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Krabbe Disease: An Overview of a Rare Genetic Neurodegenerative Disorder

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Krabbe disease (or Globoid cell leukodystrophy) is a rare mutation of a gene found on chromosome 14q31 responsible for the production of the enzyme called galactocerebrosidase (G ALC), which breaks down two galactolipids; galactosyl-ceramide and galactosylsphingosine (psychosine) found in the central nervous system (CNS). This enzyme's absence causes some substrate buildup, particularly psychosine.

Krabbe disease (KD) results from the toxicity of psychosine in the central nervous system, leading to clinical manifestations that characterize the disease. Demyelination occurs due to these cytotoxic activities of psychosine, leading to severe neuronal damage and the formation of globoid cells. Most cases present with fatal clinical manifestations and a bad prognosis.

The incidence in the United States is approximately 1:100,000 but could be more in certain parts of the country. The incidence is higher in males. The mode of inheritance is primarily autosomal. Diagnosis is best confirmed by the fibroblast's qualitative and quantitative analysis of the enzyme galactocerebrosidase (galactosylceramidase).

This disease has no cure. Numerous research works showed that cases presented earlier could be treated with HSCT to bring about more favorable outcomes. The use of low-dose morphine may help with irritability common in these patients. This review article aims to achieve a basic understanding of this rare neurological disorder among medical and health professionals/ students.

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Keywords: Krabbe disease; galactocerebrosidase (GALC); lipids; globoid cell leukodystrophy; autosomal recessive.

1. INTRODUCTION

It is the mutation of the galactosyl-ceramidase (GALC), leading to the lack of galactocerebrosidase enzyme [1], which is responsible for the metabolism of galactolipids [2]. It is a rare autosomal recessive disorder (Fig. 1). This lack leads to the buildup of psychosine in the CNS and peripheral nervous systems (PNS), causing severe neurological manifestations [3].

It is also called globoid cell leukodystrophy (GLD) or galactosyl-ceramide lipidosis. It is part of lysosomal storage diseases progressively damaging the nervous system [4]. A Danish neurologist, Knud Krabbe (1885–1961) [5], discovered it in 1916. However, it was not until the 1970's that the enzyme deficiency was discovered by Suzuki K and confirmed to be associated with GALC gene mutation [6].

1.1 Epidemiology

Krabbe disease incidence is 1:100,000 with a mortality rate of 90% before age two (early infantile KD). Those with symptoms developed at a later stage have a longer life expectancy; older children usually survive about 2-7years after the initial diagnosis [7].

Approximately 1:100,000 of every live birth in the United States are diagnosed with KD. It has a high occurrence in certain communities, such as the Israeli Druze community. 6 of every 1,000 live births has this incidence rate [8]. The late onset Krabbe is generally noticed to be higher among Japanese.

Adult-onset Krabbe disease incidence estimation is difficult because of the variation in classifying cases of late-onset and adult-onset [8].

This disease affects animals (like dogs, monkeys, and mice) and humans. The deletion of the GALC gene is the leading cause, resulting in the absence of the GALC enzyme in about 80% of European and Mexican patients [9].

1.2 Etiology

The GALC gene mutation [10] leads to galactosyl-ceramidase (also known as GALC) deficiency [1]. In rare cases, the GALC enzyme deficiency in Krabbe disease may be due to a lack of active saposin derived from prosaposin [11].

The subsequent accumulation of unmetabolized lipids hinders myelin sheath growth, leading to demyelination and severe progressive degeneration of nerve fibers. As a form of leukodystrophy, Krabbe disease results in flawed growth and myelin development [12].

