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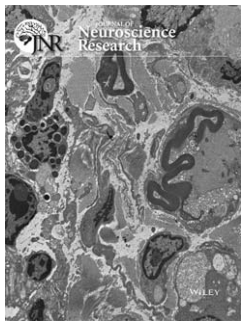
Review

Clinical Management of Krabbe Disease



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Krabbe disease (KD) is a rare neurodegenerative disorder caused by mutations in the gene encoding the galactocerebrosidase enzyme. The early- and late-infantile subtypes, which are the most common forms of the disease, are rapidly progressive and lead to early death, whereas the later-onset types are clinically heterogeneous. The only disease-modifying treatment currently available is hematopoietic stem cell transplantation, which is effective only when performed early in the course of the disease. Because most patients with KD are diagnosed too late for treatment, primary care physicians are faced with the challenge of caring for a child with severe neurologic impairment. This Review describes presenting symptoms, diagnosis, and disease manifestations of KD and provides basic guidelines for its management. Symptomatic treatment and supportive care that address the unique requirements of these patients can greatly improve the quality of life of patients and their families.

Key words: Krabbe disease; globoid cell leukodystrophy; disease management; chronic disease; palliative care; terminal care

Krabbe disease (KD) is a rare neurodegenerative disorder caused by a deficiency of the lysosomal enzyme galactocerebrosidase (GALC), which normally degrades galactolipids in the myelin sheath (Suzuki, 1998, 2003). In affected individuals, the abnormal galactolipid accumulation triggers an inflammatory response, a loss of myelin-forming cells, and a progressive demyelination of the central and peripheral nervous systems.

KD is typically divided into subtypes based on age at onset, with earlier onset associated with more rapid progression. Infantile KD, which accounts for approximately 85–90% of cases (Wenger, 2011), can be further divided into early-infantile disease, in which symptoms appear by 6 months of age, and late-infantile disease, in which symptoms typically appear between 7 and 12 months of age. Untreated children with early-infantile disease experience rapidly progressive neurologic deterioration, seizures, psychomotor regression, loss of vision and hearing, and ultimately early death, generally by 2 or 3 years of age. Initial symptoms include crying/irritability, feeding difficulties, poor head control, fisted hands, and loss of smiling. As the disease progresses, crying and irritability improve, but the child shows rapid mental and motor deterioration, hyperactive reflexes, hypertonicity, loss of vision, and seizures. In the final stage of the disease, stiffness decreases, but the child becomes blind and deaf and loses voluntary movement (Suzuki, 2003). Children with late-infantile disease experience similar symptoms but typically survive longer. In contrast, the juvenile- and adult-onset forms are clinically heterogeneous, and survival varies widely. Common initial symptoms in juvenile-onset KD are vision problems, muscle weakness, gait changes, and loss of developmental milestones (Wenger, 2011). In adults, initial symptoms include gait changes, weakness, and lower limb hypoesthesia. Spastic paraparesis is a prominent feature of adult-onset disease (Debs et al., 2013).

KD is inherited in an autosomal recessive manner, with an estimated incidence of 1 in 100,000 births in the United States (Wenger, 2011). Researchers have identified more than 75 *GALC* mutations that are known or suspected to cause KD; however, it is difficult to predict age of onset based on mutational analysis alone (Wenger et al., 2013).

Prompt diagnosis allows some children to benefit from hematopoietic stem cell transplantation (HSCT), which is currently the only disease-modifying treatment for KD. Bone marrow was originally used as the stem cell

SIGNIFICANCE

The systematic management of Krabbe disease (KD) has not been reported because of the rarity of the disease and the geographic dispersion of patients. This is the first time that a large number of patients with KD have been followed by a multidisciplinary group of specialists for more than 15 years.

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source, but umbilical cord blood (UCB) is now more commonly used (Krivit et al., 1998; Escolar et al., 2005). The transplanted stem cells are engrafted in various tissues to serve as a lifelong source of the missing GALC enzyme, leading to remyelination of the central and peripheral nervous systems (Siddiqi et al., 2006a).

Although not a cure, UCB transplantation can prolong life and preserve cognitive skills when performed in presymptomatic infants, but most treated children still experience spasticity; lower than average growth; and difficulties in expressive language, adaptive behavior, and motor function (Escolar et al., 2005; Prasad et al., 2008). A staging system based on clinical signs and symptoms has been developed to determine which patients are candidates for UCB transplantation (Escolar et al., 2006a). However, it is important that treatment decisions be made by a specialist who has expertise in KD.

