or speech therapy services.⁵ These services are often provided through early intervention to children younger than 3 years. Among children older than 3 years with a disability, services may in part be provided through the US school system. An individualized education plan should be developed that documents current performance, annual goals, special education and related services, participation in testing, participation with nondisabled peers, transition services, and methods of measuring progress. Of note, behavioral or psychiatric symptoms can also be present alongside cognitive decline and may be associated with disease pathology or frustration with ineffective communication.^{85,88}

Special consideration should be given to children with speech, hearing, and/or vision impairment. For children whose current methods of communication do not support them in meeting all of their daily communication needs (eg, severe dysarthria, anarthria, mixed receptive-expressive language disorder), functional communication evaluations may be considered. Speech devices differ in their level of complexity including symbolic representation (eg, photos, symbols, text), message types (eg, full utterance, word-by-word, spelling), voice output (eg, recorded digitized, synthesized speech), technology level (eg, no tech, low tech, high tech), and access (eg, direct with hand or eye gaze, indirect scanning) options.⁵ In the evaluation of a patient's individual communication needs, cognition, language, vision, hearing, and physical skills should all be considered.⁵ For children with anticipated hearing or vision impairment, initiation of sign language and Braille education should begin early if cognitively appropriate. Social workers or education advocates may help families work with the school system to obtain an individualized education plan and appropriate therapies.

Parent and Family Perspectives

Recognizing that disease burden extends beyond the stated neurologic domains, we collaborated with parent and family

Table 7. Recommendations for Screening, Assessment, and Management of Language and Cognitive Impairment in Children With a Leukodystrophy.

	Presymptomatic	Early symptomatic	Intermediate symptomatic	Advanced symptomatic
Screening	<ul style="list-style-type: none"> • Developmental inventory alongside review of prior milestones⁸⁶ • Standardized language screening: CDI (Communicative Developmental Inventory), ITC (Infant-Toddler Checklist)⁸⁶ 			
Assessment: Common etiologies to consider	<ul style="list-style-type: none"> • Anxiety and depression, social stressors • Subclinical seizures • Changes in sleep • Hearing impairment or recurrent ear infections • Visual impairment • Medication side effects, hormonal/metabolic imbalances • Disease progression 			
Tools	<ul style="list-style-type: none"> • Child Find assessment (communication, motor, cognitive) • Neuropsychological testing beginning at age 4-5 y and repeated every 1-2 y • Emphasis on evaluation of attention and executive skills, processing speed, and visual motor skills⁸⁹ • Standard hearing test, or BAER, as appropriate to child • Speech assessment to evaluate for dysarthria, dysphonia, anarthria, aphonia, intelligibility, comprehensibility, communication effectiveness and participation 			Neuropsychological testing recommended only if potential benefits outweigh burden to patient and family; physicians should work with families on goals of care
Management	<ul style="list-style-type: none"> • Under 3 years: referral to Child Find services • School-age children: Individualized educational plan services and relevant accommodations • Augmentative and alternative communication interventions, as appropriate⁵ • Initiation of sign language and/or Braille education for children with anticipated hearing/vision impairment 			

Table 8. Summary of Recommendations for Neurologic Care in the Leukodystrophies.

In all disease stages of a leukodystrophy, neurologic care can be optimized but requires a multidisciplinary approach and attention to stage of severity
Palliative care involvement early in the disease course can help families with coping and support as well as creating goals of care for medical procedures and treatment.
Screening for sleep disturbances, pain, seizures, and cognitive/developmental difficulties should be completed at each visit with neurology and/or pediatrics.
Treatment for sleep disturbances should focus first on good sleep hygiene and nonpharmacologic measures, followed by use of melatonin, and then progressing to other prescriptive medications as needed. Using the side effect of sedation from drugs used to treat other symptoms is recommended to avoid polypharmacy.
Recognize that severely disabled children with cognitive impairment have a higher incidence of pain. Assessment for pain should include a thorough examination and evaluation for systemic causes of pain.
Recognize that seizures tend to be more frequent in certain leukodystrophies such as Krabbe, metachromatic leukodystrophy, Alexander disease, and Aicardi Goutières syndrome. Seizures also tend to occur more frequently in earlier-onset rather than juvenile leukodystrophies and tend to become more refractory in more advanced stages of disease.
A neurologic exam with developmental surveillance should be performed and documented at every neurologic visit. Potential contributing causes of regression beyond disease progression should be considered.
Children with hearing and vision impairment should be evaluated for adaptive devices or alternative means of communication based on their cognitive abilities.

