Quantitative Volumetric Analysis of Brain MRI from Infants and Children with Neuronopathic Mucopolysaccharidosis type II (MPS II) using FreeSurfer

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1 INTRODUCTION

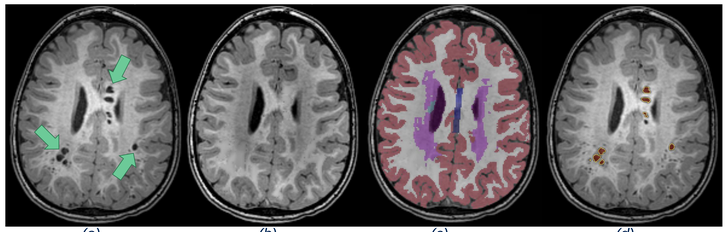
- Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is caused by a deficiency of iduronate-2-sulfatase leading to an accumulation of glycosaminoglycans (GAGs) in a variety of tissues. In neuronopathic MPS II, GAG accumulates in neuronal tissues and produces progressive cognitive deterioration, severe behavioral disturbances and global developmental delay.
- The most common brain abnormalities associated with cognitive impairment in neuronopathic MPS II are white matter lesions, enlarged perivascular-spaces (EPVS), brain atrophy and hydrocephalus[1,2].
- We present a new methodology for estimating brain volumes and tracking neuropathic MPS II disease progression across the age-span from infancy through childhood.

2 AIM

- Develop and validate an automated and reproducible imaging analysis pipeline to quantify brain volumes in children with neuropathic MPS II.
- Assess CNS abnormalities in the brain quantification to provide accurate measurements along the neuronopathic MPS II disease progression.

3 METHOD

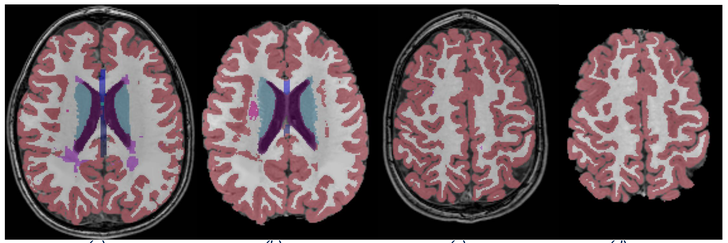
- MR 3D-T1 weighted images from the MPS II RGX-121-101 study were processed with both FreeSurfer[3] (FS) and Infant FreeSurfer[4] (IFS) (c.f. Fig 1.c and Fig 2):
  - FreeSurfer tools provide skull stripping, bias field correction, gray-white matter and sub-cortical segmentations.
  - FS has been developed to provide quantitative measurements for fully developed brains, like adults[3].
  - IFS includes prior tissues probabilities for brains under 2 years-old, with reduced MRI contrast, and can accurately segment infant brain images[4].
- To improve segmentations accuracy of the brain white matter, a semi-automated pre-processing step, called Lesion Filling (LF), was developed (c.f. Fig 1.b).
  - Regions close to EPVS were manually delineated by an imaging expert.
  - Segmented EPVS regions were replaced by pixels average intensity from surrounding normal white matter.



(a) (b) (c) (d)

Fig 1. (a) Original 3D-T1 weighted image of a neuronopathic MPS II subject with EPVS. (b) Same image after lesion filling pre-processing. (c) Brain segmentation from FS. (d) EPVS segmentation.

- An automated post-processing step was implemented to segment EPVS for volumetric quantification (c.f. Fig 1.d):
  - EPVS locations were identified inside the white matter based on their low pixel intensities.
  - Then, EPVS were segmented with a region-growing approach from the locations identified previously.
  - Only EPVS larger than 3x3x3mm were analyzed[1].
- Fractions of whole brain volume (grey/white matter) and ventricular volume over total brain volume (grey/white matter and intra-cranial cerebrospinal fluid) were used for the quantification analysis and comparison of FS and IFS results to account for child brain development.
- Intra-Class Correlation (ICC) coefficients between FS and IFS volume fractions were calculated using a mixed model.



(a) (b) (c) (d)

Fig 2. Brain segmentation result after lesion filling, using FreeSurfer (a) (c) and Infant FreeSurfer (b) (d).

4 RESULTS

- Eighteen, 3D-T1 weighted, MR images from 7 subjects, ranging from age 2 to 5 years, were successfully processed with both FS and IFS:
  - FS failed on 3 infant subjects (from age 5 to 24 months).
  - IFS failed on 2 subjects with very large lateral ventricles (from age 3 to 5 years).
- ICC for whole brain and ventricular fractions were comparable and highly correlated between FS and IFS, with 0.929 and 0.982 respectively (c.f. Fig 3).
- EPVS were correctly segmented after visual inspection (c.f. Fig 1.d).

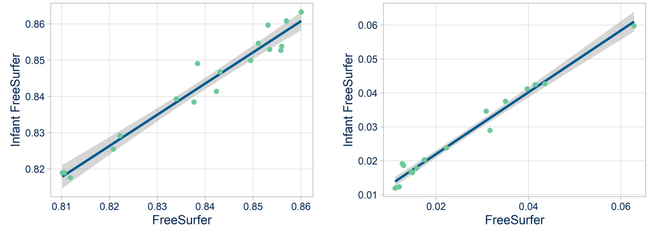


Fig 3. (left) Correlation between IFS and FS for whole brain fractions (r^2=0.958, p-value<0.001). (right) Correlation between IFS and FS for ventricular fractions (r^2=0.979, p-value<0.001).

5 CONCLUSIONS

- A strong relationship (ICC and Fig 3.) was demonstrated between FS and IFS for volumetric quantification of brains from children with neuronopathic MPS II.
- Our combined approach using FS and IFS enables accurate segmentation of brain volumes and lesions in subjects from infancy through childhood and provides a means of tracking MPS II disease progression through development.

6 REFERENCES

1. Fan et al, "Correlation of Automated Volumetric Analysis of Brain MR Imaging with Cognitive Impairment in a Natural History Study of Mucopolysaccharidosis II" , 2010, American Journal of Neuroradiology, DOI 10.3174/ajnr.A2032.
2. Vollebregt et al, "Can serial cerebral MRIs predict the neuronopathic phenotype of MPS II?", 2020, Journal of Inherited Metabolic Disease, DOI:10.1002/jimd.12342.
3. Fish et al., "FreeSurfer", 2012, Neuroimage, DOI:10.1016/j.neuroimage.2012.01.021.
4. Zöllei et al., "Infant FreeSurfer: An automated segmentation and surface extraction pipeline for T1-weighted neuroimaging data of infants 0-2 years", NeuroImage, 2020, DOI: 10.1016/j.neuroimage.2020.116946

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