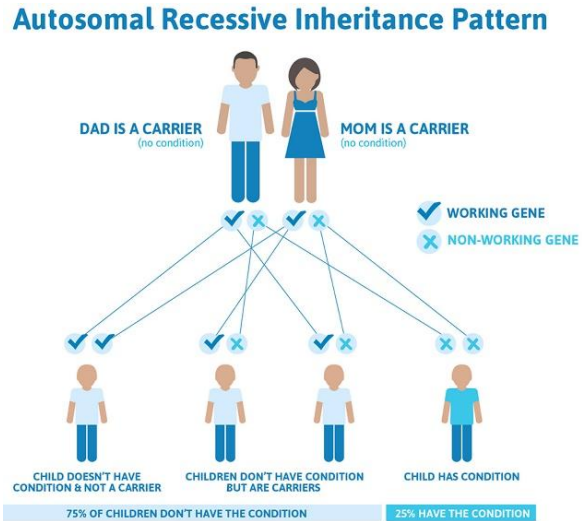

Fig. 1. Image showing the autosomal recessive mode of inheritance in Krabbe disease
Source: https://healthjade.com/wp-contents/uploads/2018/02/krabbe-disease-autosomal-recessive-inheritance-pattern.jpg

2. PATHOPHYSIOLOGY

The GALC enzyme metabolizes two galactolipids; galactosyl-ceramide and psychosine. Galactosyl-ceramide is at high levels in Schwann and oligodendroglia cells [13]. GALC breaks down galactosyl-ceramide; deficiency leads to galactosyl-ceramide accumulation in the CNS and PNS. Psychosine is derived from sphingosine lipid during myelin synthesis. It is toxic to the oligodendroglia cells, although the exact mechanism of how psychosine manifests its toxicity is unclear [14].

Krabbe disease, a rare lysosomal neurogenerative disorder, can have different molecular mechanisms existing among the various variants. The complex pathogenetic mechanism has been studied and documented in different publications, elucidating the importance of future target therapy in some cases. The variants may be due to defects in production, inability to mobilize from the endoplasmic reticulum, active sites defect, abnormality with posttranslational modifications, or defects in binding to important co-factors [15].

Researchers have documented, partially in the variants, the most likely molecular mechanism in Krabbe disease to include:

a. Missense mutations in the gene of HEK293T cells, involving the abnormality of secretion, trafficking, and processing of the enzymes [15].
b. Trapping of GALC in the endoplasmic reticulum. This mostly involves misfolded, poorly or unprocessed enzymes that most likely have undergone missense mutation [15].
c. Mutation of N279T GALC interferes with the trafficking of protein by hperglycosylation.
d. The mutation (missense) of other components and residues like Y551S, I546T, G270D, and WT GALC has also been implicated in the secretion, storage, processing, and trafficking of proteins incriminated in the development of variants of Krabbe disease [15]. Some of the known genetic mutations and their pertinent characteristics are listed below (Table 1).

3. CLINICAL MANIFESTATIONS

The signs and symptoms of Krabbe disease are fatal.Common clinical manifestations are [16, 17]:

- Irritability.
- Weakness of muscle.
- Eating or drinking problem.
- Difficulty holding the head up.
- Hand fisting.
- Stiff muscles.
- Loss of developmental milestones and motor skills.
- Seizures.
- Unexplained fever [16,17].

Early Infantile Krabbe Disease: Usually seen in babies < 6 months. It is the most severe and initially misdiagnosed as reflux, colic, food/milk allergy, or cerebral palsy. Clinical manifestations are extreme irritability, excessive crying, stiffness, a decline of motor skills, and loss of previously attained milestones, feeding difficulty, weight loss, seizures, nystagmus, clonus, and back arching [18].

Late Infantile Krabbe Disease: Manifestations begin between 6 months and three years of age. Symptoms are similar to those of Early Infantile Krabbe Disease [18].

Adolescent Krabbe Disease: Initially show regression of motor skills at >3 years of age. After the initial decline, the disease progresses more slowly than the infantile-onset, often over several years [18].

The adult onset of Krabbe Disease: Frequently starts with visual problems followed by muscle stiffness, ataxia, and pain. Those with this form of Krabbe are sometimes misdiagnosed with diseases like Multiple Sclerosis [18].

