MRI Assessment of a Novel Mouse Model of Hypertrophic Cardiomyopathy.

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Introduction

Sandhoff's disease is a lysosomal storage disease that is primarily regarded as a neurodegenerative disorder. This disease involves the excessive accumulation of the ganglioside, GM2, due to malfunctioning alpha and beta subunit s of beta-hexosaminidase. It is a more severe version of Tay-Sachs disorder. Sandhoff's patients typically die early in infancy. Although much attention has been given to the brain, GM2 accumulation occurs in many different tissue types including cardiac muscle. Previous clinical studies have shown Sandhoff's disease in humans also encompasses cardiac dysfunction. However, this phenotype has never before been confirmed in hexB -/- mice. Because the hexA-/- (mouse model of Tay-Sachs disease) does not readily mimic the human form of the disease due to the presence of a sialidase enzyme that aids in the catabolism of ganglisodes, it is important to confirm if the hexB-/- mouse actually mimics the cardiac phenotype observed in Sandhoff's disease in humans.

Methods

A total of 36 hexB-/- mice (10 control and 10 hexB-/- 15 – 19 week; 8 control and 8 hexB-/- 6-8 week old) were included in the study. Respiratory and cardiac gated images were acquired at end-diastole and end-systole utilizing a 9.4T, Bruker Avance, 21 cm bore horizontal scanner. The imaging parameters to acquire cardiac and respiratory gated spin echo images were as follows: TR = 800ms; TE = 10ms; FOV = 3.0 cm; slice thickness = 1 mm; matrix = 256 x 256; number of averages = 1. The animals' core temperature was maintained at 36.9^{0}C during scanning. Left ventricle (LV) and right ventricle (RV) volumes, along with total heart muscle mass, were determined using Amira software tools.

Results

Progressive left ventricular hypertrophy was observed in young and old HexB-/- mice, as well as overall thickening of heart muscle. Young hexB-/- mice displayed a statistically significant difference in stroke volume ($p = 0.0027$) and total heart muscle thickness ($p = 0.0086$) when compared to young control mice. Old hexB-/- mice also displayed a statistically significant difference in stroke volume ($p = 0.0487$) and total heart muscle thickness ($p = 0.0028$) when compared to old control mice **[Figure 1a/b]**. A nonparametric two-tailed test with 95% confidence was used to determine the data's statistical significance.

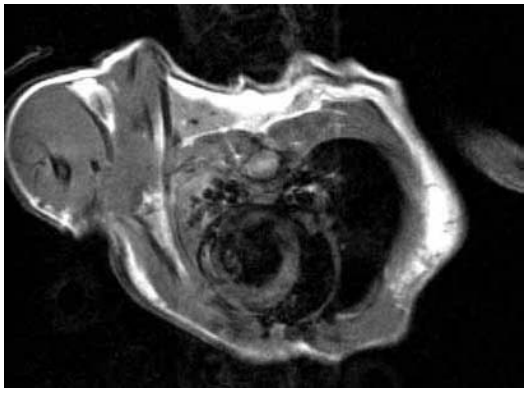

Figure 1a Control mouse (14-16 week old) at end diastole

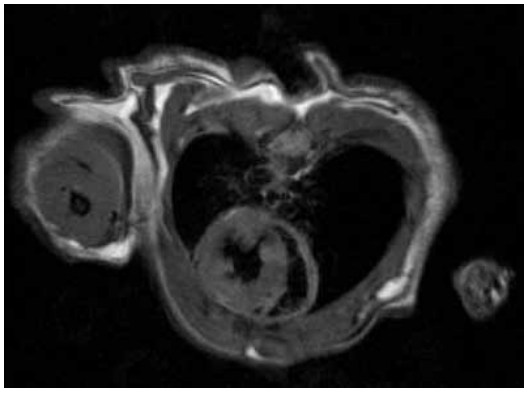

Figure 1b Hexb-/- mouse (14- 16 weeks old) at end diastole

Discussion and Conclusion

HexB-/- mice display a distinct hypertrophic cardiac phenotype, strongly mirroring cardiac symptoms observed in humans. These findings establish the hexB-/- mice as a more suitable mouse model for Sandhoff's disease and for studying connections between cardiac dysfunction and ganglioside accumulation. Lower stroke volume, as observed in the hexB-/- mice, has been shown in previous studies to lead to lower cardiac output (heart strain) which can lead to heart failure. This suggests hexB-/- mice are a novel and valuable animal model for studying cardiac dysfunction. Our current work is focused on exploring if the hypertrophic event in the hexB-/- mouse occurs via the NFAT/calcineurin signaling pathway.