

LIVING WITH LEUKODYSTROPHY



A Guide for Caring for Leukodystrophy Patients

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Foreword and Acknowledgements

This guide is intended for individuals affected by leukodystrophy, their families or caregivers and their local care teams. This guide will help you to understand more about leukodystrophy and what to expect when living with this disorder. This guide cannot replace the care provided by your local medical team, but hopefully will provide additional information and allow individuals affected by leukodystrophy and their caregivers to develop comprehensive care plans. Leukodystrophy is a disorder that can affect all parts of your life, however there are many things that can be done to help maintain health and well-being. It is very important to learn as much as possible about what your choices are so you can manage the disease and feel more in control.

Not all leukodystrophies have the same symptoms or progress at the same pace. So, it is important to understand that they vary greatly. Even individuals with the same leukodystrophy often do not share identical symptoms.

Individuals affected by leukodystrophy who are fully supported will experience better health, and feel less isolated and lonely. We hope they will have a happier state of mind and not need to go to the doctor or hospital as much as before.

We want to keep your loved one out of the hospital and empower you to become a knowledgeable and educated advocate.

Finally, we want to acknowledge the leadership of the Global Leukodystrophy Initiative who brought together doctors, researchers, nurses, medical specialists, and individual advocacy leaders together to collaborate on the original manuscript on which this guide is modeled.

You can find additional resources by going to the Leukodystrophy Family Forum (www.leukodystrophyforum.com), an interactive, community resource or contacting any number of the disease specific individual advocacy groups you can find at the Leukodystrophy Family Forum.

How To Use This Guide

It is overwhelming to learn that you or your loved one has been diagnosed with leukodystrophy. *But you are not alone.*

Not too long ago, most individuals affected by leukodystrophy were told that there was no treatment. This guide is proof that this is not true. In addition to the growing number of clinical trials in this area, this guide is to help individuals, families, and caregivers manage the common symptoms associated with this family of disorders. With recommendations from some of the world's leading experts on leukodystrophy, this guide offers information on how to manage the most common symptoms faced by individuals affected by leukodystrophy. Caregivers and medical professionals can offer supportive *treatments* to allow them to live the fullest lives they are able with leukodystrophy-related symptoms.

We have created this **Guide for Care: Resources for Leukodystrophy Families** with the support of leukodystrophy experts from around the world. The guide is not intended to replace the advice from your medical team. However, by using this guide, we hope that caregivers and individuals can become more powerful advocates in managing care to provide individuals with the highest quality of life.

What is a leukodystrophy?

Leukodystrophies are a family of dozens of inherited disorders in children and adults. In many cases the genetic cause of these disorders is known, but in some cases individuals present with all the features of a leukodystrophy but genetic testing is negative. These are called “unspecified leukodystrophy.”

Leukodystrophies all result in changes in the brain's white matter (also known as myelin). Myelin is an insulating layer that surrounds the projections of nerve cells, called axons. Axons send information from nerve cell to nerve cell, and from nerve cell to muscles, using electrical impulses. Myelin is much like the insulating layer on electrical wires in your house or appliances, and allows the efficient trafficking

of information throughout the nervous system. When myelin is absent, or doesn't work well, the nervous system cannot send messages to help us move, talk, swallow and perform many other important functions.

In this guide, we will use the term "leukodystrophy" to encompass the many different kinds of leukodystrophy, as well as unspecified leukodystrophies. This is not meant to suggest that all of these disorders are the same. However, although the genetic causes of these disorders vary greatly, there are many common symptoms that affect nearly all individuals. Additionally, in some places, where specific important symptoms affect certain types of leukodystrophy, we will mention that disorder by name. If your or your loved one's disorder is not named, this means only that there are not additional symptoms to be concerned about, beyond those which affect many individuals affected by leukodystrophy.

How many people are impacted by leukodystrophies?

Specific forms of leukodystrophy may be individually rare, but collectively, the many forms of leukodystrophy affect as many as 1 in 7500 individuals. New forms are being identified as our understanding of genetics advances, and the leukodystrophy family is growing every day.

What symptoms are associated with leukodystrophy, and what is the long-term prognosis?

Individuals with leukodystrophies encounter a wide range of health problems. The most common problems are motor difficulties with actions such as walking, sitting or controlling hand use, challenges talking (such as difficult to understand or slowly formed words) and feeding difficulties. Individuals with leukodystrophies may also have difficulties with learning or behavior, however often intellect is relatively preserved compared to motor disabilities. However, each individual experiences the disease differently.

When the leukodystrophy begins later in life, such as in adulthood, individuals may experience mild symptoms with a slower progression. In children, the disease is often more severe and may limit life expectancy. That said, with modern, improved care, medical teams can manage symptoms and may extend life expectancy. We are learning more about leukodystrophy every day, and new treatments are becoming available to manage the disease's worst symptoms.

We will now focus on the most common symptoms shared among leukodystrophies. What follows is meant to offer a guide to the types of comprehensive management possible in the care and treatment of individuals with leukodystrophy. It is important to note that this guide is not intended to replace management by qualified medical professionals, but rather provide a template that can assist in choosing appropriate members of your loved one's medical team.

TONE, MUSCULOSKELETAL AND SKIN ISSUES

Almost all individuals affected by leukodystrophy will experience abnormalities in muscle tone, which is the tension within the muscle while at rest and during passive movement. These abnormalities include “hypotonia”, “spasticity”, and “dystonia”. Tone abnormalities can result in other medical complications and have a negative impact upon breathing, mobility, hygiene, self-care, sleeping patterns, and sexual function.

Individuals affected by leukodystrophy often report a combination of muscle tone abnormalities in different parts of the body, including hypotonia (commonly known as “floppy baby syndrome” or a state of low muscle tone), hypertonia (increased muscle tone, sometimes described as spasticity), dystonia (a movement disorder in which muscles contract involuntarily like a car lurching forward; more on this below), and other movement disorders.

Caregivers and primary care physicians should take note of changes in muscle tone. A sudden increase in muscle tone can be the result of an active infection or pain, or new damage to the brain. Regardless, if you note sustained and significant changes in muscle tone, consult with a medical professional.

One of the best pieces of advice we can provide individual families is that if someone living with leukodystrophy is able to remain ambulatory, exercise or use a stander or walker, this will greatly aid in keeping them healthy. Of course, ambulation and standing are activities that can only be done if the individual is safely able to participate in these activities, lest they result in injury. Additionally, if these activities cause pain, activities need to be stopped until the individual can be re-evaluated by a medical professional. Finally, in some cases, an individual can be self-mobile by rolling or scooting and this independence is very important. However, because

human beings are designed to walk, standing is crucial for the function of our organs, bone health, digestion, skin, and respiratory system. That is why, if possible, working with a medical team to keep the individual moving (or using equipment to help keep them standing) is crucial for a leukodystrophy care plan.

Spasticity

Spasticity is a condition that causes sustained contraction of muscles, leading to abnormal movement patterns. Spasticity results from central nervous system damage (specifically damage to the myelin and/or axons of the primary motor pathways of the central nervous system). This condition ranks as one of the most common symptoms reported in individuals with leukodystrophies.

Oral medications such as baclofen or diazepam (or other medications in the category of benzodiazepines, or other classes of medications such as clonidine), in combination with physical therapy and daily stretching routines, can help manage spasticity. Botulin toxin or phenol injections (also called chemodenervation) can be useful to target focal areas of spasticity. As with any treatment, these interventions should be done in consultation by experienced orthopedic, neurologic, or rehabilitation specialists.

In some cases, a baclofen pump (intrathecal baclofen, via direct administration into the fluid surrounding the spinal cord) allows for better delivery of medication. A baclofen pump can lead to fewer side effects compared to oral baclofen, because it is delivered directly to the location it is needed. Because the pump must be surgically implanted, however, it poses the risk of infection or a mechanical failure that can lead to abrupt cessation of available baclofen and worsening of symptoms related to withdrawal. Also, individuals need to be big enough in size and weight to have the pump implanted. Thus, in some cases, children are too small to permit implantation.