4. DIAGNOSTIC FINDINGS

GALC Enzyme Activity: Krabbe Disease is tested as part of newborn screening. This includes assaying dried blood cells for GALC enzyme activity and molecular analysis for evidence of GALC gene mutations [16].

Infants showing low enzyme activity and/or enzyme mutations are referred for additional diagnostic testing and neurological examination.

Enzyme activity as low as 0%-5% of normal activity indicates Krabbe Disease in infants [16].

Psychosine Concentration: Increased concentrations of psychosine (>10 nmol/L) in newborn infants strongly support early symptomatic Krabbe disease [13,19,20]. Psychosine levels may drop significantly later on in infantile-onset Krabbe disease.

Table 1. Novel GAL gene mutations in Krabbe disease

Location	Site of nucleotide substitution*	Amino acid change***	Type of mutation
Ex.1	c.61delG	p.A21RfsX51	Frameshift
Ex.1	C175G>C	p.G59R	Missense
Ex.1	c.205T>C	p.R69X	Nonsense
Ex.2	c.236G>A	p.R79H	Missense
Ex.1	c.262A>T	p.K88X	Nonsense
Ex.3	c.302_308dupAAATAGG	p.G102GfsX5	Frameshift
Ex.4	c.379C>T	p.R127X	Nonsense
Ex.4	c.388G>A	p.E130K	Missense
Ex.5	C.408delA	p.E136EfsX35	Frameshift
Ex.5	c.521delA	p.Y174LfsX3	Frameshift
Ex.5	c.560A>T	p.D187V	Missense
Ex.7	c.749T>C	p.I250T	Missense
Ex.7	c.857G>A	p.G286D	Missense
Ex.8	c.884A>C	p.N295T	Missense
Ex.8	C.918C>T	p.S303F	Missense
Ex.8	c.941A>G	p.Y314C	Missense
Ex.9	c.953C>G	p.P318R	Missense
Ex.9	c.967G>A	p.G323R	Missense
Ex.10	c.1075_1084delAAGACAGTTG	p.K359AfsX3	Frameshift
Ex.10	c.1151T>C	p.I384T	Missense
Intr.10	c.1161+6532_polyA+9Kbdel		Deletion
Intr.10	d.171_117delCATTCinsA	p.H391IfsX65	Frameshift
Ex.11	c.1186C>T	p.R396W	Missense
Ex.11	c.1187C>T	p.R396L	Missense
Ex.13	c.1405_1407delCTinsT	p.L469YfsX22	Frameshift
Ex.13	c.1468T>A	p.Y490N	Missense
Intr.13	c.1489+1G>A	p.S488NfsX200	Splicing
Ex.14	c.1586C>T	p.T529M	Missense
Ex.14	c.1657G>A	p.G553R	Missense
Ex.15	c.1700A>C	p.Y567S	Missense
Ex.15	c.1787delT	p.F596SfsX16	Frameshift
Ex.15	c.1819_1826dupGTTACAGG	p.G609GfsX6	Frameshift
Ex.16	c.1901delT	p.L634X	Nonsense

Source: Wiley Online Library, Ex=Exon, Intr=intron

Psychosine concentrations may not increase so much in later-onset Krabbe disease, and the length of symptom exhibition determines the diagnosis [21].

Molecular testing: A single gene is tested to detect deleted genes [16].

Other tests that can be done to assist in the diagnosis of Krabbe Disease include;

Nerve conduction: This can assess nerve function.

Imaging study: MRIs or CT scans of the brain and spinal cord may also be requested. MRI scans of the brain are best in scanning the lesions in the white matter, and are more sensitive for change detection.

Lumbar puncture: It can be done in later-onset KD to show an abnormal upsurge in CSF protein level.

The characteristic grouping of certain cells (multinucleated globoid cells), nerve demyelination and degeneration, and destruction of brain cells help in diagnosing the disease. Special stains are used to aid diagnosis (Fig. 3) [22,23].

