KRABBE DISEASE: Cytotoxicity and Neuroinflammation

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Introduction

Globoid cell leukodystrophy disease (GLD) or Krabbe disease is a an autosomal recessive neurodegenerative disorder. It is characterized by a genetic defect in the lysosomal galactocerebrosidase enzyme (GALC), also called galactocerebroside β- galactosidase. The lack of GALC activity leads to an accumulation of psychosine, a cytotoxic lipid metabolite, which is considered to play a critical role in the pathogenesis. The accumulation will affect myelin- forming cells in the central nervous system (CNS), oligodendrocytes and Schwann cells from the peripheral nervous system (PNS). Psychosine might cause the death of myelin-forming cells and will result in an early demyelination and an inflammatory process.

In GLD it is also observed that some cells become multinucleated "globoid cells". The deficiency of GALC leads to myelin- forming cell death, profound neuroinflammation, reactive gliosis, and the activated macrophages influx.

GLD is a mortal disease and the prevalence is approximately 1 in 100,000 births in Europe and 1 in 100,000 to 250,000 births worldwide. There are different phenotypes in Krabbe disease; infantile form (90%) of the cases, and late-onset form. Only 8 cases have been registered on Spain.

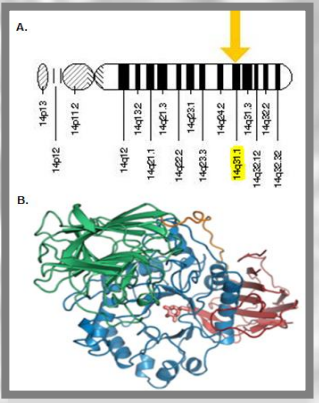

Figure 1. A) Representation of chromosome 14 and marked in yellow the localization q13. http://ghr.nlm.nih.gov/gene/GALC
B) Ribbon diagram of GALC [1]

1. GALC (galactocerebrosidase)

GALC gene is located on chromosome 14 (14q13), as figure 1 shows. This gene codes for the enzyme β-galactocerebrosidase (GALC).

GALC is essential for normal catabolism of galactosphingolipids, by catalyzing the hydrolysis of the galactose ester bonds. The enzyme degrades galactosylceramide, the main lipid component of myelin, and psychosine (galactosylsphingosine). See figure 2.

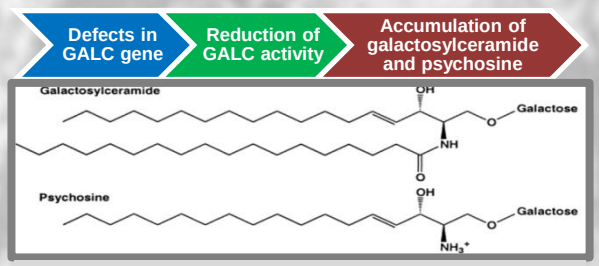

Figure 2. Chemical structure of Galactosylceramide and psychosine. http://jcb.rupress.org/content/153/2/F1/F1.large.jpg

2. Psychosine and demyelination

Psychosine is a neurotoxic lipid, which accumulates in oligodendrocytes and Schwann cells. The elevated levels of the cytotoxic lipid may cause the death in the myelin-forming cells, which results in the prominent pathology of GLD. This is called "psychosine hypothesis".

Psychosine might associates primarily with cholesterol-enriched lipid raft domains in the plasma membrane. The abnormal accumulation of this molecule of galactosylsphingosine may introduce architectural and functional changes. The toxicity could effect multiple cell signaling pathways and cause apoptotic cell death, which results in a myelin breakdown and further demyelination.

