KRABBE DISEASE: Cytotoxicity and Neuroinflammation

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Introduction

 Globoid cell leukodystrophy disease (GLD) or Krabbe disease is an autosomal recessive neurodegenerative disorder. It is characterized by a genetic defect in the lysosomal galactocerebroside 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.

1. GALC (galactocerebroside)

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

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 galactosphingolipid 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.

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.

4. Therapies

While there is no cure for GLD at this time, early Hematopoietic stem cell transplantation (HSCT), has researching 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.

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]

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

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 SNR of an 35 days GLD mouse [1]