T_2 and diffusion MRI aids in the diagnosis of Alpha-Mannosidosis in a Feline Model

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Introduction: A mutation in the MANB gene causes the lysosomal storage disease alpha-mannosidosis (AMD) in human and animals. Human AMD is characterized by a deficiency in lysosomal α-mannosidase activity which leads to intra-lysosomal accumulation of mannose-rich oligosaccharides (Ockerman 1967). AMD cats have essentially the same biochemical, clinical, and neuropathological abnormalities as human patients (Sun et al. 2001), and have a severe clinical phenotype with grossly obvious neurological signs, a generally uniform disease course, and death by six months without treatment. The progression of the CNS disease can be studied in the living animal using clinical evaluation, electrodiagnostic testing, and MRI (Vite et al. 2001). The neuropathology of this disease has been well described and is characterized by swelling of neurons and glia, neuronal loss, gliosis and demyelination (Vite et al. 2001). Since cell swelling generally leads to changes in ADC, the goal of this study was to investigate the utility of diffusion and T_2 imaging in the diagnosis of AMD using a cat model.

Methods: Two groups of 16-week-old animals were studied: normal controls (n=4) and AMD affected (n=3). *Imaging:* Multi-slice axial MR images were acquired on a 4.7T magnet equipped with 12 cm 25 G/cm gradients using a 12 cm Litz 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. To generate T_2 maps, 2D spin-echo images were acquired with four echo times (TE = 15, 35, 55 and 75 ms). Imaging parameters: TR=2.5 ms, thk=3 mm, matrix=128x128, FOV=8.0 cm, nt=1, total acquisition time ~ 25 min. The trace of tensor (ADCav) diffusion-weighted images were acquired using five b-values (0, 1038.6, 44538.5, 93461.6, 166154 sec/cm^2) with a pulse sequence described earlier (Mori et. al 1995). Imaging parameters: TR=2 ms, TE=65 ms, thk=3 mm, matrix=128x128, FOV=8.0 cm, nt=1, diffusion time (Δ)=7 ms, duration of diffusion gradient (δ)=5 ms. To minimize motion artifacts cardiac getting was implemented. Total acquisition time ~25 min.

Results: All AMD cats exhibited a significant decrease in T_2 of the gray matter (caudate nucleus, cerebral cortex, thalamus, Figure 1) and an increase in T_2 of the white matter (corona radiata, internal capsule, centrum semiovale Figure 1) compared to normal cats. The percent change in T_2 of these cats from different structures of the brain was similar and homogenous throughout the brain. ADCav of the gray matter was decreased throughout the brain in all the AMD cats compared to normal controls. Representative T_2 and ADCav maps from an AMD and control cat are shown in figure 2 and the data is summarized in Tables 1 and 2.

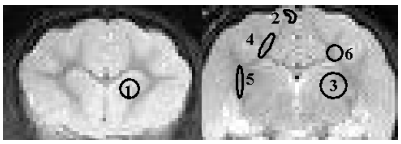

Figure 1: Spin echo T_2 weighted images of a cat brain depicting different regions of the brain that were analyzed for this study. 1- Caudate nucleus, 2 – Cerebral cortex, 3 - Thalamus, 4 – Corona radiata, 5 – Internal capsule, 6 – Centrum semiovale.

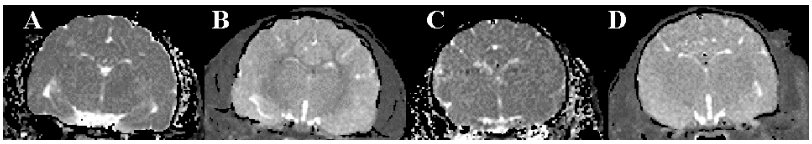

Figure 2: Reconstructed average diffusion (A, C) and T_2 maps (B, D) of normal (A, B) and AMD (C, D) cats. Diffusion maps were reconstructed from images acquired at b values of 0, 1038.6, 44538.5, 93461.6, 166154 sec/cm^2. T_2 maps were reconstructed from images acquired at TE values 15, 35, 55 and 75 ms.

Table 1: T_2 values (ms) from various regions of normal and AMD affected cats (* $p < 0.05$).

	Caudate nucleus (1)*	Cerebral cortex (2)*	Thalamus (3)*	Corona radiata (4)	Internal capsule (5)	Centrum semiovale (6)*
Normal	60.6 ± 1.8	60.2 ± 1.5	57.8 ± 1.1	53.9 ± 1.0	51.4 ± 1.4	51.1 ± 0.7
AMD	55.7 ± 0.7	55.4 ± 2.7	53.1 ± 1.7	56.5 ± 2.7	53.0 ± 2.9	56.0 ± 4.4

Table 2: ADC values (x10^{-6} cm^2/s) from various regions of normal and AMD affected cats (* $p < 0.05$).

	Frontal cortex*	Thalamus	Occipital cortex*
Normal	8.13 ± 0.5	8.17 ± 0.4	8.48 ± 0.2
AMD	7.49 ± 0.2	7.73 ± 0.4	8.06 ± 0.2

Discussion and Conclusion: Since demyelination has earlier been reported in this model using magnetization transfer contrast (Vite et al. 2001), we hypothesize that the observed decreases in T_2 of the white matter may reflect demyelination. The reason for the increase in T_2 of the gray matter is unknown, however, our working hypothesis is that it may represent changes in the extracellular space resulting from cell swelling. A major histopathological hallmark of CNS disease in cats with AMD is swelling of the neurons and glia caused by the large amounts of stored mannose-rich oligosaccharide substrate (Vite et al. 2001), which may have led to the observed decrease in the ADCav of the gray and white matter. In conclusion, we have shown in our preliminary studies that AMD can be quantitatively detected using T_2 and ADCav MRI and such studies may assist in monitoring the progression of the disease as well as evaluating response to therapeutic interventions in the management of this disease process.

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References:

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