Neurochemical profiling and volumetric MRI in the murine model of Hurler syndrome (MPS IH)

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PURPOSE

Hurler syndrome, the severe form of mucopolysaccharidosis type I, is one of the most frequent lysosomal storage diseases, causing severe neurological and somatic damage in the first years of life. Hurler syndrome is an autosomal recessive disorder caused by the deficiency in α-L-iduronidase (IDUA) which results in lysosomal accumulation of glycosaminoglycans[1]. Although the enzymatic deficiency of this disease is known, the underlying pathophysiological mechanisms that lead to its development are not well understood. The purpose of this study was to investigate neurochemical and volumetric changes in knock-out mouse model of Hurler syndrome using MRS and MRI at 9.4T.

METHODS

C57Bl/6 knock-out mice deficient for IDUA were used as a well-established model of Hurler syndrome. Heterozygote littermates were used as controls. During the MRI/MRS experiment animals were anesthetized with 1.0 – 1.5% isoflurane. In vivo ^{1}H MR spectra were acquired from the hippocampus and cerebellum of MPS (N = 10) and control mice (N = 10) at 33 ± 1 weeks of age. Measurements were performed at 9.4T using FASTMAP shimming and ultra-short TE STEAM (TE = 2 ms) localization sequence combined with VAPOR water suppression[2]. Metabolites were quantified using LCModel with the spectrum of fast relaxing macromolecules included in the basis set. The multislice FSE imaging (ESP = 10 ms, ETL = 8, slice thickness = 0.7 mm) was used for the volumetry and VOI selection. The volumetric analysis was performed by a semi-automated 3D image contour segmentation tool[3].

RESULTS

The spectral quality routinely achieved in this study (Fig. 1 A, B) enabled reliable quantification of 15 brain metabolites (Fig. 1 C, D). Small, but signify-cant increase in ascorbate (0.6 μmol/g, p = 0.003) was observed in hippocampus of MPS mice relative to controls (Fig. 2C). A significant difference between MPS mice and controls has not been observed for any MRS detectable metabolite in the cerebellum (Fig.1 D). The whole brain volumes of MPS mice (518.5 ± 11.6 mL) were significantly larger than that of controls (491.8 ± 17.2 mL, p = 0.002). The relative size of the ventricles in MPS mice (2.9 ± 0.4%) was significantly higher than in controls (2.4 ± 0.3%, p = 0.004).

DISCUSSION

Increased brain volumes and enlarged ventricles in MPS mice relative to heterozygote controls are in agreement with the phenotypes found in Hurler syndrome patients[4]. Despite IDUA deficiency and resulting differences in brain morphology, the neurochemical changes between MPS mice and controls have not been observed except for a significant increase of ascorbate in the hippocampus of MPS mice. An increase in endogenous antioxidant ascorbate (19%) indicates a protective response against the oxidative stress[1] which is in agreement with an increased superoxide dismutase and catalase observed in Hurler syndrome mice[5]. Differences between hippocampal and cerebellar data may be linked to a different gene expression in these brain regions[6].

CONCLUSION

Since lysosomes are highly susceptible to oxidative stress, these findings suggest the possibility that it might be beneficial to include antioxidants as part of treatment for MPS. Brain MRI volumes can be used as a potential indicator to evaluate therapeutic effects in the mouse model of Hurler syndrome.

References: 1. Campos et al., *Metab Brain Dis* 2012: 27,121; **2.** Tkac et al., *Magn Reson Med* 1999: 41, 649; **3**. Yushkevich et al., *Neuroimage* 2006: 31, 1116; **4.** Tolar et al., *Biologics* 2008: 2, 743; **5.** Reolon et al., *Cell Mol Neurobiol* 2009: 29, 443. **6.** Kreutz et al., *Gene* 2013: 527, 109.

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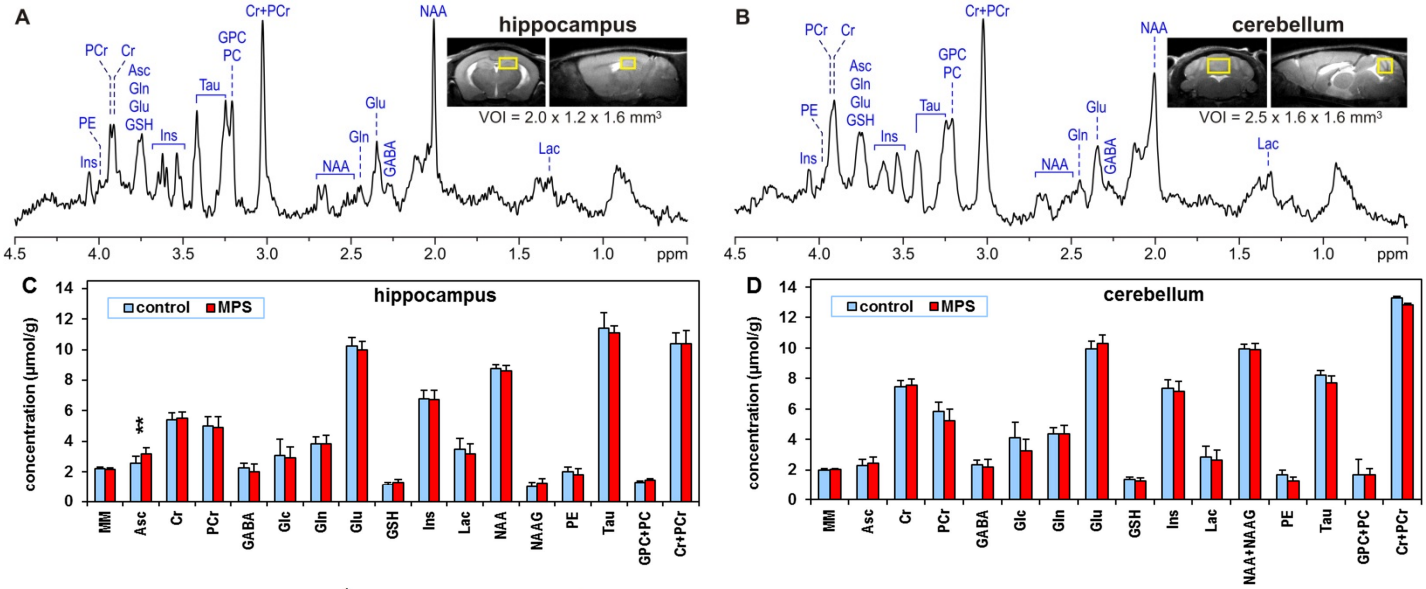

Figure 1 – Representative in vivo ^{1}H MR spectra acquired from the hippocampus (A) and cerebellum (B) of MPS mouse at 33 weeks of age. Hippocampal (C) and cerebellar (D) neurochemical profiles of MPS mice (N = 10) and WT controls (N =10) at 33 ± 1 weeks of age. ** p < 0.005