MRI Reveals Differences in Neuroanatomy of Mouse Models of NPC Disease

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Introduction

Niemann Pick Type C (NPC) disease is a rare genetic neurodegenerative disease with no effective treatment or cure. The defect underlying the pathology is located in the *NPC1* gene and results in dysfunctional NPC1 protein. The lack of functional NPC1 protein causes impaired cholesterol trafficking and accumulation of cholesterol and glycolipids in cells [1]. The disease presents most commonly in childhood with symptoms including hepatosplenomegaly, progressive ataxia, dystonia, and dementia leading to death prior to adulthood.

A commonly studied mouse model of NPC disease, *Npc1*^{nih} (Npc1$^{-/-}$), contains a severe defect in the Npc1 gene which causes the mice to produce no functional Npc1 protein, resulting in severe symptoms and early death (~10 weeks of age) [2]. This mouse model is reported to mimic a very severe neurological form of human NPC disease [3]. The Npc1$^{-/-}$ mouse model has been used in many studies of several therapies and has been shown to have deficient myelination at 23 days of age in a DTI study [4].

A newer mouse model of NPC disease, *Npc1*^{nmf164} (Npc1^{nmf}), contains a point mutation in the *Npc1* gene, causing a partial loss of Npc1 protein function and a milder disease phenotype as compared to the Npc1$^{-/-}$ model, more similar to the common human form of the disease [5]. In-vivo MRI measurements of the NMF mouse model are presented here for the first time and compared to control and Npc1$^{-/-}$ mice.

Methods

Wild-type control (WT), Npc1$^{-/-}$, and Npc1^{nmf} mice were studied in-vivo at 10 weeks of age. Imaging was carried out on a 7T Bruker Biospec instrument using a four element phased array surface receiver coil. Animals were anesthetized with isoflurane gas and placed into an animal bed restraint system with ear bars and bite bar for head fixation. Body temperature was monitored with a fiber-optic rectal probe and maintained at 37 ^{o}C via heated water pad. High-resolution (100 µm isotropic) T2-weighted images were collected with a 3D fast spin-echo sequence with the following parameters: TR=1800 ms, ETL=8, Echo Spacing=10 ms, TE_{eff}=40 ms, FOV=30 x 17 x 9.6 mm^3, and scan time: 60:08 (min:sec). T2-weighted datasets were acquired with a 2D radial fast spin-echo sequence using imaging parameters: TR=5000 ms, ETL=8, 1024 radial lines with 170 data points collected per line, resolution=100 x 100 x 500 µm^3, 21 coronal slices, and a scan time of 10:40 (min:sec). A reconstruction method taking advantage of the oversampling of the center of k-space in radial sampling [6] was used to calculate T2 maps from the T2-weighted data. A region of interest analysis was performed to obtain T2 values from the white matter areas of the corpus callosum, internal capsule, fimbria, and external capsule, avoiding inclusion of adjacent ventricular spaces.

Results and Discussion

High resolution isotropic T2-weighted datasets show hypointensities in white matter regions of the Npc1$^{-/-}$ mice compared to the WT and Npc1^{nmf} mice, and increased ventricular size in Npc1$^{-/-}$ and Npc1^{nmf} compared to WT, shown in Fig.1. The differences in white matter have been quantified with a T2 ROI analysis and show significant differences in the white matter regions of the corpus callosum and external capsule between WT and Npc1$^{-/-}$ mice, but interestingly not between WT and Npc1^{nmf} mice, as seen in Fig. 2. Quantitative T2 analysis of the Npc1^{nmf} mice compared to the NPC and WT mice suggests that the Npc1^{nmf} mice do not have the same dysmyelination at 7 weeks of age as the Npc1$^{-/-}$ model, as seen in Fig.2. Differences in brain size and ventricular size can be seen between the types of mice in Fig. 1., and will be quantified with morphometric analyses, including voxel-based morphometry and deformation based morphometry.

The results of this study indicate that although the Npc1$^{-/-}$ and Npc1^{nmf} mouse models share marked clinical similarity, they have dramatically different neuroanatomy and white matter T2 relaxation. This not only has significant implications for studies involving these models to develop therapies for NPC disease, but also demonstrates the utility of MRI for phenotyping studies of models of human neurological disease.

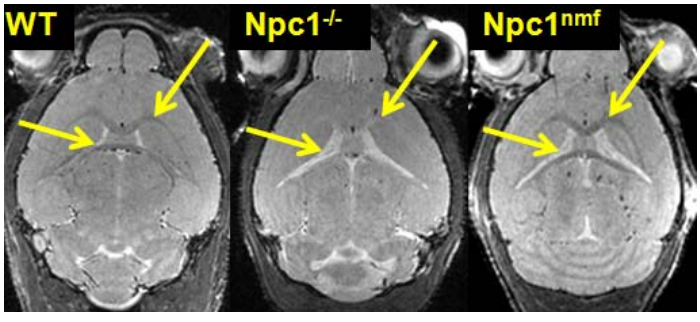

Figure 1. High resolution in-vivo T2-weighted images of WT, Npc1$^{-/-}$, and Npc1^{nmf} mice show clear differences in brain volume as well as signal contrast of white matter tracts and ventricle size in regions indicated by arrows.

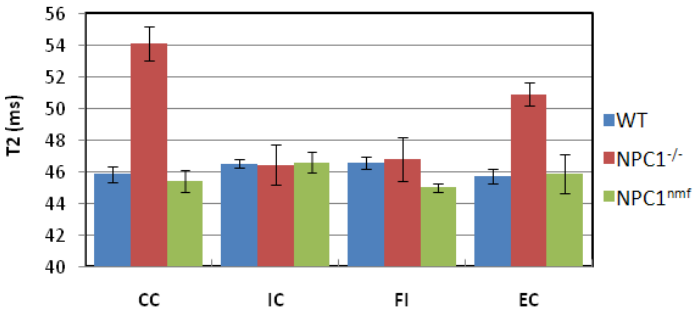

Figure 2. Results of quantitative T2 ROI analyses in white matter regions of the corpus callosum (CC), internal capsule (IC), fimbria (FI), and external capsule (EC) in WT, Npc1$^{-/-}$, and Npc1^{nmf} mice are displayed. Significant differences in T2 are seen between the WT and Npc1$^{-/-}$ mice in the CC and EC, but not between WT and Npc1^{nmf} mice.

References

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