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CASE REPORT

Krabbe Disease: Two cases of multidisciplinary symptom management

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Abstract

Krabbe disease is a rare autosomal recessive neurodegenerative condition which is ultimately fatal. We present the comprehensive, multidisciplinary symptom management of two patients with infantile Krabbe disease. Initial symptoms and clinical courses are discussed. Supportive care for patients with this disease prioritises symptom management and comfort, for perceived discomfort and irritability. Pharmacological management strategies are discussed including the implementation of various medications and doses, as well as proposed medication mechanisms of action in the context of Krabbe disease. In one patient, the adverse effects of the introduction of morphine are discussed. Non-pharmacological management strategies including therapy programs, are also considered, including the utilisation of splinting, seating, and positioning. Patients with Krabbe disease were found to benefit from a comprehensive team of multidisciplinary medical professionals in areas such as paediatrics, neonatology, palliative care, metabolics or genetics, anaesthesiology, physical medicine and rehabilitation, gastroenterology, general surgery, respirology, orthotics, physiotherapy, and occupational therapy.

Keywords: Krabbe Leukodystrophy, Multidisciplinary, Palliative, Irritability.

Introduction

Krabbe disease, or globoid cell leukodystrophy, is a rare autosomal recessive white matter disease. A deficiency of galactocerebrosidase, the lysosomal enzyme responsible for the hydrolysis of galactolipids, results in the loss of myelin and oligodendrocytes. It is generally rapidly progressive and ultimately fatal [1].

There are four variants of Krabbe disease: infantile, late infantile, juvenile, and adult, each with varying disease progression and severity [1]. Symptoms include: irritability, apathy, spells of inconsolable crying, failure to thrive, emesis, increased tone, and seizures. The disease generally progresses to cortical blindness, decerebrate posturing, and a chronic vegetative state [1].

Here we report the diagnosis and symptom management of two children with Krabbe disease. We identified that management is best provided by a multidisciplinary care team focused on symptom management.

Case reports

Case 1

A 13-month-old male born at 24 weeks gestation presented with irritability, increased peripheral muscle tone, and decreased axial tone. Developmental regression was apparent at 14 months, along with the onset of focal and absence seizures. Multiple disciplines became involved in his care including: paediatrics, paediatric neurology, chronic pain and acute pain services (anaesthesiology), and physical medicine and rehabilitation. By 15 months, he had severe dystonia, irritability, loss of head control, sleeplessness, and was unable to sit due to extensor posturing and diminished axial tone. Following genetic tests and a lumbar puncture, our patient was diagnosed with late infantile Krabbe disease.

Initial pharmaceutical management of irritability was with 0.15mg/kg of oral morphine every 4 hours as needed (PRN), which reduced the frequency and length of episodes of irritability. Omeprazole was also introduced for symptomatic management of suspected reflux. We added Clonazepam (0.01mg/kg oral three times a day [TID]) for dystonia. The introduction of oral baclofen (2mg oral TID) resulted in improved muscle tone, positioning, and a reduction in irritability episodes. Additionally, he spent more time smiling and alert.

Attempts to wean him off clonazepam coincided with increased irritability and dystonic movements. Clonazepam TID was therefore switched to diazepam two times a day (BID), resulting in more consistent tone management and day-night cycles. At 17 months, indomethacin (0.25mg/kg enteral BID) was added to further assist with pain and irritability. We started Indomethacin at this low dose to reduce the risk of adverse events, with a plan to gradually increase the dose to a total daily dose of 1 mg/kg/day. This multimodal approach allowed for slow weaning off of morphine PRN without any adverse effects.

Gabapentin was initiated early in the disease course (13mg/kg/day enteral, divided TID), and titrated up to facilitate seizure and pain management. Additional antiepileptic medications were not introduced as we were concerned about potential side effects. Diazepam and gabapentin were increased over time for partial but incomplete seizure control.

Clonidine 0.001mg/kg enteral four times a day (QID) was introduced and titrated up to 0.002mg/kg enteral five times daily to assist with irritability and tone. An additional PRN dose was available at night for sleeplessness. Other medications that were discussed but never administered included nabilone and methadone.

Rehabilitation care was provided by a multidisciplinary team including a physiotherapist, occupational therapist, and speech and language pathologist. Our patient also received massage therapy and a daily range of motion program at home. This care improved range of motion and reduced spasticity and dystonia. A standing frame, home suction machine, oscillation vest, wrist hand orthoses, ankle foot orthoses, cervical collars, elbow and knee extension splints, custom wheelchairs, and custom seating were also utilised (see Figure 1). Early in the disease course, the wrist hand orthosis together with the universal cuff, enabled our patient to participate in assisted play and colouring activities on a table top whilst in the standing frame. Clinical and radiographic screening were employed to monitor for hip subluxation. When he presented with painful hip subluxation and ankle equinovarus position, it impacted his use of the standing frame and this was addressed with botulinum toxin (Botox 200 units total distributed to several muscles IM/4 months, when our patient was approximately 20 kg), selecting muscles in the left lower extremity. Our patient's spine was also monitored clinically for scoliosis.