Treatment decisions can be particularly challenging for asymptomatic infants classified by newborn screening as being at high risk for KD. Because infantile KD progresses so rapidly, it should be treated as an emergency because treatment delays can greatly affect outcome. In contrast, the treatment window is much longer for the more slowly progressing later-onset forms of the disease, and safer, more effective therapies may be available by the time treatment is required. However, mutational analysis and residual GALC enzyme activity have only limited ability to predict age of disease onset (Jalal et al., 2012). In addition, clinical and neurodiagnostic assessments in the earliest stages of the disease are reliable only when performed by clinicians with expertise in this disease. In the first 8 years of newborn screening for KD in New York State, most of the high-risk infants did not develop the infantile form of the disease and have remained asymptomatic (Orsini et al., 2016). Thus, referring all high-risk infants for transplantation would expose many of them to unnecessary risk because this treatment is associated with considerable morbidity and mortality.

Most physicians caring for a patient with KD have no previous experience with the disease and lack adequate information on its diagnosis and disease-specific complications because of the rarity of the condition. In the past, parents were often told that nothing could be done for their child, and they still receive conflicting information from healthcare professionals about therapeutic options. Appropriate supportive care is critical to make these children more comfortable and allow them to enjoy life to the fullest extent possible. Even children who successfully undergo UCB transplantation require medical management for remaining symptoms such as spasticity and motor disability (Escolar et al., 2006b).

This Review provides a summary of best practices for the management of KD based on empirical evidence from evaluations of 133 patients conducted over 15 years. Most of the patients (65%) were followed longitudinally (i.e., seen more than once), for a median followup of 2.1 years (range 2–15.4 years). These patients underwent a median of three evaluations (range two to 22) for a total of 498 evaluations, 313 evaluations in 84 patients with early-infantile disease, 147 evaluations in 37 patients with late-infantile disease, and 38 evaluations in 12 patients with juvenile disease.

INITIAL ASSESSMENT

To help establish disease subtype and assess disease progression, the initial examination includes a comprehensive history and physical examination. In KD, feeding difficulties and failure to thrive are common in the initial stages of early-onset disease (Escolar et al., 2006a). Cerebrospinal fluid protein level is typically elevated, but cell count is normal (Barone et al., 1996; Escolar et al., 2005). Abnormal deep tendon reflexes and increased tone in the extremities are usually present, clonus and plantar extensor responses are common, and optic nerve atrophy is sometimes noted at the initial neurologic examination.

Even before symptoms are apparent, nerve conduction studies often show prolongation of distal latency, low amplitude, absent evoked response, or prolonged F-wave latency (Escolar et al., 2006a; Siddiqi et al., 2006b). These peripheral nerve abnormalities are typically among the first signs of KD and can be observed in some newborns with early-infantile disease. Later in the disease process, abnormalities can be observed in flash visual evoked potentials (absent P100 wave), electroencephalography (abnormal focal or generalized slowing, spikes, or sharp waves), and brainstem auditory evoked potentials (prolonged wave I–V interpeak latency or absence of at least one obligate wave form [I, III, or V]; Husain et al., 2004; Escolar et al., 2006a; Siddiqi et al., 2006b). Magnetic resonance imaging and computed tomography show progressive, diffuse, and symmetric brain atrophy. Magnetic resonance imaging is the best imaging technology for detecting demyelination early in the disease (Wenger et al., 2011). Together, nerve conduction and neuroimaging studies appear to be the most sensitive tests for determining disease severity and subtype (Husain et al., 2004; Siddiqi et al., 2006b; Gupta et al., 2014).

INTERVENTIONS

Because KD shares important features with cerebral palsy, medical management approaches used for cerebral palsy are often useful for infants and children with KD. Cerebral palsy is a nonprogressive neurodevelopmental disorder resulting from injury to the developing brain. Its causes include infection, low birth weight, placental abnormalities, decreased intrauterine growth, and traumatic brain injury (Aisen et al., 2011). Damage to the cerebral cortex leads to motor impairment (e.g., muscle weakness, spasticity, contractures), gastrointestinal problems, seizures, and hearing and vision problems (Aisen et al., 2011). Despite differences in disease etiology, cerebral palsy and early-onset KD show similar initial symptoms (e.g., difficulty swallowing, oral motor dysfunction). In addition, UCB transplantation halts the progression of

