Application of Diffusion Tensor Imaging to Better Understanding Pathogenesis of the Pelizaeus-Merzbacher Disease.

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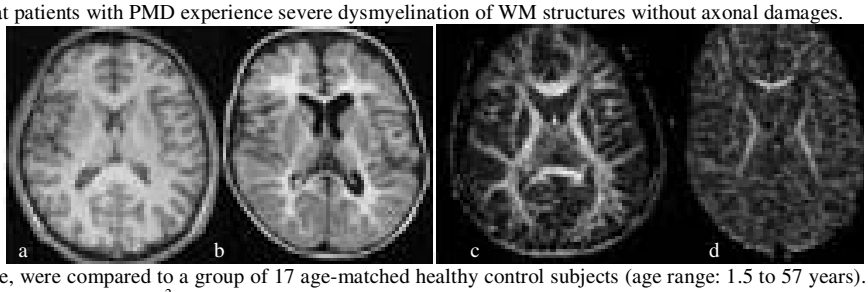
Introduction: Diffusion tensor imaging (DTI) is a non-invasive exam that can characterize the microstructural properties of the brain white matter through the molecular diffusion processes. The application of DTI to the central nervous system (CNS) can accurately discriminates among different CNS disease pathologies by evaluating the microstructural architecture of the axonal fibers and myelin membrane in diverse groups of dys- and demyelinating disorders. Pelizaeus-Merzbacher disease (PMD) is an X-linked disorder of the central nervous system (CNS), caused by a wide variety of mutations affecting proteolipid protein 1 (PLP1), the major protein in CNS myelin [1]. PLP1 is the major structural protein in CNS myelin, and is believed to form 'adhesive struts' that bind adjacent lamellae of myelin membrane in maintaining compaction of the myelin sheath [2]. The aim of this study was to quantify separately the water diffusivity components and directionality of major white-matter (WM) structures (figure 1). We hypothesize that patients with PMD experience severe dysmyelination of WM structures without axonal damages.

Figure 1: MR images showing the difference in white matter contrast between seen in 3D T1W image (a) and FA map (c) of healthy control subject compared 3D T1W (b) and FA map (d) of a typical PMD patient.



Material and Methods: Twelve patients, from 2 to 45 years of age, were compared to a group of 17 age-matched healthy control subjects (age range: 1.5 to 57 years). The DT-MRI sequence consists of a T2W image volume (~ 40 slices, b = 0 [s/mm^2]) followed by the acquisition of image volumes in 6 gradient in non-collinear directions (b-value = 1000 [s/mm^2]). For each b-value and gradient direction, 6 images were acquired and magnitude averaged to reduce artifacts and to increase signal to noise ratio. Six brain WM structures were analyzed: anterior-limb of internal capsule (ALIC), posterior-limb of internal capsule (PLIC), genu (GCC) and splenium of corpus callosum (SCC), base of the pons (PO), and cerebral peduncle (CP). ROIs were manually drawn at the structure edge to minimize partial voluming effect, in order to measure parallel ($\lambda_{//}$), perpendicular ($\lambda_{\perp}=(\lambda_2+\lambda_3)/2$), mean diffusivity (ADC) and fractional anisotropy (FA). Between groups statistical comparison was carried out separately for each structure with a post-hoc repeated measures with multiple analysis of covariance using age as covariate, and Boneferroni correction.

Results: The magnitude of the radial diffusivity ($\lambda_{\perp}$) derived from the ALIC, PLIC, GCC, SCC and CP was the most discriminating. The increase freedom of radial diffusion perpendicular to axonal fibers was proven to be significantly higher *($p < 0.001$)* in the studied WM structures in PMD patients compared to that of the normal controls (figure 2). The magnitude of water diffusion parallel ($\lambda_{//}$) to the axonal fibers in PMD patients showed no significant difference when compared to normal control subjects. Interestingly, despite the non-significant change in the parallel component of water diffusion in ALIC, PLIC, GCC, SCC, Po and CP we noticed a significant increase in the overall ADC values in these structures of PMD patients ($p<0.001$ for all structures excluding the Po $p = 0.02$). This observation demonstrates the overwhelming increases of the perpendicular component in water diffusivity. The tissue microstructure and architecture expressed by FA was significantly lower in the ALIC, PLIC, GCC and SCC *($p < 0.002$)*. This decrease in anisotropy is driven by the significant increase in radial diffusion ($\lambda_{\perp}$) rather than parallel diffusion ($\lambda_{//}$) where no significance was observed in the studied structures.

