DTI of a mouse model of Pelizaeus-Merzbacher Disease: correlating MR measures with morphometric analyses.

T. Ruest[1], J. M. Edgar[2], W. M. Holmes[1], J. A. Barrie[2], K. A. Nave[3], T. J. Anderson[2], and D. Dewar[1]

[1]Clinical Neuroscience, Faculty of Medicine, University of Glasgow, Glasgow, Scotland, United Kingdom, [2]Applied Neurobiology Group, Faculty of Veterinary Medicine, University of Glasgow, United Kingdom, [3]Dept of Neurogenetics, Max Planck Institute of Experimental Medicine, Goettingen, Germany

Introduction

Diffusion Tensor Imaging (DTI) has been applied in detecting dysmyelination, utilizing measures such as mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) and fractional anisotropy (FA). These measures help assess white matter integrity. Duplication of the *Plp1* gene is the most common cause of Pelizaeus-Merzbacher Disease (PMD), a disease characterised by dysmyelination. The aim of this study was to investigate white matter abnormalities in a mouse model of PMD, in which the *Plp1* gene is overexpressed, by correlating DTI measures with EM and immunohistochemical analyses of white matter changes.

Method

At post-natal day 120, *Plp1*-overexpressing mice (n = 5, female [1]) and control animals (n = 5, female) were fixed via transcardiac perfusion. The heads were dissected and placed in 0.5% MultiHance contrast agent for 20days[2]. The brains were placed in a Fomblin filled container and scanned using a 7T Bruker Biospin Biospec 70/30, with 35mm bird-cage RF coil and micro-imaging gradients. DTI data were acquired overnight (13 hours) using a spin-echo sequence with Stejskal-Tanner diffusion sensitizing gradient pair. Gradients were applied along six directions with b-values 1450s/mm^2 plus one b0 image. The imaging parameters were TR 500ms, TE 14.4ms, 2 averages, field of view 2.0 x 1.2x 1.0 cm^3, with voxels of 130x130x130µm^3 isotropic resolution. DTI datasets were all registered to a template to create average *WT* and *Plp1*-overexpresser datasets. Difference maps were generated and a group-wise, cluster based statistical analysis was performed[3]. Following DTI the brains were excised and processed for immunohistochemistry (n=10) using an antibody to myelin basic protein (MBP). The area occupied by the MBP staining, in 10 micron thick wax sections, was quantified in an area of known size and expressed as area occupied per micron^2. Additional *WT* and *Plp1*-overexpressing mice of the same age were processed for electron microscopy (n=8).). The area occupied by the MBP staining, in 10 micron thick wax sections, was quantified in an area of known size and expressed as area occupied per micron^2.

Results

DTI showed reduced FA and increased MD in major white matter tracts (Fig 1). Electron microscopy revealed a loss of myelin sheaths in tracts where DTI measures were altered in the *Plp1* overexpressers (Fig2 shows fibres from the corpus callosum). DTI measures were strongly associated with quantitative measures of MBP. Fig 3 shows MR measures against MBP in the anterior commissure. DTI parameters were less strongly associated with measures of axonal damage or glial activation.

Fig1. DTI

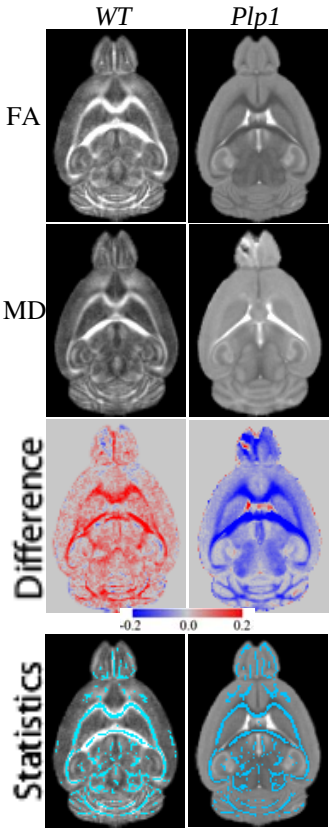


Fig2. Electron Microscopy

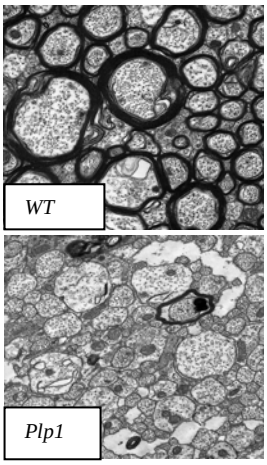
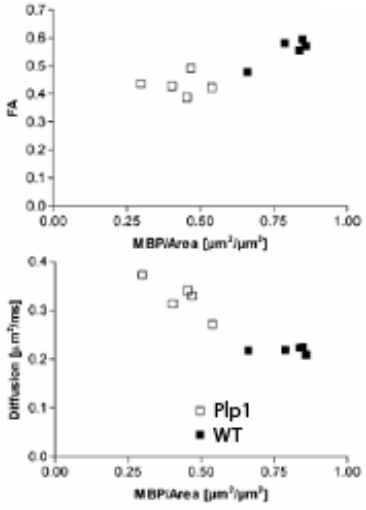


Fig 3. DTI measures versus MBP area



Conclusion

The white matter in *Plp1* overexpressing mice is highly abnormal compared to *WT* as revealed by DTI. There were anatomically widespread differences in MD, AD, RD and FA in major white matter tracts, between the *WT* and *Plp1*-overexpressing groups. The loss of anisotropy and increase in mean-water diffusion correlated with the severity of hypomyelination as reflected by MBP immunostaining and electron microscopy.

References

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Acknowledgements

Work funded by Multiple Sclerosis Society (Scotland) Junior Fellowship to JE. Neuroscience Foundation (Glasgow, Scotland)