advocate groups to develop these guidelines. This allowed perspective to the daily needs of a child with a leukodystrophy. In addition to their tips and recommendations, which are included throughout the guidelines, parents expressed several foundational viewpoints. They pointed to the importance of helping parents understand what resources are available to them: from organizations such as the Leukodystrophy Care Network, as well as, talking to other parents with experience in the leukodystrophies, and partner organizations that can assist with financial support, obtaining home medical equipment, and navigating transitions of care between hospital and home settings. Parents also emphasized many of the overlapping dynamics involved in the care of a child with a leukodystrophy: shared decision making among family members, caregiver burden and burnout, and social media support groups.

Summary Recommendations and Knowledge Gaps

In creating this set of neurologic guidelines for the care of children with a leukodystrophy, our hope is to provide the tools to standardize symptom management and optimize patient-focused care. With a focus on staging of disease, we are better able to combine recommendations for varied leukodystrophies with shared symptoms. We hope to empower providers less familiar with leukodystrophies to anticipate and prevent potential complications that may arise during the course of the disease. We summarized our recommendations in Table 8, as well as knowledge gaps for

future research in Table 1. With recent advances in the identification of leukodystrophies based on expanded access to genetic testing and newborn screening, our understanding of the full scope of these neurologic issues will greatly expand. Further, we hope that with the creation of the Leukodystrophy Care Network, specialty centers across the USA will begin to collect data to help guide the creation of leukodystrophy-specific patient-reported outcome measures and better understand the true incidence of these neurologic symptoms in children.

Acknowledgment

Hunter's Hope provided support for the Leukodystrophy Care Network meeting as well as some institutional support.

Author Contributions

SRK, EJM, JPR are co-first authors, they conducted the study, analyzed the data, and drafted the manuscript. KCE, CB and FSE are the senior authors, they designed the study and reviewed the draft for content. JAA, JAB, CSC, CE, AT, MKT, ACJ, JR, ES and KCS participated in the design and conduct of this study. ATW, JG, JLW, MRW, KW and AW helped design this study and reviewed the draft for content.


Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Eric J. Mallack, MD  <https://orcid.org/0000-0002-2678-8807>

