

## FACT SHEET: KRABBE DISEASE

### What Causes Krabbe Disease?

Krabbe Disease is an autosomal recessive disorder resulting from a deficiency in an enzyme known as galactocerebrosidase (GALC). Please see our fact sheet on genetics for more information about what this type of genetic inheritance means. GALC is an enzyme that breaks down molecules called galactolipids, which are heavily present in the brain. There are many different galactolipids, but the buildup of one in particular, called psychosine, appears to be responsible for a good deal of the pathology of Krabbe disease. In patients with Krabbe disease, psychosine can be at levels 100 times that of healthy individuals, and this buildup is thought to lead to the demyelination observed in Krabbe Disease.

Another name for Krabbe Disease is Globoid Cell Leukodystrophy. This name comes from a characteristic pathology of Krabbe Disease, where a specific type of cell (called the macrophage) accumulates high levels of undegraded galactolipids as a result of the lack of GALC activity. These cells look different from healthy cells, and are termed globoid cells.

### What are the symptoms of Krabbe Disease?

The majority of cases of Krabbe Disease appear within the first year of life. The patients rapidly regress to a condition with little to no brain function, and generally die by age 2, though some have lived longer. Death generally occurs as a result of a respiratory infection or brain fever. Symptoms that might be encountered in the infantile form of Krabbe Disease include:

- Developmental delay
- Seizures
- Limb stiffness
- Optic atrophy: wasting of a muscle of the eye, resulting in vision difficulties

- Neurosensorial deafness
- Extreme irritability
- Spasticity: presence of spasms
- Ataxia: loss of the ability to control muscular movement
- Progressive psychomotor decline: progressive decline in the coordination of movement

Although the majority of Krabbe Disease patients show symptoms within the first year of life, there have been cases diagnosed at all ages, through late adulthood. In general, the earlier the diagnosis, the more rapid the progression of the disease. Those who first show symptoms at ages 2-14 will regress and become severely incapacitated, and generally die 2-7 years following diagnosis. Some patients who have been diagnosed in the adolescent and adult years have symptoms that remain confined to weakness without any intellectual deterioration, while others may become bedridden and deteriorate both mentally and physically.

### How is Krabbe Disease diagnosed?

Krabbe Disease can be diagnosed by a biochemical assay that measures the GALC activity from a blood sample or skin biopsy. It should be noted that the absolute level of GALC activity is not an indicator of prognosis; that is, a particularly low GALC activity does not necessarily predict a more rapid progression of disease than a somewhat higher GALC activity. The genetic basis for Krabbe disease is known, so it also may be possible to perform DNA sequencing of the gene in order to confirm the diagnosis of Krabbe disease. In conjunction with genetic counseling, this knowledge may also allow relatives of patients with Krabbe disease to be tested for the presence of the genetic mutation responsible, allowing them to make informed decisions about having children.

## **How is Krabbe Disease treated?**

Most treatment of Krabbe Disease is supportive. However, one medical treatment that has been demonstrated to have some effect is hematopoietic stem cell transplant (HSCT). This method appears to be of some benefit in cases of later onset or in infantile patients who have been diagnosed before or at birth. The clinical course of patients who have received the transplants seems to be less severe, and an improvement in the pathology of the disease can be seen by MRI. However, HSCT does not appear to be beneficial in the case of infantile patients who have already begun displaying the symptoms of Krabbe Disease. HSCT has been attempted on three fetuses with Krabbe Disease, and failed in all cases, presumably because the donor cells were not sufficiently engrafted.

## **How is research on Krabbe Disease progressing towards better treatments?**

Krabbe Disease is unique in that it has three animal models of disease that can be studied; a mouse model, dog model, and a monkey model. The mouse model is sometimes referred to as the “twitcher” mouse, and carries the same genetic defect found in patients with Krabbe Disease. Various treatments have been attempted on these animal models, with varying degrees of success. One promising treatment is genetic therapy, where the deficient gene (GALC) is delivered in a harmless virus. Another promising method of treatment is stem cell therapy, which can provide healthy cells with GALC activity to allow for remyelination. However, none of these methods have yet been attempted on human subjects.

## **Are there other names for Krabbe Disease?**

Other names for Krabbe Disease include:

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