TABLE I. Management Recommendations for Complications of KD

Complication	Recommendations	References
Gastrointestinal		
Vomiting and reflux	Keep the child in an upright position both during and after feeding	Arvedson, 2008; Bell and Samson-Fang, 2013
	Proton pump inhibitors such as omeprazole and lansoprazole are useful for controlling reflux in children over the age of 1 year	Gold and Freston, 2002; Samson-Fang et al., 2003
	Nissen fundoplication is useful for preventing reflux in untransplanted children and is often performed with gastrostomy tube placement	Gold and Freston, 2002
Dysphagia	Modifying the texture and thickness of foods can help with swallowing difficulties; commercial thickening agents containing xanthan gum or starch can be added to liquids but are not appropriate for premature infants	Bell and Samson-Fang, 2013
	For nonoral feeders, swallowing ability can be improved by providing tiny tastes of food or juice several times per day	Arvedson, 2013
	A gastrostomy tube will eventually be required for untransplanted children; transplanted children at risk of undernutrition may also benefit from gastrostomy tube placement	Bell and Samson-Fang, 2013
Constipation	Ensure that fluid intake is sufficient; polyethylene glycol 3350 can prevent constipation, but lactulose or stimulant medication may eventually be required	Sullivan, 2008; Penner et al., 2013
Musculoskeletal: spasticity and contractures		
	Positioning devices such as cushions, wedges, and rolls can provide proper support to decrease spasticity, especially when sitting; contractures can also be prevented through the gentle stretching provided by orthoses, splints, standing devices, and adaptive equipment	Dunn et al., 1998; Bushby et al., 2010
	Physical therapy can improve flexibility, strength, mobility, and function	Wusthoff et al., 2007; Bushby et al., 2010
	Baclofen and clonazepam improve global spasticity for improved gait, positioning, and range of motion	Escolar et al., 2006b; Wusthoff et al., 2007; Aisen et al., 2011
	Botox injections can decrease spasticity at specific sites for 3–5 months	Aisen et al., 2011
Nervous system: neuropathic pain, seizures		
	Gabapentin controls seizures and decreases neuropathic pain; monotherapy for the treatment of seizures is preferred	Hauer et al., 2007; Wusthoff et al., 2007
	Diazepam rectal gel is useful for treating breakthrough seizures	O'Dell et al., 2005; Wusthoff et al., 2007
Respiratory system		
Respiratory distress	Airway secretions can be cleared with chest physiotherapy and postural drainage; eventually a suction machine may be required	Diebold et al., 2011; Lemoine et al., 2012
Respiratory infections	Annual influenza vaccination is highly recommended	Anderson et al., 2012
Other infections		
Opportunistic	Erythromycin may be useful as a prophylactic antibiotic and may also improve gastrointestinal motility	Weber et al., 1993
Urinary tract	Use of the Crede maneuver ensures complete emptying of the bladder	National Clinical Guideline Centre (UK), 2012
	Intermittent catheterization may be required to avoid urinary tract infections; on the other hand, indwelling catheters are generally not recommended because they pose an infection risk	Anderson et al., 2012; National Clinical Guideline Centre (UK), 2012
Prophylaxis and treatment of complications after HSCT	Prophylaxis and treatment of graft-vs.-host disease (GvHD) and other posttransplant complications should be carried out just as with any other patient	Martin et al., 2006; Kurtzberg et al., 2008

TABLE I. *Continued*

Complication	Recommendations	References
	GvHD prophylaxis: cyclosporine (200–400 ng/ml) for at least 6 months posttransplant; methylprednisolone (0.5 mg/kg twice daily on days 0–4, 1 mg/kg twice daily on days 5–21 or until absolute neutrophil count reaches 500/mm^3, then tapered to 0.2 mg/kg/week) Acute GvHD treatment (grade I): topical creams; acute GvHD treatment (grades II–IV): four high-dose methylprednisolone intravenous pulses (500 mg/m^2 every 12 hr); tacrolimus with or without daclizumab to treat unresponsive or recurrent GvHD Infection prophylaxis: antifungal, antiviral, and anti-*Pneumocystis carinii* agents for patients receiving immunosuppressive treatment Veno-occlusive disease prophylaxis: low-dose heparin (continuous intravenous infusion from initiation of conditioning regimen until day 28 posttransplant) Neutropenic fever treatment: broad-spectrum intravenous antibiotics Immunoprophylaxis: intravenous immunoglobulin (500 mg/kg weekly until day 100 and monthly thereafter) Supportive care until engraftment occurs: intravenous infusion of leukocyte-depleted, irradiated packed red blood cells and platelets as required; granulocyte colony-stimulating factor (day 0 to engraftment)	

upper motor neuron damage in KD, so, after transplantation, KD becomes almost identical to cerebral palsy.