Sometimes providers may recommend a procedure called selective dorsal rhizotomy (SDR), a surgical procedure that disconnects nerve roots to reduce spasticity. While SDR has been quite effective for treating some individuals with cerebral

palsy, the procedure should be undertaken with extreme care in individuals affected by leukodystrophy, as many leukodystrophies also have dystonia (see below), which can become more evident with SDR, worsening function. Additionally, since many leukodystrophies are progressive, SDR done at one phase of the disease may no longer address important areas of spasticity later in the disease. In most cases, it is contraindicated in individuals with leukodystrophy.

| Complications from Abnormal Muscle Tone |
|--|
| <ul style="list-style-type: none">• Discomfort or pain• Interference with key functional activities (ambulation, communication, fine motor control and self-care)• Joint dislocation or stiffening of the joints (contractures)• Pressure sores |

Dystonia and other movement disorders

Dystonia is a movement disorder characterized by involuntary muscle contractions, leading to twisting and repetitive movements. While many individuals affected by leukodystrophy suffer from dystonia, this condition can be hard to recognize and diagnose. When dystonia is severe or problematic to the individual, adequately treating it can improve mobility, so it is important to look for signs, which include a twisting of the body. This can affect the whole body or just a small part, like the hands. Dystonias can be stable or can happen only occasionally during the day. In some leukodystrophies, other movement abnormalities may exist, and are called chorea, tremor or ballismus. The medical approaches may be different - some therapies for dystonia could, for example worsen chorea or ballismus.

One of the most efficient treatments for dystonia is trihexyphenidyl, which is generally well tolerated. Because Trihexyphenidyl can result in constipation, it is important to manage this side effect, often with additional medications and treatments. Trihexyphenidyl can also result in urinary retention, which is a difficulty fully emptying the bladder. This can present as delayed urination, pain with urination, or infrequent urination. Other options include “dopaminergic” medications such as

L-dopa or the dopamine-depleting drug tetrabenazine. L-dopa and tetrabenazine should never be given together as it could lead to the life-threatening condition called neuroleptic malignant syndrome. In addition, baclofen and benzodiazepines can also be effective, but require higher doses than are typically used for spasticity. Finally, some medications also used for seizures can help in the management of dystonia and movement disorders. In individuals affected by leukodystrophy, dopamine blockers should be avoided because of the risk for serious complications, such as tardive dyskinesia. Although rare among the leukodystrophies, focal dystonias which are manifest in localized areas can be treated with botulinum toxin injections, which is typically preferable to oral medications in this situation. For more severe cases, baclofen pumps and, in some cases, deep brain stimulation (DBS), can also be effective.

Low Bone Mass, Low Bone Density, and Fractures

Individuals with leukodystrophy are at high risk for low bone mass, low bone density, and fractures due to lack of mobility, decreased sun exposure, and nutritional deficiencies. Some leukodystrophies have higher risks of additional bone-related complications including vanishing white matter disease (VWM), AARS2-related disorder, and POLR3-related leukodystrophy, because they are associated with hormone and subsequent bone dysfunction.

Bone health should be actively monitored in individuals with leukodystrophies, with particular attention paid to individuals who have epilepsy, receive steroids, or have a history of prior fractures. Similarly, families and caregivers should actively monitor individuals who cannot walk. Some drugs used to treat seizures, including phenobarbital, phenytoin, carbamazepine, and valproic acid, may change vitamin D levels and affect bones, so bone health should be monitored for individuals taking these drugs to manage convulsions. Long-term use of proton-pump inhibitors for acid reflux can also result in changes in bone density.

Physical activity and movement are critical for maintaining bone health. Maintaining muscle strength and mobility helps protect the limb during movement to

reduce the risk of fracture through mechanical means. Also contraction of the muscles around the bone through active weight bearing is thought to improve bone health by improving the strength of the bones.

Ensuring adequate supplementation of calcium and vitamin D are important in maintaining bone health. It is important to work with your doctors and nutritionist to check that vitamin D levels are sufficient, in particular in children or adults who may not often be outside due to limitations in mobility.

To maintain the individual's bone health, in addition to standard laboratory testing for vitamin D and calcium, imaging studies are sometimes helpful. For instance, basal bone density scans, typically dual-energy X-ray absorptiometry (DEXA or DXA, L-spine and Whole Body Less Head) scans, are useful screening tools to identify individuals at greater risk for fractures. After the initial study, DEXA scans should be repeated under the guidance of the medical team. Standard X-rays are not recommended as a screening tool for bone health. Consultation with a bone specialist or endocrinologist may also be recommended to help with managing the condition and determining possible treatment options over time.

Scoliosis and Hip Dislocation

Scoliosis and hip dislocation are major concerns for individuals affected by leukodystrophy, especially as the disease progresses over time. One study reported that 70% of individuals affected by leukodystrophy have scoliosis and 89% of individuals ultimately develop hip dislocation. These complications do not happen all of a sudden but are progressive. Children may first develop changes in the hip joint shape (called subluxation) which may be followed by dislocation (in which the leg bone or femur is out of the hip joint socket). Some individuals may develop a progressive "windswept" posture as a result of unequal tone in the lower half of their body, associated with hip dislocation and sometimes scoliosis.

We recommend that all individuals affected by leukodystrophy have regular evaluation of their hips and spine to help improve long-term outcomes and manage hip dislocation and scoliosis. Management includes physical examinations every

six months with imaging (X-rays) as needed. This regular monitoring can start around 2 years of age in children with gait abnormalities or spasticity. If caregivers notice pain, discomfort or other changes, individuals should have further imaging studies of the hips and spine and be referred to specialists in orthopedics, physiatry, and physical therapy. These specialists can help guide discussions about appropriate management options, which should take into consideration the overall health of the individual and the family's goals of care. Not all hip dislocations must undergo surgical intervention. Surgery should be considered if the dislocation is painful, impairs mobility, or poses other risks to the individual's well-being. In individuals under five years of age, many surgeons will recommend deferring surgery. After six years of age, reconstructive surgery may be considered.

Scoliosis in individuals with leukodystrophies is a serious concern and can create risks to respiratory and cardiac health. Over time, scoliosis may affect the ability to breath because the curve of the back does not provide enough space for the lungs to fully expand. Experts recommend a brief spinal exam at each clinic visit. If scoliosis is suspected, X-rays can be obtained, and your medical team may suggest you work with an orthopedic surgeon. In some cases, braces and external frames may be helpful. In some cases, braces improve seating position, but have not been shown to change scoliosis progression in the long term. In some cases, scoliosis can be repaired with surgery. Not all scoliosis will require surgical intervention. Surgery should be considered if the scoliosis poses other risks to the individual's well-being, including their breathing health. Orthopedic specialists and pulmonologists can help guide discussions about appropriate management options, which should take into consideration the overall health of the individual and the family's goals of care.

Mobility Difficulties

| Barriers to Ambulation |
|---|
| <ul style="list-style-type: none">• Spasticity• Weakness• Rigidity• Dislocation or contractures of joints• Ill-fitting or inappropriate adaptive equipment• Pain• Injury• Poor balance• Abnormal sensation• Involuntary movement disorders such as dystonia and chorea |

Some individuals with leukodystrophies are able to walk independently. However, over time, most will eventually experience some degree of difficulty with mobility. Preserving and optimizing the ability to walk and ensuring that an individual does weight-bearing exercises is crucial for overall health and quality of life. Without this, individuals may experience complications including bone fractures, joint dislocation, and weakened bones.

It should be noted however, that encouraging walking needs to be taken into a broader context of that individual's needs. In some cases, the patient may be mobile using rolling or scooting and this independent mobility is important. In some cases also, particularly where tone or joint problems are significant, weight bearing may be painful. In that case, the cause of pain must first be addressed prior to continuing weight bearing exercises.