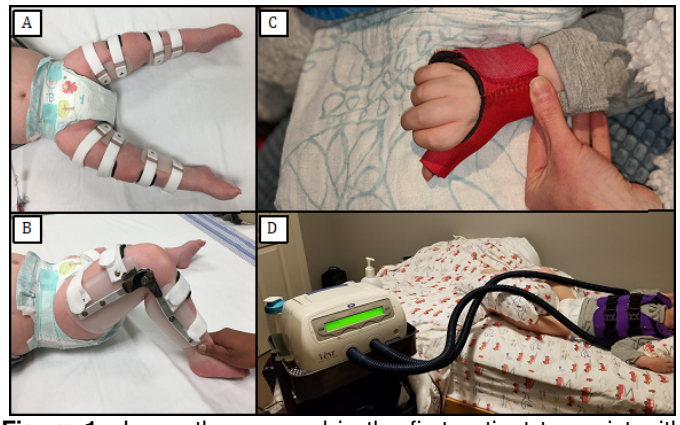

Figure 1. Leg orthoses used in the first patient to assist with comfort, standing, and range of motion (A, B). Wrist hand orthosis used in the first patient to assist with comfort and prevent skin maceration and malodour (C). The Vest© Airway Clearance System used in the first patient to mobilise airway secretions (D).

Since the time of presentation at age 13 months, our patient had significant discomfort related to gastroesophageal reflux. This reflux was likely worsened by the nasogastric tube and exacerbated extensor posturing, irritability, and sialorrhea. At age 17 months, he underwent a Nissen fundoplication and a gastrostomy tube insertion due to frequent aspiration events and pulmonary infections. Post-operatively, our patient was observed to have a significant reduction in irritability, tolerated G tube bolus feeding, and was better able to tolerate the supine position.

Case 2

Our second patient was born at term. Her clenched hands and increased neck muscle tone masquerading as head control were unusual and noted at birth. By four months, she had regular extensor posturing, frequent emesis, slow weight gain, and trouble latching. Her family identified her preferred positions (being held, using various infant swings, lying in bed, or sitting), which changed frequently as time passed.

At four months, our patient was admitted to hospital with irritability for a suspected ileus, which was soon resolved. The initial medication administered for discomfort or irritability was acetaminophen PRN. Other initial interventions that were effective in reducing irritability included: nasogastric tube feeding of hydrolysed formula for a suspected cow's milk protein allergy and dysphagia, a proton pump inhibitor medication, and topical oral nystatin for thrush.

A lumbar puncture showing increased CSF protein as well as brain MRI findings and genetic testing, confirmed the diagnosis of Krabbe disease. Hematopoietic stem cell transplantation was not pursued due to our patient's medical condition at the time of presentation and the prediction that she would have significant medical impairments even if the treatment was successful.

Additional medications were started at age five months for tone and irritability. Gabapentin was initiated at 10 mg/kg/day enteral divided TID and slowly titrated to 50 mg/kg/day enteral divided TID. Clonidine was initiated at 0.001 mg/kg/dose, given TID. Indomethacin was initiated at 1 mg/kg/day divided BID but changed to 2 mg/kg/day divided QID to address symptoms of the drug wearing off.

At six months Nitrazepam was started at 0.3 mg/kg/day divided into four doses per day. Low dose scheduled and PRN morphine were also introduced but showed no benefit and caused constipation and increased irritability. Consequently, we discontinued the use of Morphine.

At six months, our patient experienced a few days of increased irritability and posturing and was found to have blood in her NG tube. Indomethacin discontinuation resolved this issue, further reducing posturing, and improving sleep. By seven months, our patient was sleeping 90% of the time, and appeared comfortable when awake, but displayed loss of head control. At eight months, we introduced simethicone and polyethylene glycol 3350 for abdominal bloating and constipation.

Wedges and a hospital bed, were used for Trendelenburg positioning to reduce vomiting. A soft cervical collar was introduced for severely neck flexed posture due to axial hypotonia and resulted in apparent improvement of breathing and comfort. Her fisted hands resulted in maceration of her palms and malodour and this was resolved with the introduction of the tone medications mentioned above, as well as by placing rolled towels in her hands. Wrist hand orthoses were not indicated.