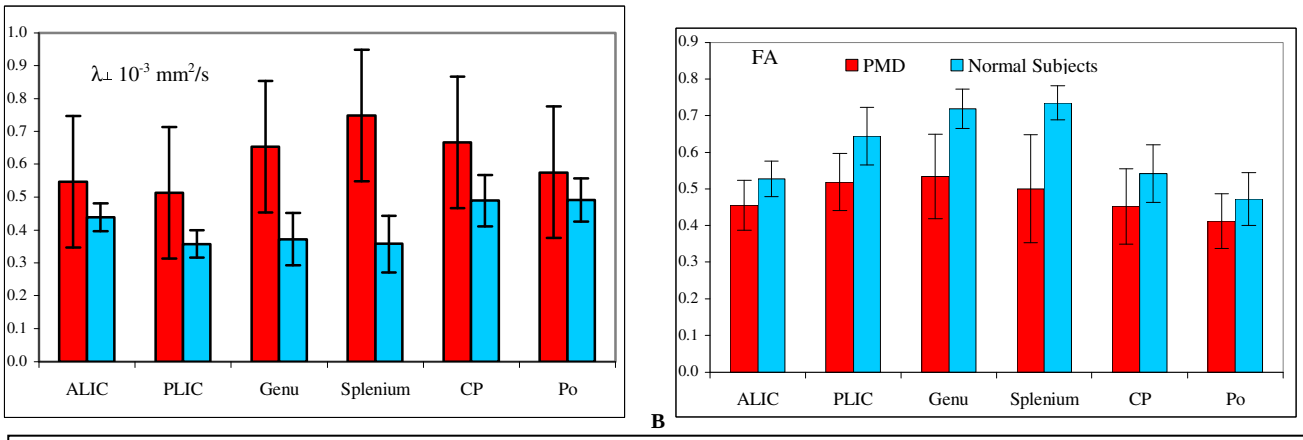


Figure 2: Graphs of mean values demonstrating the increases of (A) perpendicular diffusion ($\lambda_{\perp}$) and decrease of (B) FA in patients with PMD compared to healthy controls in the studied white-matter structures: anterior limb of internal capsule (ALIC), posterior limb interior capsule (PLIC), genu, splenium, cerebreal peduncle (CP), and pons (Po). The bars represent the standard deviations.

Conclusion: Our results of increased $\lambda_{\perp}$ in PLIC (43%), ALIC (25%), CP (36%), GCC (76%), SCC (109%) and Po (17%), are in agreement with the increased $\lambda_{\perp}$ observed in dysmyelinated animals [3]. From thinly myelinated fibers to the absence of myelin fibers water molecules to exhibit a "radial component" causing an increase in $\lambda_{\perp}$ values. In addition, modifications of intracellular and extracellular spaces may also influence radial diffusion. We found disruption of WM microstructural organization as reflected by lower FA in ALIC (-14%), PLIC (-19%), Po (-13%), CP (-16%), GCC (-26%) and SCC (-32%) in the PMD group when compared to the normal-control group. The decreased FA observed suggest that abnormalilty lies within the myelin as well as the axonal integrity being the major contributor to normal fiber tract anisotropy. The amplified decrease in FA may arise from the severe astrocyte hypertrophy detected in the brains of PMD patients. Dysmyelinating disorders, represented by PMD and other leukodystrophies, are characterized by myelination abnormalities that lead to incomplete, patchy or irregular myelin sheaths [4]. A non-invasive modality, such as DTI-MRI is capable of differentiating injury to myelin and to axons being highly beneficial in monitoring disease progression in PMD patients. Early detection of subtle changes in brain microstructure may have an important impact on the diagnosis of PMD along with other dysmyelinating and demyelinating disorders, such as MS.

References: [1]. Hudson et al. Proc Natl Acad Sci. (1989); [2]. Boison Proc Natl Acad Sci. (1994); [3]. Song et al. Neuroimage (2002); [4]. Seitelberger F. Brain Pathology. (1995)