Individuals should be screened for any treatable conditions that may impact their ability to walk or weight bear, such as abnormal muscle tone or pain. Even individuals who do walk should be regularly assessed for their risk of falling. Physical therapists and/or physiatrists can help to assess fall risk with caregivers and individuals. Physical therapists can help families understand their options for age-ap-

appropriate devices to assist with mobility and help individuals be as independent as possible. These devices include orthotics, braces, gait trainers, walkers, lifts, wheel chairs and standers. Regular physical therapy can also help to preserve motor skills and improve mobility.

Skin Care

Individuals affected by leukodystrophy commonly experience issues with skin health. Daily skin surveys by a caregiver are quite effective for maintaining skin health, and most skin infections can be prevented. We recommend a regular head-to-toe assessment, with the individual's clothes removed, to examine for areas of skin breakdown, with particular attention paid to areas where orthotic devices, braces, diapers, or other medical equipment regularly comes in contact with skin, in particular in weight bearing areas. The most important way to care for skin is to prevent skin breakdown. The best prevention of pressure related skin breakdown is to avoid pressure. For this reason, regular changes in position are very important.

| Challenges to Skin Health |
|--|
| <ul style="list-style-type: none">• Limited mobility• Orthotic devices or adaptive hardware• Nerve damage to hands and feet• Urinary or fecal incontinence• Disease-specific predispositions to skin lesions (Aicardi-Goutières Syndrome and Sjogren-Larsson Syndrome) |

NUTRITION, BOWEL, AND URINARY TRACT GUIDELINES

Nerves are present throughout the organs of the body, even if we no longer have to think about using them. Thus, swallowing, the production of saliva, the intestines and digestions, passing stool and urine, are all under the control of our nervous system. Similarly to how an individual affected by leukodystrophy may have problems with movement of the limbs, they will often have trouble with the functions of eating and evacuating bowel movements and urine.

Excessive Salivation and Drooling

It is not uncommon for individuals with neurological conditions like leukodystrophy to salivate, or drool, excessively. It is important to pay attention to drooling because it can be associated with physical, social, and psychological distress. Drool can irritate the skin surrounding the mouth over time. Excessive salivation can be a sign of the inability to swallow safely and can be associated with breathing problems as well.

Drool can result from a variety of medical issues, including dental problems (gingivitis, dental caries, and malocclusion), acid reflux, sleep apnea, and problems with swallowing. Otolaryngologists (ENTs), speech-language pathologists and occupational therapists can evaluate individuals and help to manage this condition. First-line interventions to help with excessive drooling include behavioral exercises, positioning, replacing medications that stimulate saliva secretion, and managing reflux.

Glycopyrrolate is quite effective for managing saliva and is safe to use in children older than three. However it can thicken secretions and cause sedation. Anticholinergics, which include hyoscine (oral/transdermal Scopolamine) and trihexyphenidyl (Artane), decrease mucus secretions. Sublingual 1% atropine ophthalmic solution

has also been used with success. Targeted botulinum toxin injections has also been used successfully, and more invasive procedures such as salivary gland surgery can be administered by a trained provider if the caregivers and medical team agree such interventions could be beneficial.

Swallowing and Feeding Issues

Problems with swallowing, acid reflux, and feeding issues are common among individuals with leukodystrophy. It is very important for caregivers to work with a nutritionist to ensure that the individual's nutrition and fluid intake is properly managed. Lack of fluids and improper nutrition can dramatically impact growth, brain development, immunity, bowel and bladder health, and overall quality of life. Poor nutrition for individuals affected by leukodystrophy can result from many factors, including diet, differences in metabolism, reflux problems, or difficulty swallowing. Individuals at highest risk for nutritional problems are those with limited communication, impaired mobility, and difficulty swallowing.

Caregivers need to make sure that the individual's diet will maximize health benefits. This is especially important if the individual dislikes certain foods because of texture, temperature, or consistency preferences. Even children who gain enough weight are at risk for health issues if they are too restricted in their food choices. If there is any question, caregivers should consult a dietician.

We recommend that each clinical visit include a comprehensive assessment of feeding-related risk factors. Medical professionals should check for dental problems, swallowing issues, acid reflux, and constipation. These regular feeding and nutrition assessments can occur at the time of diagnosis and every 3-6 months thereafter. The goal of these visits is to optimize oral feeding and continually assess the need for nutritional interventions like a feeding tube. Speech-language pathologists, and occupational therapists are equipped to assess swallowing and feeding-related issues. They can suggest a range of approaches, including proper positioning, adjustment of food consistency, feeding schedules, and equipment. It can be particularly helpful for a speech-language therapist or occupational therapist to observe the individ-

ual eating and evaluate chewing and swallowing. Ensuring that an individual gets enough fluids by evaluating skin color and the distribution of fat is also important for medical visits. All individuals should also be examined for signs of challenges with speech, coughing, and ability to eat. Pediatric individuals should also be evaluated for changes in height and weight. Caregivers may also provide additional information about day-to-day feeding or nutritional issues at home.

If the speech-language or occupational therapy assessment indicates difficulty swallowing or a risk for choking, further medical evaluation may be needed. Such testing could include a videofluoroscopic swallow study, modified barium swallow study, or fiberoptic endoscopic study examination of swallow. These swallowing assessments are useful in determining specific areas of concern and can alert families as to whether it is safe for individuals to swallow solid food or liquids. If these initial studies don't suggest any clear problems, individuals should be re-evaluated by observation by a speech therapist in 3 to 6 months—and sooner, if there is a sudden change in the individual's feeding habits. If the individual frequently coughs, chokes, has a wet or gurgly voice, has difficulty swallowing food, experiences weight loss or slow weight gain, vomits, or loses interest in food, this might indicate the family should work with a therapist to assess the individual. Managing swallowing is crucial for keeping an individual healthy and improving their quality of life. With proper interventions, swallowing issues can be properly managed over time.

When Do We Need a G-tube or J-tube?

Gastrostomy tubes (G-tubes) are widely considered a safe and effective way to maintain the nutritional needs of individuals at risk for choking or who may struggle to eat or drink fluids. Caregivers and medical teams might want to consider using a G-tube placement to manage insufficient weight gain, to improve nutrition or hydration, and to ensure that the individual can ingest fluids and medications.

Many families are reluctant to use a G-tube, and they may avoid the procedure out of fear. However, in many circumstances a G-tube can quickly improve an individual's quality of life. In many cases, families report that they waited too long to

use a G-tube and that it helped improve their quality of life because it is such an important tool. Children with G-tubes can still experience nausea, loss of appetite, and skin issues including granulation tissue and irritation around the G-tube site. Nevertheless, G-tubes can aid in providing additional nutrition, medication, and fluids. They may also prevent choking, and reduce the risk of pneumonia caused by aspiration. Individuals may benefit from G-tube placement even as they continue to eat by mouth. While a G-tube placement can help with care and quality of life, it does take some time to learn to use. You will need to spend time to develop a schedule for feedings and work closely with a nutritionist to ensure that, between tube and mouth feedings, your child is getting feedings at the right rate and schedule. Also, if you decide to use blenderized diets, you should take care to introduce one food item at a time to ensure that your loved one tolerates foods well.

In some cases, G-tube placement is combined with a Nissen fundoplication, a special folding of the stomach to prevent reflux. This is performed surgically, typically at the same time as a G tube is placed. This procedure may have complications, as it can be more difficult to manage gas if a Nissen is in place. Another option is to have the gastrostomy tube extended through the stomach, so that feeding enters the intestine directly (Jejunostomy tube or G-J tube) In some cases, severe reflux (see section below) may be better managed with a Nissen or G-J tube, but a complex-care pediatrician might consult with a gastroenterologist to determine what treatment options align with the medical goals of the individual's family.

Another type of tube, that is sometimes used while assessing a individual for a G-tube, is a tube from the nose to the stomach, which is called an nasogastric or N-G tube. This is a tube that connects a feeding port outside the body through a tube that runs from the nose into the stomach. N-G tubes are placed without surgery and can be used to help gain weight, but can be irritating to the individual and associated with vomiting and retching.