References

- Vanderver A, Prust M, Tonduti D, et al. Case definition and classification of leukodystrophies and leukoencephalopathies. *Mol Genet Metab*. 2015;114(4):494-500.
- Bonkowsky JL, Nelson C, Kingston JL, Filloux FM, Mundorff MB, Srivastava R. The burden of inherited leukodystrophies in children. *Neurology*. 2010;75(8):718-725.
- Heim P, Claussen M, Hoffmann B, et al. Leukodystrophy incidence in Germany. *Am J Med Genet*. 1997;71(4):475-478.
- Vanderver A, Hussey H, Schmidt JL, Pastor W, Hoffman HJ. Relative incidence of inherited white matter disorders in childhood to acquired pediatric demyelinating disorders. *Semin Pediatr Neurol*. 2012;19(4):219-223.
- Adang LA, Sherbini O, Ball L, et al. Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies. *Mol Genet Metab*. 2017;122(1-2):18-32.
- Van Haren K, Bonkowsky JL, Bernard G, et al. Consensus statement on preventive and symptomatic care of leukodystrophy patients. *Mol Genet Metab*. 2015;114(4):516-526.
- Otto C, Steffensen BF, Hojberg AL, et al. Predictors of health-related quality of life in boys with Duchenne muscular dystrophy from six European countries. *J Neurol*. 2017;264(4):709-723.
- Rooney J, Byrne S, Heverin M, et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. *J Neurol Neurosurg Psychiatry*. 2015;86(5):496-501.
- Van den Berg JP, Kalmijn S, Lindeman E, et al. Multidisciplinary ALS care improves quality of life in patients with ALS. *Neurology*. 2005;65(8):1264-1267.
- Stephens HE, Young J, Felgoise SH, Simmons Z. A qualitative study of multidisciplinary ALS clinic use in the United States. *Amyotroph Lateral Scler Frontotemporal Degener*. 2015;17(1-2):55-61.
- Paganoni S, Nicholson K, Leigh F, et al. Developing multidisciplinary clinics for neuromuscular care and research. *Muscle Nerve*. 2017;56(5):848-858.
- Pediatric palliative care and hospice care commitments, guidelines, and recommendations. *Pediatrics*. 2013;132(5):966-972.
- Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurol*. 2018;17(5):445-455.
- Stephenson JB. Aicardi-Goutieres syndrome (AGS). *Eur J Paediatr Neurol*. 2008;12(5):355-358.
- van der Knaap MS, Abbink TEM, Min R. Megalencephalic leukoencephalopathy with subcortical cysts. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews((R))*. Seattle, WA: University of Washington, Seattle; 1993.
- Espana RA, Scammell TE. Sleep neurobiology for the clinician. *Sleep*. 2004;27(4):811-820.
- Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep*. 2000;23(8):1043-1051.
- Licis A. Sleep disorders: assessment and treatment in preschool-aged children. *Child Adolesc Psychiatr Clin N Am*. 2017;26(3):587-595.
- Picchiatti DL, Bruni O, de Weerd A, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. *Sleep Med*. 2013;14(12):1253-1259.
- Tomoda A, Miike T, Matsukura M. Circadian rhythm abnormalities in adrenoleukodystrophy and methyl B₁₂ treatment. *Brain Dev*. 1995;17(6):428-431.
- Soman T, Lang AE. Movement disorders. *Continuum: Lifelong Learning in Neurology*. 2009;15(6):167-190.
- McAuley J, Taylor R, Simonds A, Chawda S. Respiratory difficulty with palatal, laryngeal and respiratory muscle tremor in adult-onset Alexander's disease. *BMJ Case Rep*. 2017;2017.
- Niakan E, Belluomini J, Lemmi H, Summitt RL, Ch'ien L. Disturbances of rapid-eye-movement sleep in 3 brothers with Pelizaeus-Merzbacher disease. *Ann Neurol*. 1979;6(3):253-257.
- Morgenthaler TI, Owens J, Alessi C, et al. Practice parameters for behavioral treatment of bedtime problems and night wakings in infants and young children. *Sleep*. 2006;29(10):1277-1281.

