Imaging the progression of Niemann-Pick Type C disease in a mouse model using DTI and high-resolution 3D MRI

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Introduction

Niemann-Pick C (NPC) is an autosomal recessive cholesterol storage disorder that results in progressive childhood physical disability with death in the second decade of life [1]. The intracellular transport of cholesterol in NPC-affected children is significantly disrupted leading to the accumulation of unesterified cholesterol in the internal organs, the dys- or demyelination of brain white matter tracts and the death of Purkinje cells in the cerebellum. Although no current therapy is effective in treating NPC, different types of therapies are under development and being evaluated in animal models of NPC. As successful therapies are demonstrated in animal models, there will be a desire to carry out clinical trials in children affected with NPC. This eventuality necessitates methods by which therapeutic responses can be monitored safely, reliably and longitudinally in both animal models and humans. In this effort, we are evaluating the use of high-resolution volumetric MRI and diffusion tensor imaging (DTI).

Methods

High-resolution T2-weighted imaging and diffusion tensor imaging (DTI) of the brain was carried out on four NPC mice and six littermate controls at 4.7T using a Bruker Biospec MRI instrument. High resolution T2 weighted imaging was carried out weekly (starting at a nominal age of 30 days and ending at approximately 67 days) using a 3D FSE sequence with the following imaging parameters: TR = 2 s, ETL = 16, echo spacing = 10 ms, matrix = 256 × 192 × 152 and FOV = 25.6 × 19.2 × 15.2 mm^3. Mice were anesthetized via isoflurane and placed into a 20 mm ID volume Litz coil (Doty scientific) that was used for excitation and reception. DTI was carried out after the final high resolution imaging session using a 2D radial spin echo pulse sequence [2] with the following parameters: TR/TE = 2000/54 ms, matrix = 128 × 128, FOV = 19.2 × 19.2 mm^2, slice thickness = 0.5 mm and b-value = 1065 s/mm^2 (Δ=25 ms, δ=9 ms). Fractional anisotropy maps were calculated using standard algorithms. Following DTI, mice were perfused with paraformaldehyde while under anesthesia. Brains were removed and sectioned in the sagittal plane for electron microscopy (EM).

Results and Discussion

Representative images from a control and NPC mouse are shown in Fig. 1. Both the cerebellar and cerebral brain volumes of NPC mouse brains were smaller than littermate controls. This difference can be seen in Fig. 1a,b where representative slices from 3D datasets are shown. Another significant difference between the NPC mice and the controls was the presence of high T2 signal in the region of the corpus callosum in the NPC mice (see arrow Fig. 1b). All NPC mice exhibited this high signal, which was absent in all control mice. This hyperintesity was visible at the earliest time points and persisted throughout the lifespan of the NPC mice. Similar patterns were observed in the T2-weighted images from the DTI datasets, as shown in Fig. 1c,d. Anisotropy maps reveal a reduced anisotropy in white matter regions of the brain, particularly in the CC and internal capsules (Fig. 1e,f). EM of the CC revealed a significant lack of myelination in NPC mice compared to controls (Fig. 1g,h).

High-resolution T2-weighted imaging demonstrates two significant differences in NPC mice brains compared to controls. First, there is a general reduction in brain size of the NPC mice. Second, the CC of the NPC mice exhibits hyperintensity in T2-weighted images, indicative of an increase in water mobility. Such behavior is consistent with the lack of myelination seen in the EM and the decreased anisotropy observed in the DTI. These observations are also consistent with DTI studies recently carried out on an NPC patient [3], where significant reductions in anisotropy were measured in the CC compared to age matched controls. These results indicate that MRI has the sensitivity to monitor the progression of NPC both in preclinical animal studies of disease and response to therapy, and has the potential to be an important facet of future human clinical trials.

References

[1] Patterson et al. in Metab. Molec. Bases of Inher. Dis. 2001; [2] T. Trouard, et al. (1999) *MRM* **42**, p11; [3] Trouard et al. (2004) submitted to Pediatric Neurology

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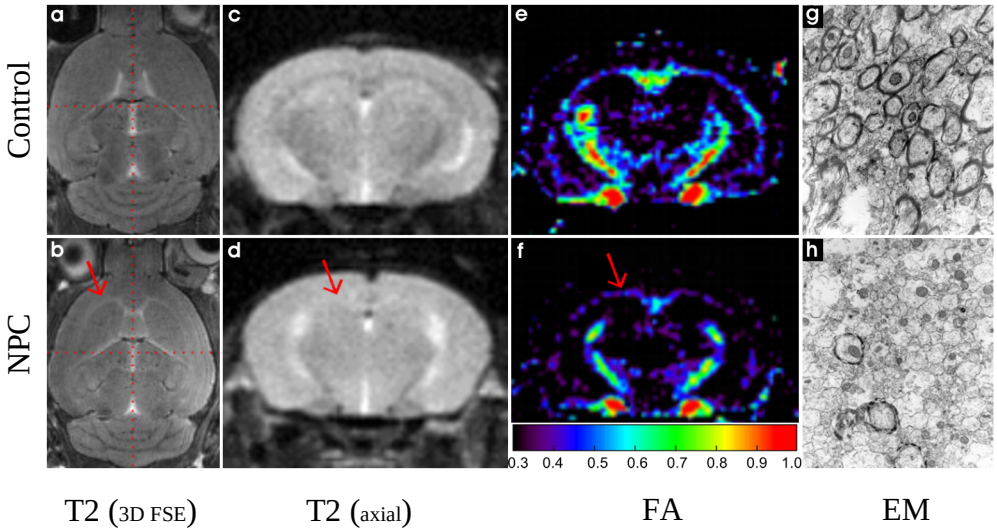

Figure 1. *(top row)* Control mouse. *(bottom row)* NPC mouse. *a, b* are T2-weighted coronal slices from a high-resolution 3D dataset. *c, d* are axial T2-weighted images corresponding to the FA maps in *e, f*. The FA maps have a threshold of 0.3. *g, h* show EM images of the CC of each brain. The CC of the NPC mouse is denoted by a red arrow. The T2- weighted images show an increase in the T2 of the CC indicating the presence of fluid, while the FA map shows a corresponding decrease in the FA of the CC. EM reveals that the CC is nearly devoid of myelin in the NPC brain. Additionally, the NPC brain is slightly smaller than that of the control mouse.