

Voxelwise Analysis of Pelizeaus-Merzbacher Disease in 17 Genetically Proven Cases Using Diffusion Tensor Imaging

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Introduction

MRI voxelwise analysis enables quantification of subtle differences between subject groups. However its results could be effected by preprocessing steps (registration, smoothing etc). Tract based spatial statistics (TBSS) is a multi-subject voxelwise diffusion analysis tool which is proposed to be less susceptible to registration and smoothing artifacts [1]. In this study, we used TBSS approach for the investigation of Pelizeaus-Merzbacher Disease (PMD), which is a rare X-linked disease, characterized by defective central nervous system myelination due to a mutation in the proteolipid protein 1 gene [2].

Methods

17 controls (mean age = 9.3 yrs, std = 7.2) and 17 patients (mean age = 9.3 yrs, std = 7.5) were scanned for this study. All MRI examinations were performed in a 3T scanner (Trio, Siemens, Erlangen). Single shot spin echo echo planar imaging (EPI) sequence was used to obtain diffusion weighted images (DWI). Two b-values (0 and 700 s/mm²) were used, number of diffusion gradient directions varied between 30-60, 60 slices covering the whole brain were acquired with 2x2x2 mm³ isotropic resolution, TR = 10100 ms, TE = 100 ms, bandwidth = 1300 Hz/pixels, FOV=256x256 mm and scan time=5.45-11.35 minutes. Parallel imaging (GRAPPA) was used with an acceleration factor 2.

Eddy current distortion correction (first b₀ image was used as reference) and brain masking of DWI sets were done using FSL [3]. To avoid negative eigenvalues corrected DWI's are translated into AFNI [4] datasets and the method offered by Cox et al.[5] is used to obtain eigenvalues of diffusion tensor. FA maps were calculated using these eigenvalues. In TBSS analysis, all subject's FA images was registered to the most typical subject's FA image. Mean FA image of subject group, calculated from all aligned FA images, were skeletonized and FA threshold = 0.2 is used to select WM voxels. Finally, each subject's FA image is projected on its skeleton. Resulting image is used in statistical analysis.

Control group and PMD group FA values was compared using unpaired t-test. Then, control group was excluded, each patient in PMD group is labeled in one of the two categories for two selected types of symptoms and his/her initial genetic diagnosis (axial hypotonia: mild-moderate, severe; cerebellar symptoms: mild-moderate, severe; mutation: X-linked, otosomal recessive) and three-factor two-level GLM analysis is conducted at the end. For all tests, nonparametric permutation test was used. Threshold free cluster enhancement (TFCE) [6] was applied for correction of statistical maps and p<0.05 is accepted to be significant.

Results and Discussion

It is observed that FA of PMD group was significantly smaller from controls in almost all WM locations [Figure 1]. For the detailed GLM-based analysis, the only significant effect was observed between the patients with and without cerebellar symptoms. FA values was reduced in PMD patients with cerebellar symptoms in superior corona (radiata right and left), posterior corona radiata (radiata right and left), body of corpus callosum, superior longitudinal fasciculus (radiata right and left), inferior fronto-occipital fasciculus (right) and thalamic radiation (right and left) [Figure 2]. Some of these tracts have roles in motor functions; others have multiple functionalities. DTI based techniques and TBSS could be utilized to investigate PMD and access objectively its progress.

References

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Acknowledgements: This work is supported by the Turkish State Planning Organization (DPT) under the Boğaziçi University TAM Project (2007K120610) and Life Sciences Research Center Project (2009K120520)

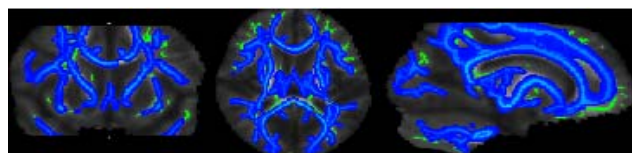


Figure 1. Significant clusters (blue) of decreased FA in PMD group compared with controls (corrected p<0.05).

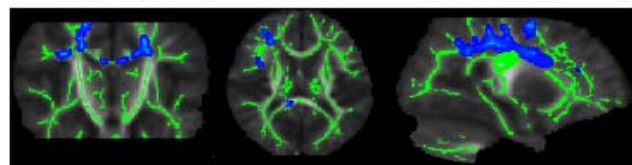


Figure 2. Significant clusters of decreased FA in patients with severe cerebellar symptoms compared with patients with mild-moderate symptoms (corrected p<0.05).