25. Braam W, Didden R, Maas AP, Korzilius H, Smits MG, Curfs LM. Melatonin decreases daytime challenging behaviour in persons with intellectual disability and chronic insomnia. *J Intellect Disabil Res.* 2010;54(1):52-59.
26. Bruni O, Alonso-Alconada D, Besag F, et al. Current role of melatonin in pediatric neurology: clinical recommendations. *Eur J Paediatr Neurol.* 2015;19(2):122-133.
27. Jankovic J. Therapeutic developments for tics and myoclonus. *Mov Disord.* 2015;30(11):1566-1573.
28. Flanagan EP, Gavrilova RH, Boeve BF, Kumar N, Jelsing EJ, Silber MH. Adult-onset autosomal dominant leukodystrophy presenting with REM sleep behavior disorder. *Neurology.* 2013; 80(1):118-120.
29. Hida A, Ishiura H, Arai N, et al. Adult-onset Alexander disease with an R66Q mutation in GFAP presented with severe vocal cord paralysis during sleep. *J Neurol.* 2012;259(10):2234-2236.
30. Francois J, Manaligod JM. Upper airway abnormalities in Canavan disease. *Int J Pediatr Otorhinolaryngol.* 2002;66(3): 303-307.
31. Carvalho Bos S, Gomes A, Clemente V, et al. Sleep and behavioral/emotional problems in children: a population-based study. *Sleep Med.* 2009;10(1):66-74.
32. Foldvary-Schaefer N. Sleep complaints and epilepsy: the role of seizures, antiepileptic drugs and sleep disorders. *J Clin Neurophysiol.* 2002;19(6):514-521.
33. Kothare SV, Kaleyias J. Sleep and epilepsy in children and adolescents. *Sleep Med.* 2010;11(7):674-685.
34. Paiva T, Gaspar T, Matos MG. Sleep deprivation in adolescents: correlations with health complaints and health-related quality of life. *Sleep Med.* 2015;16(4):521-527.
35. Al-Biltagi MA. Childhood epilepsy and sleep. *World J Clin Pediatr.* 2014;3(3):45-53.
36. Ito Y, Kidokoro H, Negoro T, et al. Paroxysmal nonepileptic events in children with epilepsy. *Epilepsy Res.* 2017;132:59-63.
37. Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and managing sleep disturbance in patients with chronic pain. *Anesthesiol Clin.* 2016;34(2):379-393.
38. Newman CJ, O'Regan M, Hensey O. Sleep disorders in children with cerebral palsy. *Dev Med Child Neurol.* 2006;48(7):564-568.
39. Taylor MA, Schreck KA, Mulick JA. Sleep disruption as a correlate to cognitive and adaptive behavior problems in autism spectrum disorders. *Res Dev Disabil.* 2012;33(5):1408-1417.
40. Blackmer AB, Feinstein JA. Management of sleep disorders in children with neurodevelopmental disorders: a review. *Pharmacotherapy.* 2016;36(1):84-98.
41. Ma ZR, Shi LJ, Deng MH. Efficacy of cognitive behavioral therapy in children and adolescents with insomnia: a systematic review and meta-analysis. *Braz J Med Biol Res.* 2018;51(6): e7070.
42. Meltzer LJ, Mindell JA. Sleep and sleep disorders in children and adolescents. *Psychiatr Clin North Am.* 2006;29(4):1059-1076.
43. Blake M, Schwartz O, Waloszek JM, et al. The SENSE study: treatment mechanisms of a cognitive behavioral and mindfulness-based group sleep improvement intervention for at-risk adolescents. *Sleep.* 2017;40(6).
