Assessing The Level Of Pathology Of The Corticospinal Pathway In Patients With PLP1 Mutations Using Diffusion Tensor Imaging.

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Introduction: Pelizaeus-Merzbacher disease is an X-linked recessive hypomyelinating disorder caused by mutations affecting the proteolipid protein 1 gene (*PLP1*). More than 100 points mutations have been identified and described in the *PLP1* coding region causing a wide spectrum of clinical heterogeneity. *PLP1* encodes the most abundant CNS protein, proteolipid protein (PLP) a major structural protein in compact myelin [1, 2]. The purpose of this study encompasses two aims ***1)*** to investigate the integrity of the corticospinal (CST) pathway in patients with null (mild), moderate and severe *PLP1* mutations, and ***2)*** to assess which DTI index has a greater sensitivity in describing the heterogeneity of the disease pathology characterized by these *PLP1* mutation subtypes.

Methods: Twelve PMD patients (mean age =17 years ± 16) underwent neurological examination, genetic testing and a comprehensive neuroimaging protocol. Of the 12 patients, three had a complete or partial deletion of *PLP1* gene (null mutation), four had severe mutations and five had moderate mutations. The heterogenous severity of *PLP1* mutations was determined by their functional disability score [3]. We applied multivariate analysis of variances statistical analysis with age entered as covariate. Each subject had DTI on 1.5T scanner performed using 6 non-collinear gradient directions and 6 repetitions with b = 1000 s/mm^2. The whole brain was covered with a voxel size = 0.85 x 0.85 x 3 mm^3. In each hemisphere, three regions were selected along the CST followed by outlining manually each ROI (Figure 1) on ***1)*** the posterior-limb of the internal capsula (PLIC), ***2)*** the cerebral peduncle (CP), and ***3)*** the pons (Po). We combined left and right values of axial (E_1), radial (E_{23}), and mean diffusion (ADC) and FA.

Results: The percentage differences between severe and null mutations, severe and moderate mutation, and moderate and null mutation, are reported in table 1. The integrity of the white matter fibers, expressed by ADC showed that for the 3 structures, the difference between moderate and null mutations is negligible; between the severe and null (CP=27%, PLIC=10%, Po=22%) and severe and moderate (CP=27%, PLIC=9%, Po=23%) is non-significant. The FA, an index of fiber integrity, we observed higher values in moderate *vs* null mutation (CP=16%, PLIC=10%, Po=6%). In the severe mutation group we observed lower values in CP (-19%) and Po (-23%) and higher in PLIC (=6%) compared to that of the null mutation group. Similarly, severe vs moderate mutation demonstrated a decrease in CP (-22%) and Po (-16%) and an increase in PLIC (15%). We found no difference in DTI metrics (E_1, E_{23}, ADC, FA) at any level (PLIC, CP, Po) of the CST between patients with null mutations and patients with moderate mutations. Between groups difference (null versus severe mutations) controlling for age pointed to significantly higher E_{23} *(p=0.002)* in the pons, and a significantly higher E_1 in the PLIC *(p=0.008)*. There was a significantly higher E_{23} in the Po in patients with severe mutation compared to that of mild mutation.

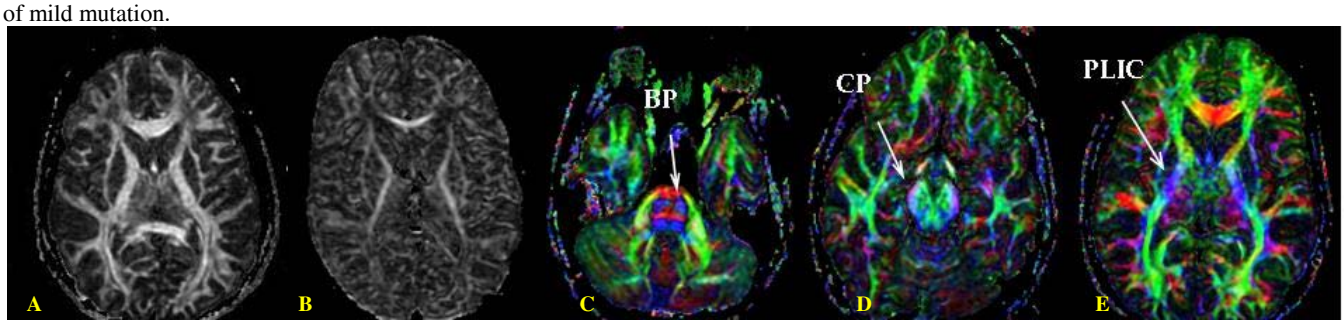

Figure1: FA maps of healthy-control subject (A) compared to a typical PMD patient (B) with a shrink of the white matter. The direction color encoded map used to delineate the base of the pons (C), the cerebral peduncle (D) and the posterior limb of internal capsula (E).

%	Moderate - Null				Severe - Null				Severe - Moderate			
difference	E1	E23	ADC	FA	E1	E23	ADC	FA	E1	E23	ADC	FA
CP	8	-6	1	16	17	36	27	-19	13	43	27	-22
PLIC	5	-4	1	10	13 *p=0.008*	7	10	6	15	2	9	15
Po	2	-2	0	6	13	31 *p=0.015*	22	-23	16	30 *p=0.015*	23	-16

Table 1: Percentage difference (corrected for age) between mutations (M=Moderate, N=Null, S=Severe) measured in axial E_1 and radial E_{23} diffusions, ADC and FA at the cerebral peduncle CP, pons Po, and posterior limb of the internal capsula PLIC.

Conclusion: Our study showed an increased E_{23} in severe mutations, which corroborate findings observed in studies involving dysmyelinated animals models [4] and in pathologic examinations of PMD autopsy tissue (*unpublished findings*). Disruption of WM microstructural organization found in the severe group was reflected by a low FA in CP and Po when compared to the null and moderate groups. The decreased FA observed may suggest that the abnormality lies within the myelin and also included the integrity of axonal fibers as being a major contributor to normal fibers anisotropy. The increase in E_1 found in severe mutations likely suggest an overall gross reduction axon fiber density, which may contribute to the decrease in FA. Furthermore, the amplified decrease in FA may arise from the severe astrocyte hypertrophy detected in the brains of PMD patients with severe mutations and augment the significant increase in E_1. The increased severity from rostral to caudal beginning at the CP extending to the Po is in agreement with a length-dependent axonopathy observed in mice and patients with null mutations [5]. DTI is a sensitive and robust biomarker capable of describing the cytoarchitectural changes that are imminent in neurogenetic disorders like PMD. The immeasurable value in monitoring disease progression noninvasively is instrumental in assessing the outcome of advanced therapeutic interventions, such as stem cells therapy [6].

References: [1] Duncan et al. (1989); [2]; Boison et al. (1995) ; [3] Laukka et al., (2013); [4] Harsan et al., (2006) [5] Garbern et al., (2002); [6] Gupta et al. (2012)