Histopathological findings: Multinucleated macrophages with large cytoplasm called globoid cells can be found in blood vessels.

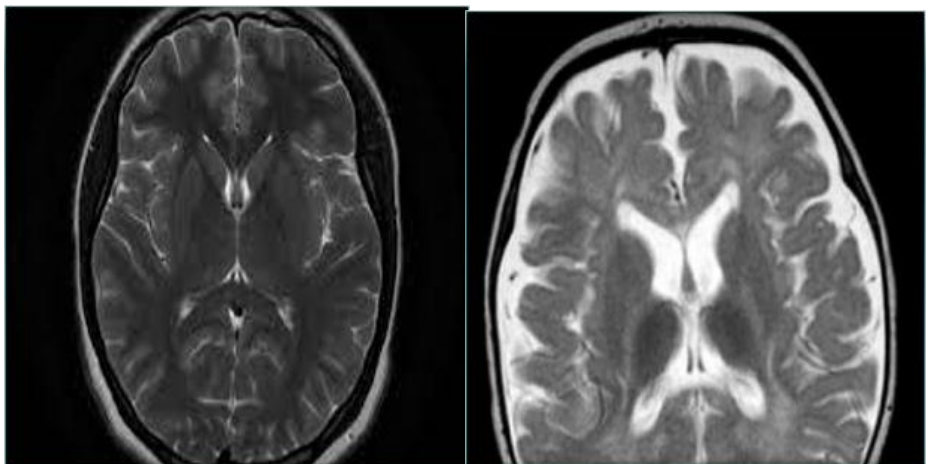

Fig. 2. MRI of normal human brain (L) and Krabbe disease(R).
Source: https://radiopaedia.org/case/normal-brain-mri-6

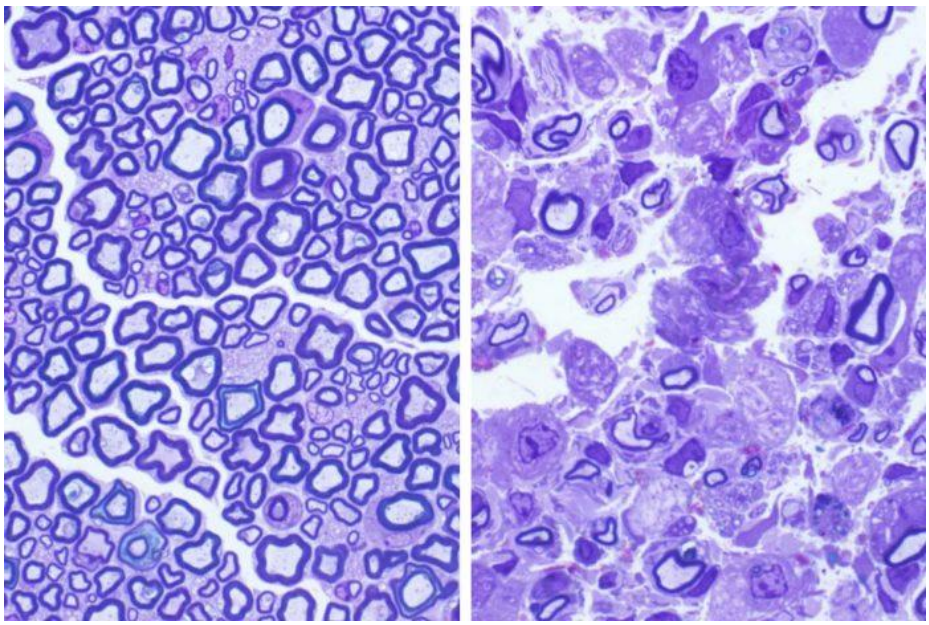

Fig. 3. Histological image showing cross-section of a normal mouse nerve (L) and a mouse nerve with Krabbe disease [R]
Source: https://www.genengnews.com/wp-content/uploads/2019/09/211505-1392x928.jpg

5. TREATMENT

5.1 Stem-Cell Transplantation

Presently Krabbe disease has no cure, although children diagnosed before having significant manifestation may be suitable for human stem-cell transplants. These aid in slowing down the advancement of this disease. In early infantile KD patients, a stem-cell transplant is the most beneficial when done within the first 30 days of life [23,24]. Unfortunately, a transplant does not repair damages [24].

