High-resolution MRI of NPC mice shows neurological changes prior to onset of disease symptoms

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Introduction

Niemann-Pick C (NPC) disease 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 white matter tracts in the brain 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 are being evaluated in animal models of NPC. Non-invasive methods that measure disease progression and therapeutic response in both animal models and humans could greatly enhance this research. In this effort, we have applied high-resolution MRI to investigate differences in brain volume and white matter over the course of life in a mouse model of NPC disease.

Methods

High-resolution volumetric T2-weighted brain imaging was carried out on NPC mice ($Npc1^{-/-}$ from the Balb/cJ background) and wild type (WT) littermates at 4.7T using a Bruker Biospec MRI instrument. Imaging was performed weekly on approximately 3 mice per group starting at 23 days and ending at 60 days of age. Mice were anesthetized via isoflurane and placed into a 20 mm ID volume Litz coil (Doty scientific) that was used for excitation and reception. Imaging employed a 3D FSE sequence with the following parameters: TR = 2 s, TE_{eff}= 75.4 ms, ETL = 16, (echo spacing) ESP = 10 ms, matrix = 256 × 192 × 152 and FOV = 25.6 × 19.2 × 15.2 mm^3. Reconstructed images were aligned to a common orientation, and the brains were segmented from the rest of the image by a human observer. The volumes of the segmented regions were then computed. Mouse weight data for Balb/cJ wild type mice were obtained from the Mouse Phenome Database [4].

Results and Discussion

NPC mice were easily identifiable from their MRI images due to hyperintensity found along the corpus callosum of the brain (compared to surrounding cortical tissue). WT mice showed neutral or occasionally dark corpus callosal intensities. The corpus callosal hyperintensity of the NPC mice indicates a lack of myelination in this region of the NPC brain. The graphs in figure 1 plot brain volume and weight versus mouse age. For large sample sizes, significant weight differences can be seen by day 40 but are generally seen closer to day 50 [2]. Brain volume differences as measured by MRI, however, are apparent at 23 days even with the current small sample sizes. Volume data also indicate a reduced brain growth rate within the first month of life compared to WT mice followed by significant brain atrophy as the disease progresses. Previous studies have shown that NPC mice undergo severe neurological and physical decline with motor impairment and weight changes at approximately 40 –50 days of age [2, 3]. The results from this study indicate that significant neurological changes have taken place prior to onset of visible symptoms. Furthermore, the difference in myelin content in white matter are seen at an early time point (day 23) suggesting dysmyelination versus demyelination as a characteristic of NPC disease in the mouse model.

References

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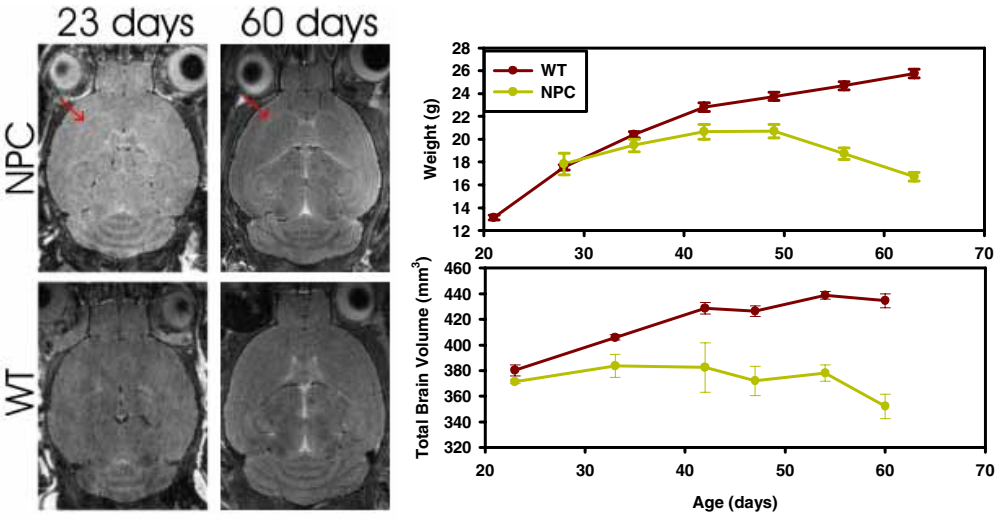

Figure 1 *(left)* Representative high-resolution T2-weighted images of NPC and WT mice. NPC mice exhibit a hyperintensity (arrow) in the corpus callosum that is not present in the brains of WT mice. This hyper-intensity is seen at an early age (day 23) and persists throughout the life of the NPC mouse. *(right top)* Weight data of WT mice (N=80) and NPC mice (N ~ 20) show separation around 35 days of age. *(right bottom)* Brain volumes of WT and NPC mice (N~3, each group) show a separation by 23 days of age.