There is no medical research to suggest whether a N-G-tube, G-tube or G-J tube with Nissen fundoplication is better. You will need to work with your medical team to consider the different options for a specific individual's needs.

The decision to use a gastrostomy tube is often complicated. Many families may be hesitant to use a feeding tube because caregivers feel as if they have failed their loved one. Some families see the G-tube as a sign of the disease's progression, or fear that it will diminish the individual's quality of life. The reality is that many families find feeding tubes helpful to make meal and medication time safer and less stressful. Indeed, when the individual has difficulty maintaining weight and trouble getting adequate nutrition, a gastrostomy (G-tube) or jejunostomy (J-tube) should be understood as a useful treatment to help manage with these medical challenges.

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is common among individuals affected by leukodystrophy. GER can have adverse effects on feeding and sleep, and can cause vomiting, damage to the esophagus, respiratory difficulties, dental issues, and malnutrition. Inhalation of any matter into the lungs, such as food or acid from the stomach, can lead to serious lung disease among individual with neurological impairments, so it is important that families of individuals affected by leukodystrophy properly manage GER.

To help with reflux, speech and physical therapy can help to optimize the seating position and food consistency during feeding, which can mitigate GER. There are many medications that can help with reflex, mainly by changing the acid of the stomach or moving along contents faster. If medical approaches fail to manage GER and its associated medical complications, surgical interventions should be considered. Nissen fundoplication is often offered in conjunction with a gastrostomy or gastrojejunal tube placement (see inset "When do we need a G-tube or J-tube?"). Some experts suggest that these procedures can be effective for reducing esophagitis, GER, aspiration pneumonia, respiratory illness, reflux-related hospitalization, and death.

Bowel Movements

Impaired bowel movements are a common problem for many individuals affected by leukodystrophy. Constipation is an easily treated—yet frequently overlooked—source of chronic pain that can significantly impact quality of life. It can also lead to serious secondary complications, such as urinary retention (withholding of urine in the bladder). While there is no standard definition for constipation, it is generally considered as two or fewer bowel movements per week, or a consistency of stool that makes passing a bowel movement uncomfortable. The diagnosis can be made by history alone. Assessment of fluid intake should also be made at time of examination, as chronic dehydration is a risk factor for constipation. X-rays are only suggested in cases of extreme constipation and are not needed for the diagnosis of constipation.

To manage impaired bowel movements, primary caregivers need to be aware of basic facts about constipation (see “Family Education on Constipation”). Caregivers can then implement appropriate prevention strategies like introducing simple dietary changes, increasing hydration, and supplementing meals with dietary fiber, or adding enteral formula with fiber if the child is fed with a G-tube. If symptoms persist, the first choice is typically polyethylene glycol followed by lactulose which can be used as stool softeners. Enemas can be effective at managing constipation in individual with limited mobility, but should not be used as a preventative approach. Stool stimulants such as senna or bisacodyl can be helpful as well. While these may lead to dependency, priority should be given to optimizing the individual’s quality of life. Finally, if disimpaction (in which stool is manually broken up) is necessary, the medical team should consider consulting a gastroenterologist or general surgeon.

Family Education on Constipation

- The GI tract is an organ with many nerve cells important for its normal function
- Neurodegenerative diseases like leukodystrophy can cause some degree of constipation
- Constipation can be painful and can result in other serious complications such as urinary tract infections
- Mobility and hydration can reduce the individual's risk of constipation
- It is better to be proactive: *prevent* rather than treat
- Caregivers should become educated on the logistics of toileting, toileting adaptive equipment, and clothing modifications that can manage constipation

Urinary Health

Urinary dysfunction is a common complication for individuals affected by leukodystrophy. Nerve problems to the bladder, bowel and problems and constipation, and dehydration are risk factors for urinary dysfunction. Urinary incontinence represents a significant source of embarrassment, but it is important to destigmatize the issue and shift the focus to improving individual quality of life.

Symptoms of urinary dysfunction include urinary incontinence, urgency to urinate, or inability to urinate, all of which increase the risk of a bacterial infection of the bladder and kidney. In nonverbal individuals, untreated urinary tract infections (UTIs) may result in serious pain and discomfort, and may contribute to hospitalizations. Diagnostic tests for UTIs should be ordered urgently, as delays can increase the severity of UTIs and decrease quality of life. This evaluation should include a urinalysis with urine culture. However, this is not recommended for individuals with a history of intermittent or chronic catheterization.

In addition to bladder problems, individuals with Aicardi Goutieres syndrome can experience inflammatory complications to the kidneys, including a lupus-like glomerulonephritis, and these individuals should have regular urinalysis to assess for proteinuria (excessive protein in the urine, which can indicate kidney damage).

It is our general recommendation that a urology consultation should be considered if a female individual experiences two or more UTIs annually, or if a male individual experiences one or more UTIs annually. Consultation can also be helpful if the individual exhibits symptoms such as delayed urinary stream, urgency, or bed-wetting. Kidney and bladder ultrasounds monitoring urination may be helpful to assess for bladder dysfunction, and these studies can also help identify issues related to sphincter or bladder control. Prophylactic antibiotics should be used on a case-by-case basis under the guidance of a urologist or infectious disease specialist. Individuals taking anti-seizure medications should be monitored closely for urinary dysfunction, as some of these medications can predispose individuals to kidney stones. In cases of bladder retention, caregivers should consider urinary catheterization as guided by a urology specialist.

It cannot be overstated that caregivers and families play a necessary role in destigmatizing urinary complications in order to directly address individual well-being. Although urinary problems might be an uncomfortable topic, it is vital that caregivers pay close attention to promote the individual's well-being.

Gall bladder disease

As gallbladder disease has been detected in more than half of individuals with metachromatic leukodystrophy (MLD), we recommend that individuals with MLD have scheduled gallbladder ultrasounds with a gastroenterologist. Abdominal computed tomography (CT) scans can be used if gallbladder ultrasounds are not available. The most common abnormalities include gall bladder wall thickening and polyps. Polyps smaller than 5 mm may be tracked with annual tests. As determined by gastroenterologists, gallbladder removal should be considered for polyps larger than 5 mm. Gallstones have also been reported in patients with cerebrotendinous xanthomatosis, although this complication has not been formally studied. A common symptom of gallbladder dysfunction is abdominal pain, which can be difficult to distinguish from pain related to other issues, such as spasticity.

RESPIRATORY HEALTH, SLEEP, AND COMMUNICATION

Nerves are present throughout the organs of the body, even if we no longer have to think about using them. Thus, swallowing and breathing are all under the control of our nervous system. Similar to how an individual affected by leukodystrophy may have problems with bowels or bladder, they will often have trouble with the functions of coordinating swallowing and breathing, and may have weakness of the muscles needed for breathing, and coughing.

Pneumonias and Progressive Respiratory Insufficiency

Respiratory complications such as pneumonias are a common source of serious illness and even death among individuals with leukodystrophy. Fortunately, many potentially life-threatening complications are preventable. Respiratory failure may occur in the late stages of some leukodystrophies, particularly those associated with peripheral nerve dysfunction, such as MLD. Bulbar dysfunction, such as seen in Alexander disease, is associated with apneas or lack of the brain's command to take deep breaths. Finally, obstructive symptoms seen in many leukodystrophies with hypotonia can also result in intermittent apnea by blocking the outlet of the lungs at the vocal cords.

Symptoms of Respiratory Insufficiency and/or Aspiration

- Frequent coughing
- Coughing during meals
- Drooling
- Snoring
- Sleep apnea and wakefulness
- Persistent drowsiness
- Diminished cough and/or pneumonia
- Prolonged recovery from respiratory illness
- Prolonged supine positioning
- Neck flexor weakness
- Tachypnea, or rapid breathing
- Stridor, or a grating, vibrating sound when breathing

Difficulty swallowing, as discussed in detail in the Upper Gastrointestinal section, can contribute to acute or chronic lung disease. A clinical swallow assessment by a speech-language or occupational therapist in combination with diagnostic studies is helpful in the identification of aspiration risk. After the initial evaluation, we recommend check-ups every 6-12 months, or more frequently if new symptoms or risk factors arise. More frequent swallowing assessments are recommended for high-risk individuals, including those with clinical signs of weakness of the swallowing muscles, oral coordination issues, excessive salivation, a clinical history of pneumonia, or coughing during meals.