5.2 Cord Blood Stem Cell Transfusion

Before the appearance of symptoms, stem cells collected from the umbilical cord of an unrelated donor are transfused into the patient. This form of treatment is only advantageous when done at this stage [22].

5.3 Gene Therapy

Although not available yet, investigations on gene therapy for KD are ongoing. Gene therapy for KD would replace abnormal GALC gene copies with normal copies [24].

Generally, treatment for this disorder is symptomatic and supportive. These treatments may include [23,25,24]:

- Medications for irritability and pain, such as gabapentin
- Medications to help relax muscles, such as baclofen
- Various therapies to help with movement and flexibility
- Antiseizure medications
- Feeding tubes to assist with eating and drinking [24].

6. DIFFERENTIAL DIAGNOSIS

Krabbe disease and several neurodegenerative conditions are similar, especially in neuroimaging studies, neurodevelopmental delay and white matter abnormalities [16,22].

6.1 Autosomal Recessive

- Arylsulfatase A deficiency (metachromatic leukodystrophy, MLD) is also described by three clinical subtypes that closely look like late-onset Krabbe disease:
- Hexosaminidase A deficiency (Tay-Sachs disease) has loss of motor skills with progressive proof of neurodegeneration, including seizures, macular cherry-red spots, and blindness.
- Canavan deficiency - developmental delays by age three to five months with extreme hypotonia and failure to achieve self-dependent sitting, movement, or talking.
- Saposin A deficiency shows abnormal myelination resembling Krabbe disease and may also be due to less GALC enzyme activity and high psychosine levels [22].

6.2 Autosomal Dominant

- Alexander's disease presents a reduced psychomotor function, loss of developmental milestones, big head, frontal bossing, and seizures.
- Autosomal dominant leukodystrophy with dysautonomia: Autonomic dysfunction includes bladder dysfunction, constipation, postural hypotension, feeding problems, erectile dysfunction, and (less frequently) impaired sweating [22].

6.3 X-Linked

- X-linked adrenoleukodystrophy - childhood cerebral form is in the differential diagnosis of KD.
- Pelizaeus-Merzbacher disease (PMD) manifests in infancy or early childhood with nystagmus, hypotonia, and cognitive impairment and progresses to severe spasticity and ataxia [22].

7. CONCLUSION

Krabbe disease is a rare neurodegenerative disorder with known variants with variable subtypes. It is a genetic disorder with an autosomal recessive mode of inheritance. KD is primarily caused by the deletion of the GALC gene found on chromosome 14(14q31). However, there are variants of the disease associated with a missense mutation of several identified residues of the gene leading to the misfolding of the protein, distortion of secretion process, assemblage, and trafficking of the enzymes produced [10,15]. Regardless of the pathogenetic mechanisms which cause a deficiency of the GALC enzyme and/or its activities, lipid dysmetabolism and toxic metabolites accumulation occur [26,1,23].

The lack of this enzyme results in an upsurge of the substrate psychosine, which is cytotoxic to Schwann and oligodendroglia cells [15,23]. Demyelination occurs, resulting in the clinical manifestations associated with KD. There is no cure for most subtypes of KD, but treating this disease with human stem cell therapy is only effective in early onset asymptomatic patients [24]. Supportive therapy and symptomatic relief of clinical manifestations exist and may ameliorate the agony of patients.

The prognosis of Krabbe disease is generally not good [25,24]. The prognosis of Krabbe disease is generally poor.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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