Our patient was under the care of a multidisciplinary team from the departments of paediatrics, palliative care, neurology, metabolic, respiratory, and physical medicine and rehabilitation. Occupational therapists and physiotherapists saw her consultatively and her family participated in a home range of motion program. She also received supplementary home oxygen as needed, to provide respiratory reserve and decrease the need for hospitalisation during respiratory tract infections. Over our patient's clinical course, her preferences for the way she was held, the way she was positioned, and the use of infant swings changed frequently. For extensor posturing, a car bed was initially considered, but was not necessary at that time. Our patient used a commercially available stroller and car seat, and no additional medical equipment. Our patient passed away at the age of 16 months.

Pharmacological Management

Many medications have been utilised for symptom management in Krabbe disease. Cautious introduction and titration can help to avoid adverse events [2]. Below we review several medications.

Morphine

Patients with neonatal Krabbe disease have shown significantly reduced irritability with the administration of 0.06-0.1mg/kg of oral morphine q4-6h [3]. The pathophysiology of irritability is multifactorial and is in part related to central irritability and tone [3, 4].

Baclofen

Baclofen, a GABA-agonist, reduces dystonia and spasticity in neurodegenerative diseases when administered orally or intrathecally [2]. Current oral dosing guidelines in other populations recommend 10-20mg/day for children younger than 2 years old, 20-30mg/day for children two to seven years, and 30-40mg /day for children older than seven years with a maximum of 60-80mg/day divided TID [5]. Caution must be used, since baclofen is associated with the potentiation of seizures [6].

Indomethacin

Indomethacin is a cyclooxygenase-1 and 2 inhibitor typically used to manage inflammatory conditions and mild to moderate pain. There have been no studies specifically directed at indomethacin in Krabbe disease. However, animal models have suggested an increase in life span and a decrease in immune-related factors associated with indomethacin treatment for Krabbe disease [7]. Suggested paediatric dosing is 1-2 mg/kg/day, with a maximum of 3mg/kg/day, in up to four divided doses administered orally [8]. Indomethacin was associated with reduced irritability and dystonia in our first patient. However, for our second patient, indomethacin was associated with a gastrointestinal bleed, and discontinuation resolved issues with posturing, dystonia, and gastrointestinal bleeding. Despite potential side effects, indomethacin may be beneficial in disease progression and symptom relief but should be validated by a larger sample size.

Gabapentin

Gabapentin affects voltage-dependent calcium ion channels at the postsynaptic dorsal horns and is effective in combating neuropathic pain [9]. Evidence suggests that it decreases irritability in children with severe neurological impairment [10]. For neuropathic pain, we typically started gabapentin at doses of 5-15 mg/kg/day and titrated to 15-35mg/kg/day divided TID or QID. Anticonvulsant dosing is generally 40mg/kg/day divided TID with a maximum of 3600mg/day [11]. Dosing for central irritability is derived from these guidelines.

Benzodiazepines

Benzodiazepines have been used successfully for decreasing dystonia, spasticity, and irritability in children with neurodegenerative conditions [2]. The World Health Organisation Essential Medicines List for children in palliative care recommends benzodiazepines for anxiety, irritability, and co-analgesia with spasticity [10]. The type of benzodiazepine selected depends on the available formulations, route of administration, and pharmacokinetics. For Krabbe disease, it is recommended that a moderate half-life benzodiazepine, like nitrazepam, is introduced for the purpose of rapid initiation and dose titration. Nitrazepam can then be converted to a longer half-life benzodiazepine like diazepam. Potential adverse effects include sedation, respiratory depression, increased oral secretions, and paradoxical behavioural reactions [2].

Clonidine

Clonidine is an alpha-2-agonist with analgesic, sedative, and anxiolytic properties. It may also be effective in managing spasticity [5]. Overall, data regarding its use in pain and symptom control in children is limited. Current guidelines for neuropathic pain recommend doses initiated at 0.001mg/kg/dose and titrated up to 0.004mg/kg/dose every 4 to 6 hours [12]. In our patients, doses of clonidine at the lower end of this range appeared to effectively reduce irritability and assist in pain control. Adverse effects including somnolence, bradycardia, and hypotension were not observed.

Nabilone

Nabilone, a synthetic cannabinoid, is an emerging treatment that has been proposed for the management of neuropathic pain, fibromyalgia, chronic non-cancer pain, and spasticity [13]. Current guidelines support its use as a third line agent in the management of neuropathic pain [14]. However, further studies are required to establish the efficacy and appropriate dosing in paediatric patients.