It is important to identify the cause of difficulties with breathing (e.g. weakness, obstruction, chronic injury, severe scoliosis), as this information can guide treatment options. Clinical recommendations and goals of care should take into account the family's quality-of-life considerations, and cultural and religious beliefs. Consultation with pulmonologists, gastroenterologists, and otolaryngologists should be considered early in the disease course to guide preventive strategies, foster therapeutic relationships, and enable anticipatory discussions of future supportive measures such as G-tube, tracheostomy, and mechanical ventilation. Pulmonary care ideally should be *preventative* rather than reactive.

A comprehensive strategy for treating respiratory problems should include infection prevention, airway maintenance, and mechanical support. Infection prevention includes annual flu vaccination, positioning and feeding modifications, regular hand washing, and avoidance of sick contacts when possible. Palivizumab, which targets respiratory syncytial virus (RSV), may be advised in select cases. Key airway maintenance strategies include repositioning, ambulation, physical therapy, as well as targeted interventions such as chest physical therapy, vest therapy, or cough-assist devices. Some individuals may benefit from regular use of a suction aspirator machine at home. Additional medical and surgical options are available to treat persistent salivation, as discussed above.

Because of the risk of progressive respiratory insufficiency, families may discuss the possibility of using mechanical ventilation with their treatment team. Available options, which can be considered in consultation with a qualified pulmonologist, include mechanical ventilation, continuous positive airway pressure (CPAP), bi-level positive airway pressures (BiPAP), or supplemental oxygen. In contrast to neuromuscular disorders, primary respiratory failure in individuals affected by leukodystrophy typically occurs in the context of severe cognitive impairment, once the disease is very advanced. This means that the family, individual, and medical team should discuss mechanical ventilation in the context of ongoing goals of care discussions, to decide whether they feel this is the best fit for a particular individual.

Communication

Maintaining communication between the individual and caregivers is among the most important and underappreciated goals of a comprehensive care strategy for leukodystrophy. Put simply, a language disorder is an impairment in understanding and use of spoken or written systems. The array of language impairments in an individual with leukodystrophy depends largely on the specific regions of the brain impacted by the disease. The progressive loss of language in individual with leukodystrophy is an area needing further formal study.

Individuals with leukodystrophy, like others affected by neurological impairments, often have problems with neuromotor speech. The two most common speech disorders are dysarthria and apraxia. Dysarthria is used to describe a group of speech disorders that are caused by abnormal strength, speed, range, steadiness, tone or accuracy of speech. Features of dysarthria include spastic, flaccid, hypokinetic, hyperkinetic, or ataxic speech. Unlike dysarthria, apraxia of speech is caused by difficulty planning or programming commands that direct speech movements in sequence. An individual with dysarthria or apraxia has difficulty with sound production, and this is often accompanied by reduced intelligibility and comprehensibility of speech. As a result, these individual can experience social isolation, exhibit maladaptive behaviors for communication, and have limited communication partners.

To help individuals affected by leukodystrophy with communication, families should consider a speech-language pathology (SLP) evaluation. A comprehensive exam will assess motor speech function, verbal and written expression and comprehension, communication effectiveness, and evaluation for communication tools. In order to best guide the individual family, the speech-language pathologist should work in coordination with caregivers to understand how they communicate with the child. This often serves as a good introduction to a broader “goals of care” conversation, and also provides valuable insight into the communication abilities of the individual at home.

A comprehensive augmentative and alternative communication (AAC) evaluation should be considered for any child whose current methods of communication are not effective in meeting the child’s daily communication needs. For some individuals, AAC may be used in specific situations identified as problematic, while others may use AAC as a primary means of communication. During the AAC assessment, the family and child work with a SLP to identify appropriate symbolic representations (photos, symbols, text), message types (full utterance, word-by-word, spelling), voice output (recorded, digitized, synthesized speech), technology level (no tech, low tech, high tech), and access (direct with hand or eye gaze, indirect scanning) options. In order to meet a individual’s individual communication needs, cognition, language, vision, hearing, and physical skills should all be considered.

It is important to adapt to an individual's evolving communication needs, which include new communication environments and changes in physical, cognitive, and language skills associated with typical development as well as disease progression.

The value of communication cannot be overstated. The difference between a complete absence of communication and the simple ability to communicate “yes” or “no” represents a drastic change in quality of life. Working with a SLP can help individual families find a system that can work for them.

Sleep

Sleep dysregulation, characterized by recurring episodes of difficulty initiating and maintaining sleep, is a common feature in individuals affected by leukodystrophy and can negatively affect the quality of life of both individuals and caregivers. While the specific incidence of sleep disorders in the leukodystrophy population has not been adequately studied, sleep disorders occur in over half of all individuals with severe multi-system disabilities. Common sleep problems include difficulty with sleep onset or maintenance, sleep-related breathing disorders, abnormal circadian rhythms, and excessive sleeping. Obstructive and central sleep apneas are also common in individuals with leukodystrophy and may necessitate specialist care and interventions. Untreated obstructive sleep apnea (OSA) can result in a variety of medical issues, including excessive daytime sleepiness, headaches, and even serious secondary cardiac complications. Neurologic irritability, such as that seen in early onset disorders such as infantile Krabbe and Aicardi-Goutieres Syndrome, can in some cases severely impact sleep as well. Sleep dysfunction can also result from other medical issues, including gastroesophageal reflux, pain, and spasticity that interrupt sleep. Each of these causes should be managed accordingly, and in consultation with the medical team.

An important first step in managing sleep disorders is optimizing sleep hygiene, with an emphasis on a consistent sleep schedule, avoiding screen time 1-2 hours prior to bedtime, and minimizing unnecessary medical interventions at night. Primary caregivers can record a sleep diary to help track the individual's sleep patterns

to identify problem areas. While there are no FDA-approved medications for the treatment of insomnia in children, off-label options include clonidine, tricyclic antidepressants, and benzodiazepines. In clinical practice, melatonin is often used to help with sleep initiation. Referral to a sleep medicine provider should be considered, particularly if OSA is suspected.

OTHER NEUROLOGIC ISSUES

Many individuals affected by leukodystrophy experience a wide range of other neurologic complaints, including pain, irritability, and cognitive impairment, all of which may negatively impact the quality of life of the individual and primary caregivers. The degree of cognitive impairment depends on the severity of the neural networks affected. Even within a family, each affected individual may demonstrate different rates of cognitive decline. Because leukodystrophy typically progresses in severity, caregivers should continually re-assess school and home accommodations and adjust them to the individual's evolving needs. In addition to the medical team, social workers can help families navigate these complex issues.

Pain and irritability

Managing pain and irritability is central to maintaining quality of life, but this is often overlooked by caregivers. Validated pain assessment tools are categorized by age and cognitive ability. In babies, we look towards crying, sleeplessness, and activity levels to determine if they are in pain. Vital signs, like heart rate and blood pressure, can also be helpful. An individual with an AAC system for communication may use alternative methods for describing discomfort or pain, such as a gesture dictionary or photographic body representations.

After it is determined that the individual is in pain, caregivers and the clinical team should investigate common triggers for discomfort. The list of potential causes that are invisible to the caregiver is extensive. Common pain triggers include dental abscesses, bowel obstruction and constipation, pancreatitis, bone fractures, acute joint dislocation, muscle tone issues, respiratory compromise, skin breakdown, and urinary tract infections. In addition, current medications should be reviewed for agents that may contribute to pain or worsen existing neurologic symptoms. Peripheral neuropathies (nerve damage to the arms and legs) are common in select

leukodystrophies, such as Krabbe (globoid cell) and MLD, and can result in dysfunction as well as discomfort.