Just as in cerebral palsy, the complex challenges of KD require an ongoing team approach. The disease requires monitoring at frequent intervals and coordination of multiple specialists (e.g., physiotherapist, ophthalmologist, physical therapist, neurologist, audiologist, nutritionist). The primary care physician should work collaboratively with a specialist who understands the disease-specific complications and the most appropriate interventions. Clinical assessment by a KD specialist should be performed as soon as possible after diagnosis and every 3 months thereafter for at least the first year, when most neurodegenerative changes occur. Specialists may be located with the help of KD advocacy groups, the National Organization for Rare Disorders, or the Genetic and Rare Diseases Information Center of the National Institutes of Health.

A proactive approach is essential for managing KD. Assistive/mobility devices and medical equipment should be requested soon after diagnosis because there is usually a delay of several months before the equipment is ordered, fitted, and delivered to the family; additionally, several months may pass before a piece of equipment is approved by a health insurance plan. Disease management recommendations are summarized in Table I.

Gastrointestinal System

Similarly to cerebral palsy (Aisen et al., 2011), difficulty feeding is often the first sign of infantile KD. For example, the infant may have difficulty latching on, exhibit uncoordinated suck and swallow, take a long time to feed, or refuse to eat (Escolar et al., 2006a). Feeding is often improved by altering the baby's position and providing adequate physical support (Arvedson, 2008; Bell and Samson-Fang, 2013). Holding the baby in an upright position during feeding and for 30–40 min after feeding can help prevent vomiting and reflux.

Coughing, gagging, and increased fatigue are common signs of difficulty feeding that result from oral motor impairment. A speech pathologist can diagnose swallowing disorders with a modified barium swallow test (Aisen et al., 2011). Infants who have difficulty swallowing can often manage formula and other liquids that are thickened (Arvedson, 2013). Liquids and pureed foods can be thickened with commercially available products such as Thick-It and SimplyThick (Bell and Samson-Fang, 2013). As the disease progresses, swallowing becomes more difficult. Providing the child with tiny amounts of food or a few drops of juice on a spoon several times per day stimulates swallowing, which should be maintained as long as possible to prevent drooling and aspiration (Arvedson, 2013). For older children, a mesh feeder can be used to introduce new flavors. This device holds fruit, vegetable, or meat and allows only very small pieces of food to pass through. A clinical feeding specialist may be able to provide additional strategies to overcome swallowing difficulties.

Brain lesions disrupt the neural modulation of gastrointestinal motility, leading to dysphagia, gastroparesis, regurgitation and vomiting, gastroesophageal reflux, and chronic constipation, which is exacerbated by prolonged

immobility and weak muscles (Del Giudice et al., 1999; Aisen et al., 2011). The use of polyethylene glycol 3350 (MiraLAX) can reduce constipation; however, some children eventually require lactulose or stimulant medication (e.g., suppository laxative; Sullivan, 2008; Penner et al., 2013). We also use the motilin receptor agonist erythromycin to stimulate gastrointestinal motility (Weber et al., 1993).

Children who do not undergo transplantation eventually require enteral feeding for adequate nutrition and hydration. Gastrostomy tubes are generally preferred for long-term enteral feeding because they are relatively comfortable and easy to insert, allow bolus feeding, and require fewer tube changes (Bell and Samson-Fang, 2013). The gastrostomy tube should be inserted for supplemental feeding while the child is still able to swallow rather than waiting until the child is undernourished and dehydrated. A Nissen fundoplication to control gastroesophageal reflux performed at the same time avoids the requirement for a second operation (Samson-Fang et al., 2003), and children recover more quickly from surgery because they are still relatively healthy. For children who do not undergo the Nissen fundoplication, antireflux medications should be given (Gold and Freston, 2002; Samson-Fang et al., 2003). Because children with severe motor disability are inactive, they require fewer calories than typical children (Bell and Samson-Fang, 2013). Overfeeding can result in excessive weight gain, which makes breathing and motor function even more difficult. Caloric intake provided by an enteral formula should be based on the child's length rather than age or weight (7–9 calories/cm/day, adjusted to the child's activity level).