Nonpharmacological Management

Gastroesophageal reflux is common in Krabbe disease patients and can contribute to discomfort, respiratory symptoms, and irritability [3]. Medical management has been shown to provide transient improvement of symptoms, but surgical intervention is often required [3, 15].

Range of motion exercises, positioning, adaptive strategies and equipment, and massage are known to reduce spasticity, contractures, and pressure injuries in this population [2]. We found support for this in our first patient, who had reduced spasticity after undergoing massage therapy and a daily range of motion program. The implementation of standing frames also led to reduced constipation and improved sleep in our patients. Clinical assessment (range of motion, tone, and skin assessments) together with radiographic screening as needed, were used to monitor musculoskeletal complications such as: spasticity, contractures, skin maceration or ulceration, and joint subluxation. The principles from hip surveillance guidelines established for patients with cerebral palsy, were considered and applied to all patients in our physical medicine and rehabilitation clinic [16].

Adaptive equipment such as knee and elbow extension splints resulted in decreased contractures in one of our patients. A multidisciplinary rehabilitation team, led by a physiatrist, may be the best approach to coordinate trials of positioning (standing frames, specialised seating, mobility devices, ankle foot orthoses, car seats, and vehicle modifications), personal care (bathing equipment, incontinence supplies, and hospital beds), adaptive equipment (universal cuffs, and communication devices), and other equipment (infant swings, infant carriers, oscillation vests, suction machines, and chest physiotherapy handheld devices).

Both of our patients were managed by multidisciplinary teams. Clinicians often assessed our patients in pairs or groups, to facilitate discussion and determine the most appropriate care.

Family psychological support

Various services were employed for the purpose of family psychological support. In addition to the clinicians already mentioned, palliative care nurse specialists and social workers are a core part of the palliative care team at our hospital. This team coordinated much of both patients' medical care and offered palliative care centre admissions for either respite or symptom management.

Conclusion

Patients with Krabbe disease benefit from a comprehensive and multidisciplinary approach to symptom management. Due to the rarity of the condition and the complex nature of the patients' symptoms, a multidisciplinary team provides the best option for determining the most appropriate care, as each medical professional's expertise can be utilised when necessary.

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Table 1. Pharmacologic and non-pharmacologic management strategies for each patient, organised by symptom (PRN = as needed, QD = once a day, BID = two times a day, TID= three times a day, QID = four times a day). All medications were administered enterally, unless otherwise specified. All medications were scheduled, unless specified as PRN.

Symptom	**Management strategy**	
	Patient 1	**Patient 2**
Pain and irritability	1. Acetaminophen PRN 2. Morphine PRN 3. Indomethacin BID 4. Clonidine QID	1. Acetaminophen PRN 2. Proton pump inhibitor 3. Topical oral nystatin 4. Gabapentin TID 5. Clonidine TID 6. Indomethacin QID (discontinued due to side effects of gastrointestinal bleeding) 7. Nitrazepam BID 8. Morphine (various dosing schedules over time and PRN; discontinued due to side effects of constipation) 9. Gripe water
Gastro-oesophageal reflux	1. Omeprazole QD 2. Nissen fundoplication 3. Gastrostomy tube	1. Omeprazole QD 2. Positioning foam wedges, hospital bed
Tone	1. Gabapentin TID 2. Baclofen TID 3. Clonazepam TID (later switched to diazepam BID) 4. Clonidine QID 5. Botulinum toxin intramuscular injections 6. Range of motion exercises 7. Massage therapy 8. Positioning equipment (standing frame, ankle foot orthoses, cervical collar, elbow and knee extension splints, custom wheelchair, custom seating)	1. Gabapentin TID 2. Range of motion exercises 3. Massage therapy 4. Positioning equipment (positioning foam wedges, hospital bed, soft cervical collar)
Seizures	1. Gabapentin TID 2. Diazepam BID	None needed
Sleep	Clonidine QID	None needed
Skin management	Wrist hand orthoses	Rolled towel placed in fists
Secretions	Home suction machine	None needed

Hip subluxation	Botulinum toxin intramuscular injections	Not applicable (patient did not have hip subluxation)
Abdominal bloating and constipation	1. Polyethylene glycol 3350 QD 2. Glycerine suppository per rectum PRN 3. Dietary modification of home blended diet	1. Simethicone PRN 2. Polyethylene glycol 3350 PRN 3. Paediatric glycerine suppository per rectum PRN 4. Hydrolysed infant formula (for suspected cow's milk protein allergy)
Secretion management	1. Chest physiotherapy 2. Oscillation vest 3. Ventolin nebulizer BID and PRN 4. Pulmicort nebulizer 5. Saline 1% PRN 6. Bilevel positive airway pressure (BiPAP)	None needed
Other	Vitamin D (for bone health)	