In Vivo Brain NMR Spectroscopy of Alpha-Mannosidosis in a Feline model

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Introduction: Lysosomal storage diseases (LSDs) are a group of well-characterized, single gene disorders that affects approximately 1 in 5000 humans [1] due to insufficiency of a certain enzyme. The protein deficiencies result in severe degenerative processes affecting a number of tissues including the brain and causing early death [2]. A number of LSDs occur naturally in feline models; which are valuable for understanding the pathophysiology of disease as well as for testing new therapies [3-5]. Alpha-mannosidosis (AMD) is an inherited lysosomal storage disease caused by the deficiency of acidic-mannosidase. This deficiency results in cellular swelling due to the intralysosomal accumulation of mannose-rich oligosaccharides in neuronal and glial cells, as well as gliosis and demyelination [6, 7]. The objective of this study was to determine the utility of proton MRS in identifying the differences between normal and AMD affected cat brain, which could, in the future, be used to monitor the efficacy of therapy.

Methods: Two groups of 16-week-old animals were studied: normal controls (n=3), AMD affected (n=2). A 4.7 T magnet equipped with 12 cm 25 G/cm gradients using 11 cm Litz coil was used for the studies. The animal was placed in the magnet with its head positioned in the center of the coil. Core body temperature and ECG were monitored during MRI exam using a MRI-compatible unit. The body temperature was maintained by blowing warm air through the magnet bore and kept at 38^0 C. *Imaging:* In order to determine the position of the voxel for spectroscopic experiments, multi slice transverse gradient echo MR images were acquired, using a repetition time (TR) 100 ms, echo time (TE) 5 ms, slice thickness (thk) 3 mm, matrix=128x128, FOV=8.0 cm, nt=1. In vivo spectra were acquired with single voxel STEAM sequence with following parameters: TR=1500 ms, TE=10 ms, mixing time 40 ms, voxel dimensions 6 x 6 x 6 mm^3, nt=256. The voxels were placed in cortex and cerebellum of the brain. An unsuppressed water spectrum was also acquired from these voxels and the metabolite signals were normalized to the unsuppressed water.

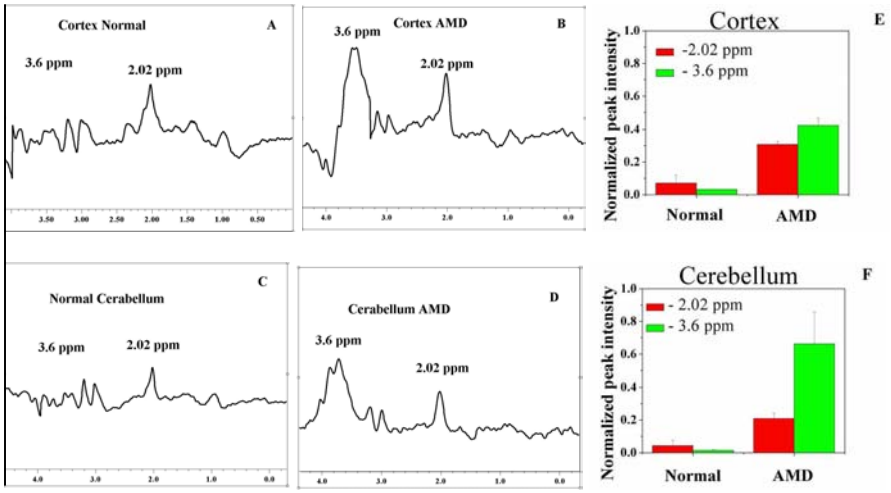

Figure 1: In vivo MR spectrum of a normal (A, C) and AMD (B, D) cat. Normalized peak intensity at 2.02 and 3.6 ppm of the cortex and cerebellum regions of normal (E) and AMD (F) cats.

Results: AMD cats exhibited a significant increase in signal intensity at 2.02 ppm and 3.6 ppm in cortex and cerebellum regions of the brain compared to the normal animals (Figure 1).

Discussion and conclusion: Since accumulation of mannose-rich oligosaccharides has earlier been reported in vitro [8], we believe that the observed increase of signal intensity at 3.6 ppm in in vivo experiments corresponds to the non-aromatic sugar skeleton protons. The peak at 2.02 ppm corresponds to the N-CH_3 protons of Glc-Nac group associated with oligosacchorides suggesting that these resonances could be used as specific markers for the diagnosis of AMD. The spectra from the cortex and cerebellum of the AMD cats exhibited similar features supporting the fact that AMD is a global disease that affects all regions of the brain. In conclusion, we have shown in our preliminary studies that AMD can be detected using in vivo MR spectroscopy and such studies may assist in monitoring the progression of the disease.

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