Musculoskeletal System

Musculoskeletal problems include spasticity, which must be aggressively managed with baclofen and botulinum toxin (Botox) injections (Escolar et al., 2006b; Aisen et al., 2011). Baclofen has also been shown to reduce gastroesophageal reflux in children, including those who are neurologically impaired (Kawai et al., 2004).

A physical therapist can instruct caregivers on passive stretching and range-of-motion exercises to maintain range of motion and function as long as possible (Wusthoff et al., 2007; Bushby et al., 2010). The physical therapist can also recommend specific equipment and assistive devices and monitor their use for proper fit and support as the child grows. A stander (also known as a standing frame or standing device) is particularly beneficial because it stretches the muscles, facilitates hip and bone development, and improves respiratory function and gastrointestinal motility (Dunn et al., 1998; Bushby et al., 2010). The child is strapped to the stander while it is in the supine position and gradually moved into a vertical position for partial to complete weight bearing. For proper fit, we suggest performing a hip X-ray before the child's first birthday.

Orthotics can prevent or slow secondary consequences of spasticity such as misalignments, contractures, and pain (Bushby et al., 2010). Hand splints should be worn as much as the child can tolerate to prevent contractures. Nonambulatory children benefit from ankle–foot orthoses for use in the stander. For mobility, we recommend measuring these children for a kid cart (i.e., pediatric stroller wheelchair), which maintains the body in proper alignment, is adjustable, and can be modified as required. Positioning systems (wedges, cushions, rolls) are useful for improving alignment and relieving pressure on the skin while the child is seated or lying on the floor or bed.

Nervous System

Neurologic symptoms include neuropathic pain and seizures. These symptoms can be controlled with gabapentin (Neurontin; 10–15 mg/kg/day TID; Hauer et al., 2007; Wusthoff et al., 2007), which is also useful for gastric motility problems (Chumpitazi and Nurko, 2008). Seizures in KD are not frequent until the later stages. If a seizure occurs and lasts for more than 3–5 min without color changes, we suggest that parents use diazepam rectal gel (Diastat) before calling 911 or taking the child to the emergency department (O'Dell et al., 2005; Wusthoff et al., 2007). In later stages of the disease, the brainstem is unable to control body temperature; therefore, environmental modifications are required to keep the child's temperature stable.

Respiratory System

Although the lungs are healthy in KD, muscle weakness and eventual spinal deformities result in progressive respiratory insufficiency. Aspiration pneumonia is a frequent complication, but use of a gastrostomy tube reduces aspiration (Samson-Fang et al., 2003). When the child is ill or experiencing respiratory distress, a pulse oximeter should be prescribed. As the disease progresses, salivation and lung secretions increase, but children are unable to clear these secretions (Seddon and Khan, 2003). Just as in other neuromuscular diseases, respiratory interventions can extend life and improve its quality (Diebold, 2011; Lemoine et al., 2012). Chest physiotherapy and postural drainage should be performed first thing in the morning and just before bedtime and naps. A suction machine is required when the child is no longer able to clear thick mucus and secretions from the throat.

Infections

Children with leukodystrophies are particularly prone to infections (Anderson et al., 2014). However, KD patients who are in the later stages of the disease may have high and low temperatures caused by brainstem involvement, which makes temperature a poor indicator of infection. Therefore, patients should be checked for ear infection, pneumonia (X-ray), and urinary tract infection, and antibiotics should be given as soon as possible. The antibiotic erythromycin, which is used to stimulate gastrointestinal motility, may also help prevent respiratory and urinary tract infections; however, additional studies

are required to understand its utility as a prophylactic antibiotic (Seddon and Khan, 2003; Williams and Craig, 2011; Onakpoya et al., 2015). In addition, long-term antibiotic use carries risks such as the emergence of resistant bacteria and *Clostridium difficile* infection. Probiotics may be useful to prevent *C. difficile*-associated diarrhea in children treated with antibiotics (Goldenberg et al., 2015).

Development of urogenic bladder is common in later stages and may require massaging the bladder (Crede maneuver; National Clinical Guideline Centre [UK], 2012). Eventually the child may require intermittent catheterization to avoid urinary tract infections (National Clinical Guideline Centre [UK], 2012). To avoid respiratory infections, an annual influenza vaccination is recommended (Anderson et al., 2014). However, we recommend against routine childhood immunizations and live vaccines because the immune response may increase disease progression.

