[711] Intravenous Neonatal Gene Therapy Corrects G_{M2} Gangliosidosis in Sandhoff Mice for Long-Term, By Using AAV Viral Vector Expressing a New Hexosaminidase Variant

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G_{M2} gangliosidosis is a group of neurodegenerative disorders, characterized by the malfunctioning Hexosaminidase A (HexA) enzyme, for which there is no treatment. HexA is composed of two similar, but non-identical subunits, the alpha and the beta, which must interact with the G_{M2} activator protein, a substrate-specific co-factor, to hydrolyze G_{M2}. Mutation in either subunit (or the activator) results in the development of G_{M2} gangliosidosis. In these diseases, the malfunctioning protein is unable to play its role in cleaving G_{M2} ganglioside, whose accumulation within the neurons of the central nervous system is ultimately toxic. The resulting neuronal death induces the primary symptoms of the disease; motor impairment, seizures, and sensory impairments. The aim of this study is to observe the long-term in vivo effects of a novel treatment in a Sandhoff (beta deficient) mouse model. The treatment utilized a new Hex isoenzyme, Hex M, which functions as a homodimer in the treatment of G_{M2} gangliosidosis. The HexM subunit is a variant of the human Hex alpha subunit containing critical beta-components that allow it to form stable homodimers and interact with the G_{M2} activator protein to reduce substrate storage. Our methods include intravenous injections of the neonatal mice with a self-complementary vector (with a synthetic promoter) expressing *HexM* at day 0-1. We monitored one cohort for 8 weeks and another cohort long-term (>40 weeks) for biochemical, behavioural and molecular analyses. Through the enzymatic and G_{M2} ganglioside lipid analyses, we see that with a slight increase in enzyme activity, there is a significant increase in the clearance of G_{M2} gangliosides. On behavioural tests, the treated mice outperform their knockout age matched controls. While the untreated controls die before the age of 15 weeks, treated animals have survived to more than 40 weeks and are still being monitored. The molecular analyses reveal a uniform distribution of the vector between brain and spinal cord regions. In conclusion, the neonatal delivery of our newly synthesized viral vector expressing HexM to the Sandhoff mice provided long-term correction of the disease. This study will have implications not only for treatment of Sandhoff, but also Tay-Sachs disease (alpha deficiency).
Keywords: Other-GM2 Gangliosidosis, Hexosaminidase; AAV Vectors; Other-GM2 Gangliosidosis, Hexosaminidase

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