Disease statistics

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KRABBE DISEASE

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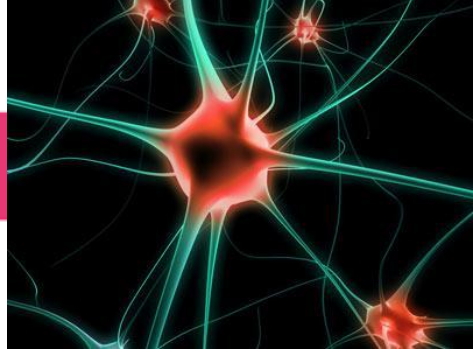
INTRODUCTION



- Krabbe disease is a genetic defect that affects the nervous system.
- It is caused by the shortage (deficiency) of an enzyme called galactosylceramidase.
- This enzyme deficiency impairs the growth and maintenance of myelin, the protective covering around certain nerve cells that ensures the rapid transmission of nerve impulses.
- Krabbe disease is part of a group of disorders known as leukodystrophies, which result from the loss of myelin (demyelination).
- This disorder is also characterized by the abnormal presence of globoid cells, which are globe-shaped cells that usually have more than one nucleus. [1]

1. http://ghr.nlm.nih.gov/condition/krabbe-disease

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- Globoid cell leukodystrophy, or Krabbe disease, was described in 1916. Krabbe reported the clinical and neuropathologic description of 5 cases that appeared to represent a new disease entity.[1]
- In 1970, Malone reported a deficiency of leukocyte galactosylceramide beta-galactosidase in a Krabbe disease patient.[2]
- This was confirmed by Suzuki K and Suzuki Y, who demonstrated the enzyme deficiency in the brain, liver, and spleen of 3 Krabbe disease patients.[3]

1. Krabbe, K (1916) A new familial form of diffuse brain-sclerosis. Brain 39: pp. 74-114.
2. Malone MJ: Deficiency in a degradative enzyme system in globoid leukodystrophy. Trans Am Soc Neurochem 1:56, 1970.
3. Suzuki K, Suzuki Y: Globoid cell leukodystrophy (Krabbe's disease): deficiency of galactocerebroside r-galactosidase. Proc Natl Acad Sci USA 66:302-309, 1970.

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ARE THERE OTHER NAMES FOR KRABBE DISEASE [1]

Other names for Krabbe Disease include:

- globoid cell leukodystrophy
- globoid cell leukoencephalopathy
- Galactosylceramide beta-galactosidase deficiency
- Galactocerebrosidase deficiency
- GALC deficiency

1. http://ulf.org/krabbe-disease

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HOW COMMON IS KRABBE DISEASE ?

- In the United States, Krabbe disease affects about 1 in 100,000 individuals. [1]

- A higher incidence (6 cases per 1,000 people) has been reported in a few isolated communities in Israel.

- Nine children (age ranging from 2½ months to 8 years) of which 5 had the classical infantile disease, 3 had late infantile form and one was diagnosed as juvenile Krabbe Disease at Seth G.S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra, India.[2]

1. http://ghr.nlm.nih.gov/condition/krabbe-disease
2. Milind S. Tullu, Mamta N. Muranjan et al. Krabbe Disease - Clinical Profile. Indian Pediatrics 2000;37: 939-946.

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- Krabbe disease is panethnic, although most reported cases have been among people of European ancestry. Late-onset Krabbe disease may be more common in southern Europe.
- Tappino et al. (2010) noted that the median prevalence of Krabbe disease is estimated to be about 1 in 100,000 (1.0 x 10(-5)) with wide variations between countries: 1.35 in the Netherlands, 1.21 in Portugal, 1.00 in Turkey, 0.71 in Australia, and 0.40 in Czech Republic. [1]

1. Tappino, B., Biancheri, R., Mort, M., Regis, S., Corsolini, F., Rossi, A., Stroppiano, M., Lualdi, S., Fiumara, A., Bembi, B., Di Rocco, M., Cooper, D. N., Filocamo, M. Identification and characterization of 15 novel GALC gene mutations causing Krabbe disease.Hum. Mutat. 31: E1894-1914, 2010. Note: Electronic Article.