44. Grigg-Damberger M, Ralls F. Treatment strategies for complex behavioral insomnia in children with neurodevelopmental disorders. *Curr Opin Pulm Med.* 2013;19(6):616-625.
45. Hauer J, Houtrow AJ, Section On H; Palliative Medicine COCWD. Pain assessment and treatment in children with significant impairment of the central nervous system. *Pediatrics.* 2017; 139(6).
46. WHO Guidelines Approved by the Guidelines Review Committee. In: *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses.* Geneva: World Health Organization; 2012.
47. von Baeyer CL. Children's self-reports of pain intensity: scale selection, limitations and interpretation. *Pain Res Manag.* 2006; 11(3):157-162.
48. Herr K, Coyne PJ, McCaffery M, Manworren R, Merkel S. Pain assessment in the patient unable to self-report: position statement with clinical practice recommendations. *Pain Manag Nurs.* 2011; 12(4):230-250.
49. Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A systematic review of faces scales for the self-report of pain intensity in children. *Pediatrics.* 2010;126(5):e1168-e1198.
50. von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the numerical rating scale (NRS-11) for children's self-reports of pain intensity. *Pain.* 2009;143(3):223-227.
51. Voepel-Lewis T, Malviya S, Tait AR, et al. A comparison of the clinical utility of pain assessment tools for children with cognitive impairment. *Anesth Analg.* 2008;106(1):72-78, table of contents.
52. Hauer J. Identifying and managing sources of pain and distress in children with neurological impairment. *Pediatr Ann.* 2010;39(4): 198-205; quiz 232-234.
53. Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Mol Genet Metab.* 2015;114(4):501-515.
54. Beltran-Quintero ML, Bascou NA, Poe MD, et al. Early progression of Krabbe disease in patients with symptom onset between 0 and 5 months. *Orphanet J Rare Dis.* 2019;14(1):46.
55. van Rappard DF, Bugiani M, Boelens JJ, et al. Gallbladder and the risk of polyps and carcinoma in metachromatic leukodystrophy. *Neurology.* 2016;87(1):103-111.
56. Escolar ML, Poe MD, Martin HR, Kurtzberg J. A staging system for infantile Krabbe disease to predict outcome after unrelated umbilical cord blood transplantation. *Pediatrics.* 2006;118(3): e879-e889.
57. Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis, and treatment. *Neurologist.* 2009;15(6): 319-328.
58. Helman G, Van Haren K, Escolar ML, Vanderver A. Emerging treatments for pediatric leukodystrophies. *Pediatr Clin North Am.* 2015;62(3):649-666.
59. Chelimsky G, Chelimsky TC. Evaluation and treatment of autonomic disorders of the gastrointestinal tract. *Semin Neurol.* 2003;23(4):453-458.
60. Galvis DA, Nakazato Y, Wells TR, Landing BH. Demonstration of myenteric plexus abnormalities in genetic diseases by a

