

**[646] Dramatic Phenotypic Improvement after Adeno-Associated Virus Gene Therapy in a Feline Model of Sandhoff Disease**

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Deficiency of lysosomal hexosaminidase (Hex) causes storage of GM2 ganglioside in the central nervous system, resulting in progressive neurological deterioration and death, often in infancy. AAV gene therapy has been extraordinarily successful in the GM2 mouse model, (*Proc Natl Acad Sci USA*, 103:10373, 2006), resulting in substantial clearance of storage material and extension of life span from ~4 months (untreated) to 24 months (AAV-treated). The mouse brain is ~1000 times smaller and much less complex than the human brain, however, and it is imperative to test AAV gene therapy in an authentic GM2 animal model with a larger, more complex brain before initiation of human clinical trials. In the current study, monocistronic AAV2/rh8 vectors expressing feline Hex  $\alpha$  and  $\beta$  subunit cDNAs (2e12 g.c. per vector) were injected bilaterally into the thalamus and deep cerebellar nuclei of 1-month old GM2 cats (disease onset ~2 months). In treated brains collected 16 weeks post-injection, Hex activity was distributed throughout the entire anterior-posterior axis of the cerebrum (2.7-46.8 fold normal) and cerebellum (6.9-32.9 fold normal). GM2 ganglioside storage was drastically reduced or absent in many areas of the treated brain. Little evidence of an inflammatory cellular infiltrate was observed in H&E-stained brain sections, though serum antibody titers to the AAV vectors were pronounced (~1:65,000). Long-term therapeutic experiments in 1-month old GM2 cats were performed using the same vector dose and route of delivery. Currently, 4 AAV-treated GM2 cats are 12, 11, 9 and 9 months of age (untreated humane endpoint,  $4.5 \pm 0.5$  months, n=11). Though treated GM2 cats demonstrate varying degrees of hind limb weakness, all are ambulatory and self-sufficient, with little or no evidence of the debilitating whole body intention tremors and balance difficulties typical of untreated GM2 cats. In addition, treated GM2 cats demonstrate normalization of MRI brain lesions found in untreated cats. As anticipated, evidence of disease correction in the periphery has been minimal, with extensive vacuolation and undetectable Hex activity in peripheral blood mononuclear cells. Other than serum antibody titers, no evidence of vector toxicity has been documented. GM2 cats treated with a ten-fold lower dose are currently 7.6, 7.1, 7.1 and 6.7 months of age. Though still ambulatory and self-sufficient, GM2 cats treated with the low dose of AAV demonstrate obvious intention tremors. These translational studies provide strong support for the initiation of AAV-based clinical trials for human GM2 gangliosidosis.

**Keywords:** AAV Vectors; Neurological Disorders; Animal Models

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