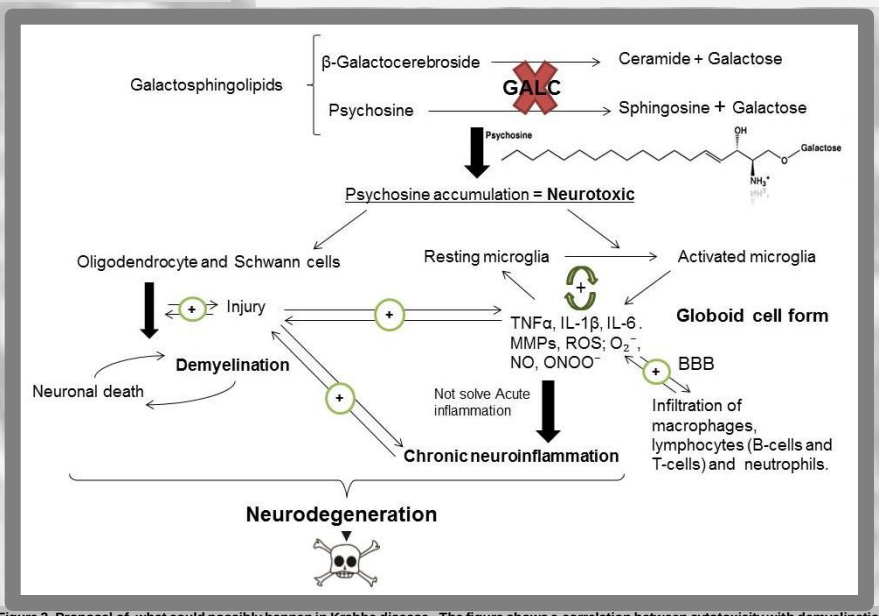

Figure 3. Proposal of what could possibly happen in Krabbe disease. The figure shows a correlation between cytotoxicity with demyelination and chronic neuroinflammation, which may results in neurodegeneration.

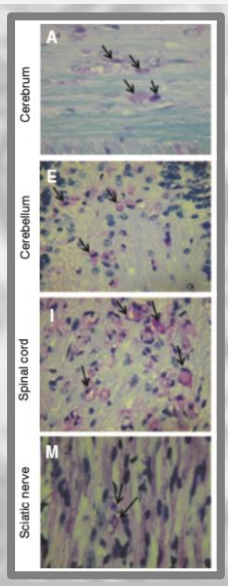

Figure 4. Black arrows show globoid cells in different parts of SNC and SNP of an 35 days GLD mouse [1]

3.Neuroinflammation

Psychosine causes damage and injury which can result in the development of neuroinflammation. The inflammation leads with an increase in pro-inflammatory cytokines and chemokines, and also the increase of B-cells and T-cells in the CNS, and infiltration of peripheral macrophages. This chronic neuroinflammation causes neuronal degeneration and damage produced by the accumulation of pro-inflammatory mediators and other inflammatory facts, and other factors as we can see in figure 3.

Globoid cells.

A characteristic trait of GLD is the formation of globoid cells, as is show in figure 4. Known to be develop from phagocytes during the course of this disease. However, it is not clear whether these giant multinucleated cells arise from.

4. Therapies

While there is no cure for GLD at this time, early Hematopoietic stem cell transplantation (HSCT), has researches pointing towards HSCT as a viable treatment to be beneficial in slowing the progression of the disease.

Animal studies have been used to assess various therapy options, such as bone marrow transplantation (BMT) or stem cell transplantation, in vivo and ex vivo substrate reduction therapy, enzyme replacement therapy, gene therapies, and small molecule administration. None of them resulted in satisfactory outcomes yet.

Conclusion

As a conclusion of this bibliographic research we can assume that the main contributing factor of Krabbe disease is the accumulation of psychosine.

The cytotoxic lipid may be the cause of demyelination, as well as more of the traits of Globoid cell leukodystrophy; Gliosis, globoid cell forming and neuroinflammation. We see that chronic neuroinflammation can occur secondarily to primary cell death and demyelination, and become an important pathological trait,

There is no consensus yet on what type of cells become globoids**.** The study made in this project "Krabbe disease; cytotoxicity and neuroinflammation", shows that there are unknown concepts of Globoid cell Leukodystrophy that are still being researched.

Reference

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