Gabapentin can be particularly helpful for managing neuroirritability and neuropathic pain, though this approach has not been formally studied in the leukodystrophy population. Benzodiazepines may also be effective for managing agitation. Many of the same principles can be effective for older individuals affected by leukodystrophy.

Seizures

Seizures affect almost half of individuals with leukodystrophy. In rare cases, seizures may be the symptom that indicates an individual has a leukodystrophy, such as in Alexander Disease. Epilepsy is a common feature of several other leukodystrophies, including Krabbe disease, Aicardi Goutieres Syndrome (AGS), megalencephalic leukoencephalopathy (MLC), sialic acid storage disorders, and peroxisomal disorders. Epilepsy is defined as two or more unprovoked seizures, a single seizure with a high risk for a second seizure, or the presence of a known epilepsy syndrome. Seizure mimics (see table, “Common Seizure Mimics”) are common and should be considered during the evaluation of any potential epileptic event.

| Common Seizure Mimics |
|---|
| <ul style="list-style-type: none">• Gastroesophageal reflux (Sandifer syndrome)• Breath-holding spells• Fainting and dysautonomia• Movement disorders (including tics and dystonias)• Behavioral events• Pain crises• Sleep disorders (including periodic limb movements and night terrors)• Metabolic disturbances (including hypoglycemia)• Staring spells or inattention |

A careful clinical history may allow providers to determine whether an individual has had a clinical seizure or a seizure mimic. Features such as the type of move-

ment, duration, and context are important in the evaluation of seizures. A routine electroencephalogram (EEG) may help establish a formal diagnosis of seizures and guide subsequent medication selection, and video EEG monitoring can be useful to distinguish between seizures and non-epileptic events. Following a clinically diagnosed seizure, we recommend that individuals be referred to a neurologist, who will guide the need for and selection of anti-seizure medication. There is no evidence to support the use of anti-seizure medications prior to the onset of clinical seizures, as these medications do not prevent the development of epilepsy, and many individuals affected by leukodystrophy will not develop seizures. Therefore, the first step after a seizure ends should be an assessment for provoking factors, such as fever, electrolyte dysregulation, medication withdrawal, and infection. Urinary tract infections are an especially common risk factor for seizure in the leukodystrophy population because of underlying issues with urinary retention and voiding. When there is an underlying cause (such as a fever), individuals typically do not require a daily prevention medication. Medications used to stop a seizure (therapies such as rectal diazepam and oral or intranasal midazolam) can be provided for individuals with prolonged or clustered seizures.

Autonomic Nervous System Dysfunction

The autonomic nervous system are those nerves that control involuntary activities such as breathing, heart rate, digestion, and evacuation of stool or urine. Autonomic dysfunction affects many individuals with leukodystrophy and, given the autonomic nervous system's role in maintaining homeostasis, can result an array of symptoms (See table, "Autonomic Dysfunction").

Autonomic dysfunction can be inherent to the neurodegenerative process or can be triggered acutely by pain or infection. The acute onset of a cluster of dysautonomic symptoms is referred to as an "autonomic storm." Potential triggers should be evaluated in individuals who are at risk for autonomic dysfunction. Medications that may be helpful in the preventative management of dysautonomia include gabapentin, cyproheptadine, baclofen, beta-blockers, and clonidine. For acute attacks, diphenhydramine, acetaminophen, or ibuprofen can be useful.

| Autonomic Dysfunction | | |
|------------------------------|--|--|
| System | Examples of Dysfunction | Potential Evaluation and Management |
| Genital-urinary | <ul style="list-style-type: none"> • Urinary retention • Urinary incontinence • Excessive nighttime urination | <ul style="list-style-type: none"> • Evaluation by a urologist • Management of urinary retention by bladder training, medications, and/or catheterization • Routine assessment for urinary tract infections |
| Gastrointestinal | <ul style="list-style-type: none"> • Feeding difficulties • Dysphagia • Esophageal dysmotility • Delayed emptying of the stomach into the intestines • Recurrent abdominal pain • Intestinal dysmotility • Incontinence or constipation | <ul style="list-style-type: none"> • Speech/occupational therapy evaluation of feeding • Assessment of nutritional status • Assessment for aspiration risk • Dietary management: optimize hydration and dietary fiber for constipation • Medical management (e.g. stool softeners and laxatives) for constipation |
| Cardiac and vascular | <ul style="list-style-type: none"> • Arrhythmias • Tachycardia • Hypertension • Postural hypotension (sudden drop in blood pressure upon standing) • Acrocyanosis (limited blood flow to hands and feet) | <ul style="list-style-type: none"> • Evaluation by a cardiologist • Keeping hands and feet warm and elevated • Optimization of hydration and salt intake for postural hypotension |
| Sudomotor function | <ul style="list-style-type: none"> • Temperature regulation (hyperthermia or hypothermia) • Flushing • Sweating issues | <ul style="list-style-type: none"> • Regulating the temperature of the room |
| Ophthalmologic | <ul style="list-style-type: none"> • Alacrima • Pupillary changes • Ptosis (drooping eyelids) | <ul style="list-style-type: none"> • Evaluation by an ophthalmologist • Eye lubrication or eye patching at night to prevent corneal abrasions |
| Pulmonary | <ul style="list-style-type: none"> • Apneas • Disordered breathing • Respiratory insufficiency | <ul style="list-style-type: none"> • Evaluation by a pulmonologist • Consider sleep study for diagnosis |

| | | |
|------------|---|---|
| Neurologic | <ul style="list-style-type: none"> • Pain • Sleep cycle dysregulation • Spasticity • Dystonia • Seizures • Irritability | <ul style="list-style-type: none"> • Pain management medications • Sleep management interventions |
|------------|---|---|

Additional Neurologic Considerations

Several leukodystrophies are associated with significant behavior issues, including inattention, irritability, hyperactivity, and aggression. Infantile Krabbe disease classically is characterized by hyperirritability. Many adult presentations of leukodystrophy are associated with early psychiatric or behavioral symptoms that can sometimes precede other difficulties such as changes in gait by many years.

Although not evaluated by controlled clinical studies, gabapentin is often chosen as the first line medication for neuro-irritability given its safety of use. Alternatives that await further study include pregabalin, topiramate, tricyclic antidepressants, and valproic acid. If the individual does not respond to these medications, benzodiazepines can be used with caution. Clinical experience suggests that valproic acid may be a helpful mood and behavior stabilizers. Neuroleptic agents should be avoided if possible as they may worsen movement problems seen in leukodystrophy.

Certain leukodystrophies can result in significant involvement of the nerves in the arms, hands, legs and feet, causing pain. Because the signs of peripheral neuropathy may be overshadowed by brain dysfunction, and individuals may be unable to communicate the symptoms of neuropathy, careful attention should be given to detect the presence of peripheral nerve involvement. Testing for dysesthesia (abnormal sense of touch) should be included in routine neurologic examinations, in particular for early-onset disorders such as Krabbe and MLD. When peripheral neuropathy is identified, the medical team should identify appropriate treatment for these often painful symptoms.

After genetic diagnosis, most individuals with leukodystrophy do not necessarily require subsequent brain imaging such as MRI outside of clinical trials. The evi-

dence behind which disorders need follow up imaging and the frequency of testing is not fully known. Individuals affected by L-2-hydroxyglutaric aciduria, *SAM-*HD1**-associated Aicardi-Goutières Syndrome (AGS), Multiple Sulfatase Deficiency, and Alexander Disease may benefit from repeated brain imaging to assess for progressive complications, but some other individuals may not need repeated imaging. The decision to repeat brain MRIs should be weighed with whether sedation is necessary to achieve sedation, the overall health of the affected person, and what new information might be gained by doing the imaging.

ENDOCRINE COMPLICATIONS

Certain leukodystrophies can also affect the glands in the body that make hormones. The reason for this is poorly understood in most cases, but the effects can in some cases cause significant health concerns. The most common of these are mentioned here.