- microdissection technique: preliminary studies. *Am J Med Genet Suppl.* 1987;3:329-342.
61. Downing J, Jassal SS, Mathews L, Brits H, Friedrichsdorf SJ. Pediatric pain management in palliative care. *Pain Manag.* 2015;5(1):23-35.
 62. Hauer JM. Treating dyspnea with morphine sulfate in nonverbal children with neurological impairment. *Pediatr Pulmonol.* 2015; 50(4): E9-E12.
 63. Helman G, Van Haren K, Bonkowsky JL, et al. Disease specific therapies in leukodystrophies and leukoencephalopathies. *Mol Genet Metab.* 2015;114(4):527-536.
 64. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. *Paediatr Anaesth.* 2006;16(3):258-265.
 65. Verberne LM, Kars MC, Schouten-van Meeteren AY, et al. Aims and tasks in parental caregiving for children receiving palliative care at home: a qualitative study. *Eur J Pediatr.* 2017;176(3): 343-354.
 66. Hauer JM, Solodiu JC. Gabapentin for management of recurrent pain in 22 nonverbal children with severe neurological impairment: a retrospective analysis. *J Palliat Med.* 2015;18(5):453-456.
 67. Breau LM, Camfield CS, McGrath PJ, Finley GA. The incidence of pain in children with severe cognitive impairments. *Arch Pediatr Adolesc Med.* 2003;157(12):1219-1226.
 68. Massaro M, Pastore S, Ventura A, Barbi E. Pain in cognitively impaired children: a focus for general pediatricians. *Eur J Pediatr.* 2013;172(1):9-14.
 69. Kolodny EH, Raghavan S, Krivit W. Late-onset Krabbe disease (globoid cell leukodystrophy): clinical and biochemical features of 15 cases. *Dev Neurosci.* 1991;13(4-5):232-239.
 70. Lyon G, Hagberg B, Evrard P, Allaire C, Pavone L, Vanier M. Symptomatology of late onset Krabbe's leukodystrophy: the European experience. *Dev Neurosci.* 1991;13(4-5):240-244.
 71. Tullu MS, Muranjan MN, Kondurkar PP, Bharucha BA. Krabbe disease—clinical profile. *Indian Pediatr.* 2000;37(9):939-946.
 72. Raymond GV, Moser AB, Fatemi A. X-Linked adrenoleukodystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews((R))*. Seattle, WA: University of Washington, Seattle; 1993.
 73. Prust M, Wang J, Morizono H, et al. GFAP mutations, age at onset, and clinical subtypes in Alexander disease. *Neurology.* 2011;77(13):1287-1294.
 74. Lee CW, Bawle EV. An infant with myoclonic jerks, global developmental delay, and failure to thrive. *Clin Pediatr (Phila).* 2011;50(6):570-572.
 75. Nalini A, Christopher R. Cerebral glycolipidoses: clinical characteristics of 41 pediatric patients. *J Child Neurol.* 2004; 19(6):447-452.
 76. Bostantjopoulou S, Katsarou Z, Michelakaki H, Kazis A. Seizures as a presenting feature of late onset metachromatic leukodystrophy. *Acta Neurol Scand.* 2000;102(3):192-195.
 77. Major P, Greenberg E, Khan A, Thiele EA. Pyridoxine supplementation for the treatment of levetiracetam-induced behavior side effects in children: preliminary results. *Epilepsy Behav.* 2008;13(3):557-559.
 78. Hargrove JL, Greenspan P, Hartle DK. Nutritional significance and metabolism of very long chain fatty alcohols and acids from dietary waxes. *Exp Biol Med (Maywood).* 2004;229(3): 215-226.
 79. Soni S, Skeens M, Termuhlen AM, Bajwa RP, Gross TG, Pai V. Levetiracetam for busulfan-induced seizure prophylaxis in children undergoing hematopoietic stem cell transplantation. *Pediatr Blood Cancer.* 2012;59(4):762-764.
 80. Mamoli B, Graf M, Toifl K. EEG, pattern-evoked potentials and nerve conduction velocity in a family with adrenoleukodystrophy. *Electroencephalogr Clin Neurophysiol.* 1979;47(4): 411-419.
 81. Wang CL, Shi Q, Xiang XJ, et al. Double contrast percutaneous transhepatic cholangiographic CT in patients with obstructive jaundice: an initial experience of seven cases. *JBR-BTR.* 2012; 95(4):251-256.
 82. Drake ME Jr, Pakalnis A, Phillips BB, Denio LS. Sleep and sleep deprived EEG in partial and generalized epilepsy. *Acta Neurol Belg.* 1990;90(1):11-19.
 83. Morse LE, Rosman NP. Myoclonic seizures in Krabbe disease: a unique presentation in late-onset type. *Pediatr Neurol.* 2006; 35(2):154-157.
 84. Cox CS, Dubey P, Raymond GV, Mahmood A, Moser AB, Moser HW. Cognitive evaluation of neurologically asymptomatic boys with X-linked adrenoleukodystrophy. *Arch Neurol.* 2006;63(1): 69-73.
 85. Kehrer C, Groeschel S, Kustermann-Kuhn B, et al. Language and cognition in children with metachromatic leukodystrophy: onset and natural course in a nationwide cohort. *Orphanet J Rare Dis.* 2014;9:18.
 86. Wallace IF, Berkman ND, Watson LR, et al. Screening for speech and language delay in children 5 years old and younger: a systematic review. *Pediatrics.* 2015;136(2):e448-e462.
 87. Hamilton EMC, Tekturk P, Cialdella F, et al. Megalencephalic leukoencephalopathy with subcortical cysts: characterization of disease variants. *Neurology.* 2018;90(16):e1395-e1403.
 88. Van Haren K, Bonkowsky JL, Bernard G, et al. Consensus statement on preventive and symptomatic care of leukodystrophy patients. *Mol Genet Metab.* 2015;114(4):516-526.
 89. Kaga M, Furushima W, Inagaki M, Nakamura M. Early neuropsychological signs of childhood adrenoleukodystrophy (ALD). *Brain Dev.* 2009;31(7):558-561.