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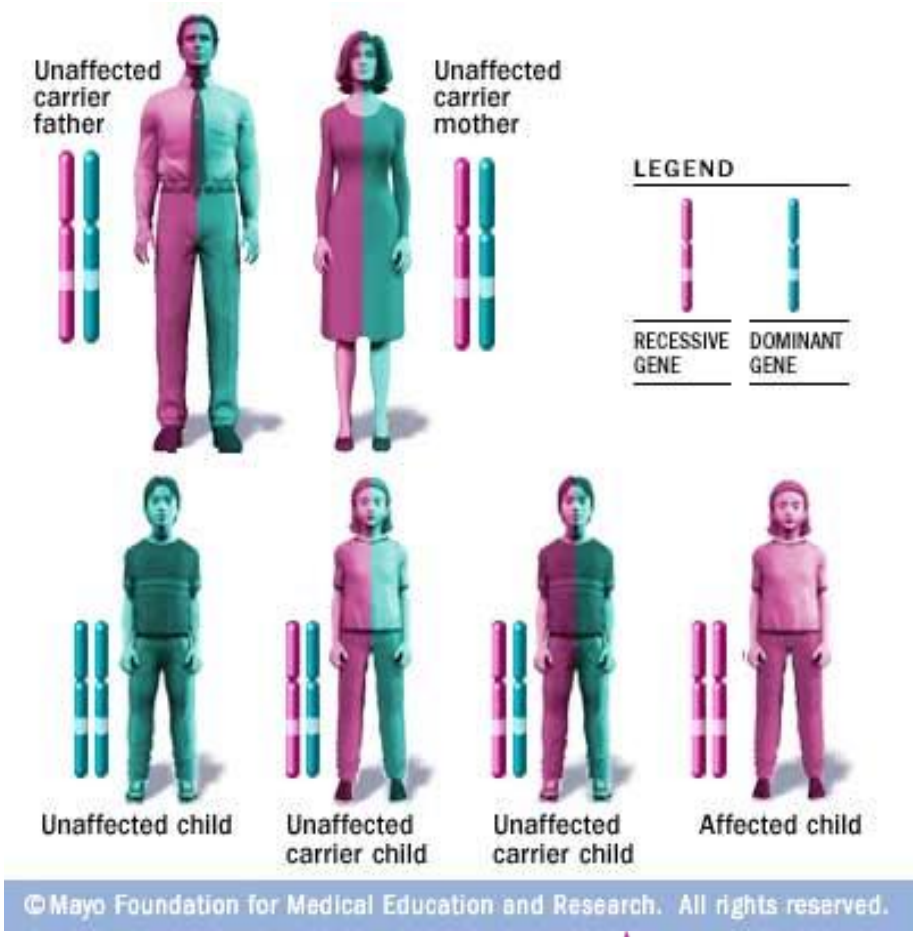
INHERITANCE PATTERN

- The gene mutation associated with Krabbe disease only causes the disease if two mutated copies of the gene are inherited.

- If each parent has one mutated copy of the gene, the risk for a child would be as follows:

1. 25 % chance of inheriting two mutated copies, which would result in the disease.
2. 50 % chance of inheriting only one mutated copy, which would result in the child being a carrier of the mutation but would not result in the disease itself.
3. 25 % chance of inheriting two normal copies of the gene. [1]



1. http://www.mayoclinic.org/diseases-conditions/krabbe-disease/basics/risk-factors/con-20029450