Adrenal Insufficiency

The vast majority of male individuals affected by X-ALD will ultimately develop adrenal insufficiency between infancy and adulthood. Adrenal insufficiency should be tested for in any individual in the general population with malaise, fatigue, low blood pressure, low blood sodium, hyperpigmentation, weight loss, vomiting, and poor growth. A simple and reliable screening test known as very long chain fatty acids (VLCFA) can help to diagnose X-ALD and should be considered for all boys with suspected adrenal insufficiency.

Although life threatening, when diagnosed, adrenal insufficiency can be easily treated with corticosteroid supplementation. Adrenal insufficiency is assessed through laboratory measurements of adrenocorticotrophic hormone (ACTH) and morning cortisol levels. An endocrinologist may also recommend additional studies such as aldosterone, plasma renin activity, and ACTH stimulation tests.

Individuals with X-ALD should be screened regularly for adrenal insufficiency beginning at the time of diagnosis, although the frequency of this testing has yet to be formally studied. Once present, adrenal insufficiency in X-ALD is usually chronic, requiring daily oral steroid administration with increased dosing at times of clinical stress such as an illness or surgery. It is important that families receive from their medical team a letter of instruction on steroid stress dosing and testing to give to outside providers and emergency rooms.

Ovarian Failure

Ovarian failure is a complication in which the ovaries fail to properly function and release hormones such as oestrogen. Ovarian failure may be primary, in which the ovaries themselves do not respond to hormones made by the brain, or secondary, in which the brain does not make the necessary hormones to induce the ovaries to function. Girls with ovarian failure may not have menstruation or fully develop puberty. Primary ovarian failure may arise as a complication of a number of leukodystrophies, including AARS2-related disorder, as well as some mitochondrial and chromosomal (such as 18q) disorders. Females diagnosed with vanishing white matter (VWM) disease may experience primary or secondary ovarian failure. These individuals may need screening measurements of hormones related to ovarian function, including estradiol, luteinizing hormone (LH), and follicular stimulating hormone (FSH) as recommended by an endocrinologist or gynecologist.

Other Leukodystrophy-specific Endocrine Issues

Individuals with 4H leukodystrophy (hypomyelination, hypogonadotropic hypogonadism and hypodontia) typically experience a variety of endocrine abnormalities, including hypogonadotropic hypogonadism (in which the brain does not make hormones necessary for puberty), and, less commonly, hypothyroidism (low thyroid hormone) and growth hormone deficiency. Individuals with 4H should see an endocrinologist at diagnosis and regularly thereafter. Although there are no agreed-upon clinical guidelines, we recommend that individuals be screened at diagnosis and then annually for growth failure. A slow or flat rate of growth may be indicative of growth hormone failure. Additionally, testing of testosterone, luteinizing hormone, and follicular stimulating hormone levels should be considered at the age of expected puberty. Thyroid stimulating hormone (TSH) and T4 can be used as marker of hypothyroidism, with hormone replacement therapy administered as needed. For cases of hypogonadotropic hypogonadism, the benefits and risks of sex steroid replacement should be discussed thoroughly with the medical team. Hypothyroidism has also been reported in individuals with cerebrotendinous

xanthomatosis and in individuals with Aicardi-Goutieres syndrome, so these individual populations should be specifically screened for this condition.

Post-transplantation Endocrine Considerations

Specific leukodystrophies, when identified before the onset of full symptoms, can be treated with bone marrow transplantation. Individuals who have undergone therapeutic stem cell transplantation are at increased risk for endocrine disorders because of the effects of medication, irradiation, and the transplant itself. If growth failure is observed, these individuals should be considered for referral to an endocrinologist for regular growth evaluation or for growth hormone screening. These individuals also may benefit from regular monitoring of thyroid function, with clinical follow-ups for thyroid nodules. After transplant, individuals are also at risk for gonadal failure (of the ovaries or testes) which can present as delayed puberty. Post-transplant osteoporosis should also be assessed and treated as deemed necessary.

ADDITIONAL SYSTEM-SPECIFIC CONCERNS

Although this guide cannot be exhaustive, in order to be as complete as possible, several other possible health complications that are not included in other sections are mentioned here.

Cardiac Issues

Some leukodystrophies are known to be associated with cardiac issues and require regular visits with a cardiologist. These most notably include AGS, 18q- syndrome, infantile sialic acid storage disorders, and fucosidosis. Mitochondrial leukoencephalopathies can also be associated with cardiomyopathy (weakened heart muscles) and cardiac rhythm abnormalities (irregular beating of the heart).

Due to the underlying abnormalities in cholesterol metabolism, cerebrotendinous xanthomatosis may be associated with accelerated coronary heart disease and hypertrophy of the atrial septum. Additionally, respiratory complications such as obstructive sleep apnea can cause secondary cardiac abnormalities.

Finally, individuals with AGS may have an inflammatory cardiomyopathy and pulmonary hypertension and should be followed by cardiologists on a yearly basis. If suspected, prompt referral to a cardiologist is recommended.

Ophthalmologic Issues (or issues with eyes and vision)

Regular ophthalmological monitoring can prevent many of the eye-related complications associated with leukodystrophies. Potential problems range from glaucoma (which results in increased pressure inside the eye, damaging vision), which is observed in individuals with Aicardi-Goutières Syndrome and peroxisomal disorders,

to the ocular malformations found in oculodentodigital dysplasia (ODDD) (See table, “Ophthalmologic Complications of Leukodystrophies”).

Progressive myopia, or near-sightedness, is a common manifestation of 4H or POLR3-related leukodystrophy and requires regular ophthalmological assessments. In 4H, individuals with very severe myopia can be at risk for a complication called retinal detachment and any rapid change in vision should prompt emergent evaluation by your ophthalmologist.

Additionally, several other complications can affect vision in individuals affected by leukodystrophy. Optic atrophy is a common feature in a number of leukodystrophies. Eye movement abnormalities, including the nystagmus common to many hypomyelinating leukodystrophies including Pelizaeus-Merzbacher disease, can impair function and activities such as reading. Macular degeneration or damage to the part of the retina crucial for vision is common in Sjogren-Larsson syndrome, a disorder of lipid metabolism. With any eye-related concerns, we recommend evaluation with an ophthalmologist, and vision services as appropriate.

Finally, facial weakness and decreased blinking can result in significant risk of ocular dryness, which can cause injury to the cornea. This can be easily prevented through regular use of eye moisturizing drops or gel. Careful observation and questioning to determine if the individual has any concerns with vision or the function of the eye should be included in general health maintenance.

Dental Guidelines

In addition to the regular dental care needed for all individuals, individuals affected by select leukodystrophies require regular dental evaluations, preferably by specialists who are aware of leukodystrophy-specific considerations. Individuals affected by Cockayne syndrome are predisposed to cavities. 4H, or POLR3-related leukodystrophy, is associated with variety of teeth abnormalities, including a delay in tooth growth. Individuals with Aicardi-Goutieres syndrome and cerebrotendinous xanthomatosis are at increased risk for tooth loss. A specialist in pediatric special-needs dentistry may be particularly helpful.

| Ophthalmologic Complications of Leukodystrophies | |
|---|--|
| Leukodystrophy | Potential Issues |
| 4H or POLR3-related leukodystrophy | <ul style="list-style-type: none"> • Severe myopia • Retinal detachment |
| Aicardi-Goutières Syndrome (AGS) | <ul style="list-style-type: none"> • Glaucoma |
| Peroxisome biogenesis disorders | <ul style="list-style-type: none"> • Pigmentary retinopathy • Progressive visual loss • Glaucoma • Cataracts |
| Oculodentodigital dysplasia (ODDD) | <ul style="list-style-type: none"> • Glaucoma • Microphthalmia • Microcornea • Iris malformations • Optic atrophy |
| Cerebroretinal microangiopathy with calcifications and cysts disease (CRMCC, Coats plus syndrome) | <ul style="list-style-type: none"> • Bilateral retinal telangiectasia • Retinal exudates |
| Leukoencephalopathy, brain calcifications, and cysts disease (LCC) | <ul style="list-style-type: none"> • Bilateral retinal telangiectasia • Retinal exudates |
| Retinal vasculopathy with cerebral leukodystrophy (RVCL) | <ul style="list-style-type: none"> • Bilateral retinal telangiectasia • Retinal exudates |
| Sjogren-Larsson Syndrome (SLS) | <ul style="list-style-type: none"> • Macular degeneration with perifoveal crystalline inclusions |
| Hypomyelination and congenital cataracts (HCC) | <ul style="list-style-type: none"> • Cataracts |
| Pelizaeus-Merzbacher disease | <ul style="list-style-type: none"> • Nystagmus |
| Cerebrotendinous xanthomatosis | <ul style="list-style-type: none"> • Cataracts |

COORDINATION OF CARE

As described above, the care of an individual with leukodystrophy can involve multiple subspecialists and experts. Navigating the coordination of the multiple appointments can be time consuming and difficult. In some cases, one family member becomes the person who coordinates all of these appointments. In other cases this is a shared responsibility. It is important to note however, that this effort places a significant burden on that family member(s) time and resources. We include below some recommendations some families have found helpful.

