MESENCHYMAL STEM CELL THERAPY FOR THE THE MOUSE MODEL OF KRABBE’S DISEASE.


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The twitcher mouse is the murine model of Krabbe’s disease which is a lysosomal storage disorder resulting from the lack of the functional lysosomal enzyme galactocerebrosidase (GALC). This is an autosomal recessive neurodegenerative disease affecting both the central and peripheral nervous systems that in its most severe form results in death before the age of 2 years old for humans and approximately 35-40 days in the mouse model. To date there is no cure for this disease, though bone marrow transplants have been helpful with prolonging the onset of the disease if administered before symptoms appear. However, bone marrow transplants often are complicated by graft vs. host disease and do not actually cure the disease. This study attempts to evaluate the effect of intraventricular administration of mesenchymal stem cells on the pathology of Krabbe's disease in the twitcher mouse model using adult murine mesenchymal stem cells isolated from the bone marrow or adipose tissue.

Pups were injected bilaterally on post-natal day (PND) 3-4 with either adipose derived or bone marrow derived mesenchymal stem cells (ASCs or BMSCs respectively) at a dose of 20,000 cells/ul and 1 ul per hemisphere for a total of 40,000 cells. Body weights, lifespan, and motor function were evaluated beginning with PND15. Tissues were also harvested when the mice were euthanized for immunohistochemistry, GALC enzymatic assays, cytokine analysis, cell tracking, and Western blot analysis.

Survival analysis curves indicate a significant difference in lifespan between cell treated and control twitcher mice. Body weights for treated twitchers were also higher than those of controls, and motor function analyzed by the wire hang maneuver and gait analysis was also improved in cell treated twitchers. These injected cells also seem to exert potent anti-inflammatory effects in the central nervous system. iNOS levels in the brains of treated mice were reduced and expression of several inflammatory cytokines appears to be suppressed in the treated mice. Western blot analysis for CD163 also revealed decreased macrophage infiltration in the brains of twitchers treated with ASCs and BMSCs.

While these improvements are promising, the twitcher mice still exhibited symptoms associated with Krabbe's disease. This approach only targets the central nervous system, therefore a combination therapy approach to treating this disease will most likely be more beneficial.