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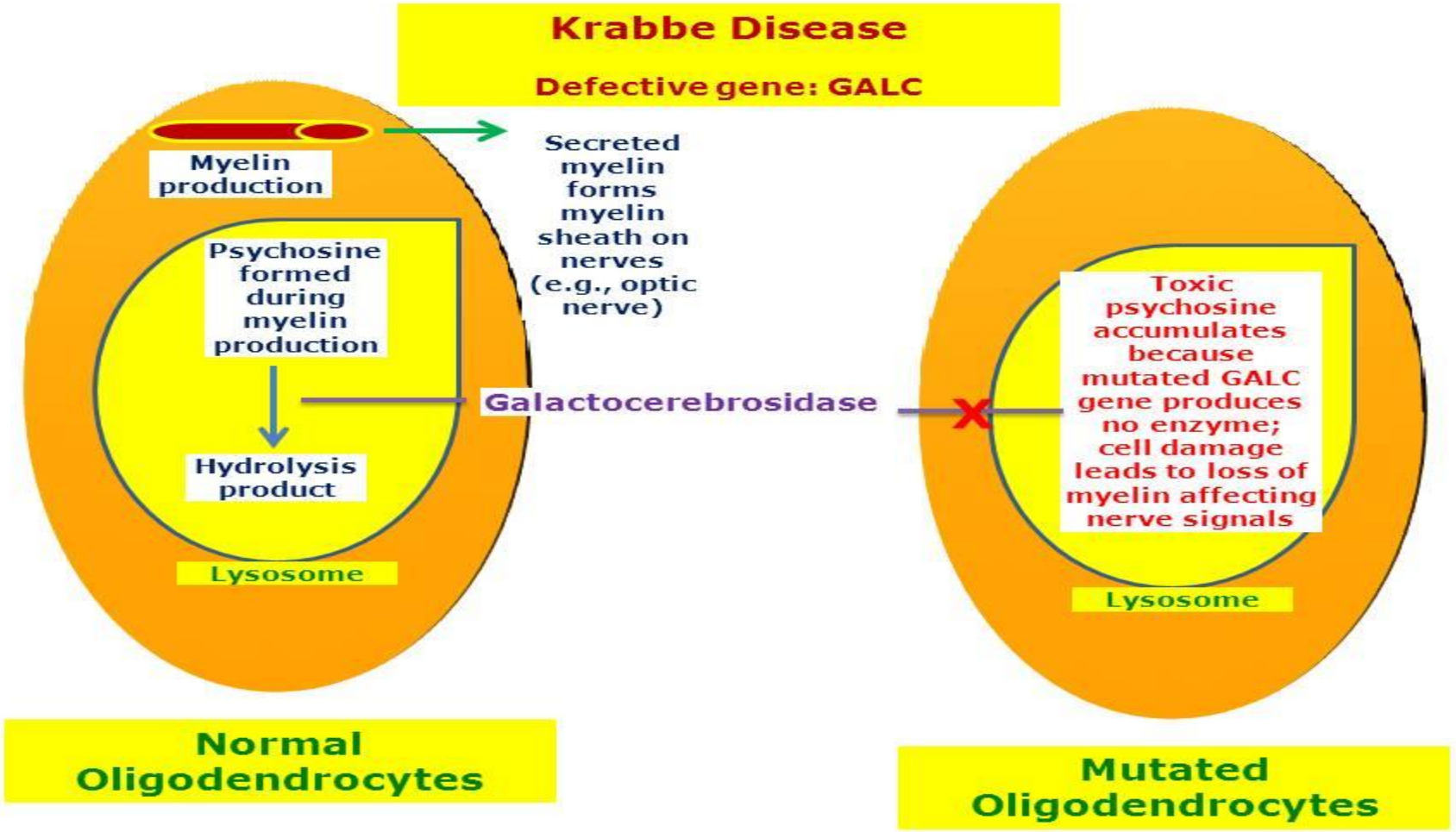
PATHOGENESIS



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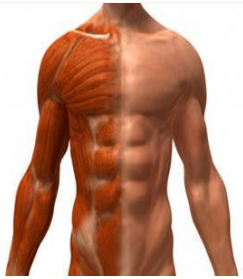

- Krabbe's disorder affects an enzyme called Galactocerebrosidase (GALC). Lack of GALC can damage cells in brain by letting the cells produce toxins that affects that nerves.
- It affects CNS by affecting muscle tone and movement. Also, by making your CNS work slower.
- As the diseases progresses, muscles began to weaken, affecting the individual ability to walk, move, chew, swallow, and breath.

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CLINICAL CHARACTERISTICS

- Krabbe disease is characterized by **infantile-onset** progressive neurologic deterioration and death before age two years (85%-90% of individuals)

or

late-onset (**juvenile- or adult-onset**) Krabbe disease -- by onset between age one year and the fifth decade with slower disease progression (10%-15%).

- Children with the infantile form appear to be normal for the first few months of life but show extreme irritability, spasticity, and developmental delay before age six months.
- The onset and progression in the late-onset forms can be quite variable. Individuals can be clinically normal until weakness, vision loss, and intellectual regression become evident.[1]

1. David A Wenger. Krabbe Disease. GeneReviews® [Internet]. June 19, 2000.

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SYMPTOMS

- Early-onset of Krabbe disease [1]:

1. Changing muscle tone from floppy to rigid (decerebrate posturing)
2. Hearing loss that leads to deafness
3. Failure to thrive
4. Feeding difficulties
5. Irritability and sensitivity to loud sounds
6. Severe seizures (may begin at a very early age)
7. Unexplained fevers
8. Vision loss that leads to blindness
9. Vomiting

- Late-onset Krabbe disease [1]:

Vision problems may appear first, followed by walking difficulties and rigid muscles. Symptoms vary from person to person. Other symptoms may occur.