Families and caregivers should ask their medical providers to help them outline a longitudinal clinical care plan: starting at diagnosis and continuing over the course of the individual's medical care. This will improve the relationship between family and clinical care team by fostering transparency and communication. Families can ask for information including basic disease information and a summary of the key areas of clinical focus in writing. The handout should list each provider and their specific recommendations for follow up visits, studies, and medications (See table, "Sample Clinical Care Plan").

In addition, families may find it helpful to organize a binder, that includes sections for copies of important medical records, contact information for key medical providers, up to date lists of medications and which pharmacy dispenses them, and photographs of home equipment and resources. Some families also use pre-printed forms for daily diaries, to note symptoms and challenges, as well as medications or unusual medical events. These can become invaluable when trying to understand responses to a medication or trace back to when a new symptom began or how often it occurs.

Additionally, the family or caregivers may find it helpful identify a primary medical provider, who can be a pediatrician, or one of the many sub-specialties seen by

affected individuals, to play the role of “quarter back.” This medical provider will help the family to set priorities in care, and make sure each medical decision that is made is consistent with those goals of care. Additionally, to empower families, individuals and families should independently keep track of their local care team visits, medication changes, lab results, and medical treatments.

Families should ask the care team for information about which “red flags” that may warrant consultation with a specialty care center or seeking emergency care, such as the symptoms of adrenal failure in boys with adrenoleukodystrophy. All individuals with leukodystrophy should have the opportunity, if desired, to be involved in clinical research, including natural history studies, so families should ask their providers about these opportunities and seek additional information on www.clinicaltrials.gov.

| Sample Clinical Care Plan | |
|---|---|
| Today your child/loved one saw the following providers: | |
| Neurology (Dr. X, contact information) | Prescribes X medication (dosage and schedule) for seizures Prescribes X medication (dosage and schedule) for behavioral issues Recommends X study to be completed |
| Physiatry (Dr. X, contact information) | Prescribes X medication (dosage and schedule) for spasticity Prescribes X equipment for X |
| Physical Therapy (X, contact information) | Recommends the following exercises and stretches |
| Nutrition (X, contact information) | Recommends the following changes to your child’s /loved one’s diet |

Transitions in Care

There are several key transitions of care that occur during the life of individuals affected by leukodystrophy: inpatient to outpatient, pediatric to adult care, and home to group care. Additionally, there are insurance coverage changes, changes in

access to services, and end-of-life care to consider. Conversations on transitions of care should be started early to become familiar with evolving needs. Earlier access to palliative care can guide the families with difficult decision-making and work to set a “compass” for care. In pediatrics in particular, palliative care services are available to any individual with a chronic or life-threatening condition. As a whole, our health care systems need to dedicate more effort to educating families in order to overcome longstanding stigmas associated with palliative care, and to help distinguish palliative care from hospice care. The primary goal of palliative care is the treatment of suffering and improvement of quality of life; hospice, on the other hand, can be a valuable resource for end of life care.

An additional important transition, is the legal transition from the status of a child to that of an adult, that occurs at age 18. After age 18, individuals need to provide consent for and provide independent decision making around health care choices. That can be very complex for teens with complex medical histories, or with cognitive or physical impairments that limit their ability to make decisions or communicate their wishes. Several years before a child’s 18th birthday, or in any adult with compromised decision-making ability, work with a social worker or family lawyer to understand regional laws applying to adults with limited decision-making capacity. Putting in place the right guardianship or medical advocate roles in place before a medical emergency care reduce stress and improve care transitions.

Other resources

Online resources are able to quickly report on relevant innovations and changes in care strategies and resources. These resources allow families of individuals affected by leukodystrophy to communicate about research and therapeutic opportunities, and foster a more active role as parents, clients, and individual advocates. Additionally, social media groups can be an invaluable source of social and practical information from other parents, families and individuals living with the same day to day concerns. However, information gathered from such sources should be verified with the medical care team to ensure that recommendations are accurate and appropriate for a specific individual affected by leukodystrophy.

CONCLUSIONS

Our goal with this document is to provide a framework to address the multi-faceted needs of individuals with leukodystrophy in order to maximize their quality of life. A dedicated leukodystrophy center is only one part of the important network of providers. In some cases a leukodystrophy center may not currently be accessible to all individuals and their families, but a local provider can assemble needed resources. A primary goal of the leukodystrophy community is to create a wider network of physicians who are qualified to accommodate individuals who do not have regular access to sites within formal leukodystrophy care centers. Efforts are underway to develop a system that allows more experienced specialists to train providers beyond the geographical reach of the current clinical sites and have specialized physicians actively communicate with local physicians and help them access the resources they need.

The ultimate goal of care for an individual affected by leukodystrophy is to enhance both their quality and duration of life. While a definitive diagnosis may inform disease-specific therapies and research eligibility, and represents a major milestone in the individual's clinical odyssey, the lack of a diagnosis should *not* preclude comprehensive preventative and symptomatic care. All individuals deserve a comprehensive prevention and symptom management plan. Delivery of such care requires the involvement of a multidisciplinary team, ideally in the context of a dedicated leukodystrophy center, working in collaboration with local pediatricians and health care providers. As guided by the individual's changing needs, the team may include geneticists and genetic counselors, neurologists, complex care pediatricians, pulmonologists and respiratory therapists, gastroenterologists, speech therapists, endocrinologists, physiatrists, orthopedic surgeons and physical/occupational therapists, specialists in palliative and hospice care, and social workers. Finally, contact with

advocacy groups specialized in individual leukodystrophies may provide additional specific information as well as much needed support from other families.

Together, this network represents our leukodystrophy family, which we hope will work together until each disorder has a curative treatment.

About the Global Leukodystrophy Initiative

We would like to acknowledge that the information provided in this guide is modified from the original article “Revised consensus statement on the preventive and symptomatic care of individuals with leukodystrophies,” *Mol Genet Metab.* 2017 Sep;122(1-2):18-32 with permission from the journal.

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The Global Leukodystrophy Initiative (GLIA), a consortium of leukodystrophy experts and individual advocates, was founded in 2013 with the aim of standardizing guidelines for the diagnosis and management of leukodystrophies. For more information, please visit theglia.org or contact the GLIA Coordinator at lce@email.chop.edu.

This guide was created through the leadership of the Global Leukodystrophy Initiative (GLIA) and represents an international collaboration among researchers, clinicians, and patient/parent advocates. The guide is intended to help patient families become “champions” for the care and treatment of people living with leukodystrophy.

Even though there is no cure for leukodystrophy, there are treatments that can help provide the highest quality of life possible.

YOU ARE NOT ALONE.

You can learn more at the Leukodystrophy Family Forum (LFF) leukodystrophyforum.com and the Global Leukodystrophy Initiative (GLIA) (theglia.org).

Please do not hesitate to contact the LFF or GLIA if have more questions.

