Cells other than oligodendrocytes and Schwann cells may be involved in the rapid progression of Krabbe Disease

Karen J. Fernandez1, Nadav I. Weinstock1, Daesung Shin1,3, Nicholas Silvestri2, L. Wrabetz1,2,3 and M. Laura Feltri1,2,3
(1) Hunter James Kelly Research Institute, (2) UB Department of Neurology, (3) UB Department of Biochemistry

Abstract

Globoid Cell Leukodystrophy, or Krabbe disease (KD), is an autosomal recessive disease of the nervous system characterized by the deficiency of the enzyme galactocerebrosidase (Galc). KD occurs in infants and leads to death within two years of life. In KD, apoptosis of oligodendrocytes and Schwann cells (SC) leads to demyelination and neurodegeneration of the brain, spinal cord and nerves. Besides oligodendrocytes and SC, Galc is also present in other cells, like neurons and macrophages, which suggests that they may play an autonomous role in the disease. To further explore this hypothesis, mouse models were developed that can precisely remove Galc function in all cells, or only in Schwann cells, neurons or macrophages. These mice were compared based on morphology, and on behavior and clinical progression. By doing so, a better understanding of the existing role and interaction among these cells will be defined. This work will help us to better understand the pathophysiology of KD in the PNS, and to better understand the pathophysiology of KD in the PNS, and to better understand the pathophysiology of KD in the PNS, and to better understand the pathophysiology of KD in the PNS.

Results

Morphology

Comparison of P35 WT and the WT.

Axon degeneration. The top three images are close-ups of the semithin reconstructions of P35 Sciatic nerves in the WT, Galc(fl/fl);P0-Cre(tg), and Galc (-/-) mice. Clearly, in the Galc (-/-) mice, the myelinated axons are less densely packed and have more debris (probably due to nerve swelling and degeneration) than the Galc(fl/fl);P0-Cre(tg) and WT mice. Myelinated Fibers. There isn’t a big difference in the number of myelinated fibers between the WT and the Galc(fl/fl);P0-Cre(tg) mice, but, in the Galc (-/-) mice there is a large decrease in the number of myelinated fibers. Myelin Abnormalities. When compared to the Galc(fl/fl);P0-Cre(tg) mice, the Galc (-/-) mice have twice as many myelin abnormalities (infoldings and outfoldings). There are no myelin abnormalities in the WT. Axon degeneration. The percent of axonal degeneration is higher in the Galc (-/-) mice than in the Galc(fl/fl);P0-Cre(tg) and WT mice. Amelinated Fibers. Almost no amelinated fibers are present in the WT. There are approximately six times more amelinated fibers in the Galc (-/-) than in Galc(fl/fl);P0-Cre(tg) mice.

Electrophysiology

Nerve Conduction Velocity. NCVs were extremely lower in both Galc(fl/fl);P0-Cre(tg) and Galc (-/-) mice, when compared to WT mice. This indicates the presence of a demyelinating neuropathy. A small, but statistically significant, decrease in NCV was seen in Galc (-/-) mice compared to Galc(fl/fl);P0-Cre(tg) mice. Amplitude. The amplitude of the Galc (-/-) Sciatic nerves were decreased from WT, but Galc(fl/fl);P0-Cre(tg) mice were not. Latency. Galc (-/-) nerves had an increased latency for electrical signal to spread along the nerve. Galc(fl/fl);P0-Cre(tg) nerves had increased latency at long (distal) distances but not when measured proximally. Tests were performed by Dr. Nick Silvestri.

Conclusions

It was found that the Galc(fl/fl);P0-Cre(tg) mouse had a strong demyelinating neuropathic phenotype, despite endogenous Galc expression in the remaining cell types. Even though a strong demyelinating phenotype was seen, Galc(fl/fl);P0-Cre(tg) mice had a less severe phenotype when compared to the Galc (-/-) mice. Despite this demyelination, Galc(fl/fl);P0-Cre(tg) mice showed only moderate decreases in weight loss and motor function in comparison to the Galc (-/-) mice, and had no mortality in the 6-month survival curves. Sciatic nerves from Galc(fl/fl);P0-Cre(tg) mice were morphologically different from Galc (-/-) mice. They had more myelin and fewer myelin abnormalities. It was hypothesized that these differences were caused by Galc in cells other than SCs, specifically macrophages and neurons. The incomplete Galc(fl/fl);P0-Cre(tg) phenotype may therefore be caused by a small, but insufficient, amount of Galc delivered to SCs by Galc-producing macrophages or neurons.

Future Directions

To compare the morphology, behavior and clinical progression of the motor neuron and macrophage Galc cKO mice to the WT, Galc(fl/fl);P0-Cre(tg), Galc (-/-), and twitcher mice, in order to have a more clear understanding of the specific cells that play a role in the rapid progression of Krabbe Disease.

References