Vision and Hearing

Because children with early-infantile KD develop motor disability very rapidly and cannot explore the world on their own, sensory stimulation becomes critical to their wellbeing. Visual evoked potentials are used to determine degree of involvement of the optic tracts and cortical vision impairment. Vision therapists can help the family understand how to facilitate visual processing by manipulating light and background and selecting toys with specific patterns that prolong the use of vision. For example, the child may find it difficult to focus on objects that are too stimulating. By watching for subtle changes in the child's behavior (e.g., shift in gaze, tracking of objects), it is possible to determine the child's visual reception, field preference (central or peripheral), and optimal lighting conditions.

For children with multiple disabilities, audiologic assessment requires the use of physiologic measures, such as auditory brainstem response, auditory steady-state response, otoacoustic emissions, and acoustic immittance measures (Roush et al., 2004). In general, hearing is retained much longer than vision (Wenger et al., 2013), and children enjoy listening to music and being read to. Because they have delayed processing, it is important to read and speak slowly and use language consistently (i.e., everyone who works with the child should use the same simple word cues).

CHILDREN TREATED WITH UNRELATED UCB TRANSPLANTATION

Children who have successfully undergone transplantation still have multiple motor disabilities that range from mild to severe. Development of spasticity can be treated successfully with baclofen or Botox (Escolar et al., 2006b), and contractures can be prevented by early introduction of orthotics and ambulatory devices such as ankle–foot orthoses, standers, walkers, and gait trainers. More severely affected children may require a wheelchair (Escolar et al., 2006b; Bushby et al., 2010). Although most children are able to take in food by mouth, some have oral motor difficulties that affect how rapidly they can chew and swallow. These patients benefit from modifying the consistency of their food or placement of a gastrostomy tube to supplement nutritional intake (Escolar et al., 2006b). Augmentative communication devices and therapy (speech, occupational, physical) may be required to help patients overcome oral motor dysfunctions, including apraxia and speech articulation difficulties, which occur in varying degrees (Escolar et al., 2006b). Augmentative communication devices can be especially important for young children, who understand more than they are able to express. Parents should be strongly encouraged to purchase or borrow equipment and devices before their child actually requires them for optimal cognitive development and improved quality of life.

END-OF-LIFE CARE

Without disease-modifying treatment, children with infantile KD experience neurologic devastation and eventually lapse into a vegetative state. To improve end-of-life care, families should be encouraged to develop a written plan to be shared with family members and the child's primary care provider. In addition, parents should be prepared to give this written plan to local emergency medical personnel, who may otherwise be legally obligated to do everything possible to keep a patient alive. Elements of the plan may include home hospice care, eventual withdrawal of medications for spasticity (as generalized weakness and low muscle tone develop with the progression of peripheral neuropathy), and a do-not-resuscitate order.

SUPPORT AND INFORMATION FOR FAMILIES

Most parents have many questions about their child's condition, and lack of available information about KD is an additional cause of stress. Families should be directed to specialized centers that can provide counseling about the disease stage, potential complications, and risks of treatment. Families often understand the importance of research for the development of new therapies and improved diagnosis and may be interested in participating in research studies or clinical trials.

Caring for a child with KD can be exhausting, especially in the later stages of the disease when the child requires around-the-clock care. These families benefit from nursing support or respite care, even if only for a few hours per day. Joining a support group will connect them to other families of affected children. These groups are often excellent resources for practical advice. Some groups loan expensive equipment to families who cannot afford them or facilitate their rapid exchange as the child's requirements advance. In addition, a pediatric social worker can provide support, identify educational resources, and refer families to local, state, or federal government programs for which they may qualify.

CONCLUSIONS

The diagnosis of KD can be devastating for parents and difficult for the primary care physician, who is likely to have insufficient information and resources to care for the patient properly. Few patients are eligible for HSCT, currently the only available disease-modifying treatment. However, all children with KD benefit from supportive care and therapies that can make the child more comfortable and greatly improve the quality of life. For the best possible outcomes, a proactive team-based approach and close collaboration with specialists knowledgeable about the disease are essential.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

ROLE OF AUTHORS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: MLE. Acquisition of data: AD, MDP. Drafting of the manuscript: TW, KL. Critical revision of the Review for important intellectual content: MLE. Obtained funding: MLE. Study supervision: MLE.

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