1. http://www.nytimes.com/health/guides/disease/krabbe-disease/overview.html

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DIAGNOSIS

- Diagnosis of Krabbe disease can be confirmed with enzyme analysis and mutation analysis.
- Genetic testing, such as three-primer PCR analysis, may also be carried out
- Enzyme analysis can be carried out by taking a sample of blood or skin cells and testing the activity of the GALC enzyme. GALC activity is expected to be low in those with Krabbe disease.
- Prenatal testing for Krabbe disease is also possible. This is carried out using amniotic fluid or chorionic villus (CV) sampling. The latter involves taking cells from the mother's placenta.

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CLINICAL MANAGEMENT

- For infants who have already developed symptoms of Krabbe disease, there is currently no treatment that can change the course of the disease.
- Treatment, therefore, focuses on managing symptoms and providing supportive care. Interventions may include the following:

1. Anticonvulsant medications to manage seizures
2. Drugs to ease muscle spasticity and irritability
3. Physical therapy to minimize deterioration of muscle tone
4. Nutritional support, such as the use of a tube to deliver fluids and nutrients directly into the stomach (gastric tube)

- Interventions for older children or adults with less severe forms of the disease may include:

1. Occupational therapy to achieve as much independence as possible with daily activities
2. Physical therapy to minimize deterioration of muscle tone [1]

1. http://www.mayoclinic.org/diseases-conditions/krabbe-disease/basics/treatment/con-20029450

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CORD BLOOD TRANSPLANTATION

1. Escolar et al. (2005) assessed the safety and efficacy of transplantation of umbilical cord blood from unrelated donors in 11 asymptomatic newborns and 14 symptomatic infants with infantile Krabbe disease.

- All were prepared with myeloablative chemotherapy. The rates of donor-cell engraftment and survival were 100% and 100%, respectively, among the asymptomatic newborns and 100% and 43%, respectively, among symptomatic infants.
- Surviving patients showed durable engraftment of donor-derived hematopoietic cells with restoration of normal blood galactocerebrosidase levels. [1]

1. Escolar, M. L., Poe, M. D., Provenzale, J. M., Richards, K. C., Allison, J., Wood, S., Wenger, D. A., Pietryga, D., Wall, D., Champagne, M., Morse, R., Krivit, W., Kurtzberg, J. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. New Eng. J. Med. 352: 2069-2081, 2005.

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- Infants who underwent transplantation before the development of symptoms showed progressive central myelination and continued gains in developmental skills.
- Most had age-appropriate cognitive function and receptive language skills, but a few had mild to moderate delays in expressive language and mild to severe delays in gross motor function.
- The results of this study show that transplantation of umbilical-cord blood from unrelated donors in newborns with Krabbe's disease is associated with substantially better neurologic outcomes and survival than is no therapy or transplantation after symptoms develop.
- The marked differences in outcome when transplantation is performed in asymptomatic newborns and when it is performed in older symptomatic infants have implications for decisions regarding the implementation of newborn-screening programs for lysosomal storage diseases.

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2. Siddiqi et al. (2006) found that 25 of 27 children with Krabbe disease, aged 1 day to 8 years, showed abnormal motor and/or sensory nerve conduction studies with uniform slowing of conduction velocities.

- Motor and sensory responses were abnormal in 82% of patients.
- The severity of the demyelination on NCS correlated with clinical severity of the disease.
- There were no conduction blocks, indicating uniform rather than focal demyelination of peripheral nerves.
- Marked NCS abnormalities were found in a 1-day-old and 2 3-week-old neonates, indicating that peripheral neuropathy occurs very early in Krabbe disease and that nerves are likely affected even in intrauterine life. [1]

1. Siddiqi, Z. A., Sanders, D. B., Massey, J. M. Peripheral neuropathy in Krabbe disease: electrodiagnostic findings. Neurology 67: 263-267, 2006.

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- Siddiqi et al. (2006) concluded that nerve conduction studies are a sensitive tool to screen for Krabbe disease. [1]

3. In an accompanying paper, Siddiqi et al. (2006) found that nerve conduction studies improved in 7 (60%) of 12 patients after hematopoietic stem cell transplantation followed for an average of 18 months. However, some patients showed further decline after an initial improvement. There was greater improvement if the transplant was performed earlier in life. [2]

1. Siddiqi, Z. A., Sanders, D. B., Massey, J. M. Peripheral neuropathy in Krabbe disease: electrodiagnostic findings. Neurology 67: 263-267, 2006.
2. Siddiqi, Z. A., Sanders, D. B., Massey, J. M. Peripheral neuropathy in Krabbe disease: effect of hematopoietic stem cell transplantation. Neurology 67: 268-272, 2006.

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Thank you