Microstructural Abnormalities in the Corpus Callosum of Patients with Pelizaeus-Merzbacher Disease with Different PLP1 Mutations.

Malek I Makki[1], Jeremy Laukka[2,3], and James Garbern[4]

[1]*MRI Research, University Children Hospital Zurich, Zurich, Switzerland,* [2]*Radiology and Neurology, Michigan State University, East Lansing, Mi, United States,* [3]*Neurology, Wayne State University, Detroit, Mi, United States,* [4]*Molecular Medicine and Genetics, Wayne State University, Detroit, Mi, United States*

Introduction: Neonates with transposition of the great arteries (TGA) undergoing open heart surgery are at risk for brain injury and impaired neurodevelopmental and behavioral outcome [1,2]. It has been shown that white matter injury in neonates with congenital heart disease (CHD) is similar to that of preterm born infant [3] in regards to regional predilection of delayed brain maturation [4,5]. Previous studies have demonstrated a correlation between thalamus abnormalities and cognitive disabilities due to different pathophysiologic origins [7,8]. To date no study have examined the involvement of the thalamus in children with CHD undergoing cardiopulmonary bypass (CPB) surgery although it is considered as a central relay station to the cortical connections. We hypothesized that neonates with TGA would experience abnormal microstructural development of their thalamus before and after CPB surgery compared to healthy age matched controls (HC).

Materials and Methods: Fifteen neonates with TGA born at term (mean gestational age = 40 ± 1 weeks) underwent CPB surgery in the neonatal period. They were scanned in natural sleep and monitored by an anesthesiologist during the exam. They successfully completed both pre-surgery (Pre) and post-surgery (Post) DTI on a 3T scanner using single shot spin-echo EPI with 35 gradient directions (b = 700 s/mm^2), FOV=22 cm, matrix = 128 x 128 reconstructed on 256 x 256 and slice thickness = 2.5 mm covering the whole brain. In addition ten healthy neonates born at term (mean gestational age = 39 ± 1 weeks) were scanned as control subjects. Left and right thalamus were separately delineated in axial planes by 2 observers (one did test re-test) over at least 3 adjacent slices. The 3 measurements were combined in one value and repeated measures analysis of variances was performed for each side and the level of statistical significance was set to $p = 0.05$. Age at DTI was entered as a covariate and group (Pre, Post, and HC) was entered as between-subjects factor. We also assessed the left-right asymmetry of DTI indices within each group using paired T-test.

Results: The HC group exhibited asymmetric development with significantly lower left E_1 ($p = 0.02$), and lower left FA ($p = 0.009$). The pre-surgical group (Pre) showed different asymmetric development with a significantly higher left E_{23} (left > right) and no difference neither in E_1 nor in FA (Table 1). The asymmetry of the post-surgery group (Post) resembled that of HC (lower left E_1 $p = 0.003$; lower left FA $p = 0.004$) and differed from that of pre-surgical group. No difference could be reported between left and right ADC in any group. The Pre group was 11 days younger than the HC, nevertheless there was no significant difference in any DTI metrics except lower left E_{23} *($p=0.034$)*. Compared to HC, we observed a significantly higher left FA *($p=0.007$)* in the Post (9 days older). Between group analysis (Pre versus Post) demonstrated no significant difference in any DTI indices. Although 20 days separated the pre and post DTI exams it is noteworthy to add that the post-surgical left E_{23} was higher than that of the pre-surgical one, the ADC was bilaterally higher after surgery and the left FA was lower that that of the pre-surgical value (Figure 1).

Left - Right	E_1	E_{23}	ADC	FA
HC	**(-) 0.020**	**(+)**	**(-)**	**(-) 0.009**
Pre	**(-)**	**(+)0.001**	**(-)**	**(-)**
Post	**(-) 0.003**	**(+)**	**(-)**	**(-) 0.004**

Table 1: Asymmetric left-right differences (paired T-test) measured separately for parallel diffusion (E_1), perpendicular diffusion (E_{23}), ADC, and FA. The significance p was set at <0.05. The values in parenthesis express the sign of the difference left - right. HC=healthy controls, Pre=pre-surgery, Post=post-surgery

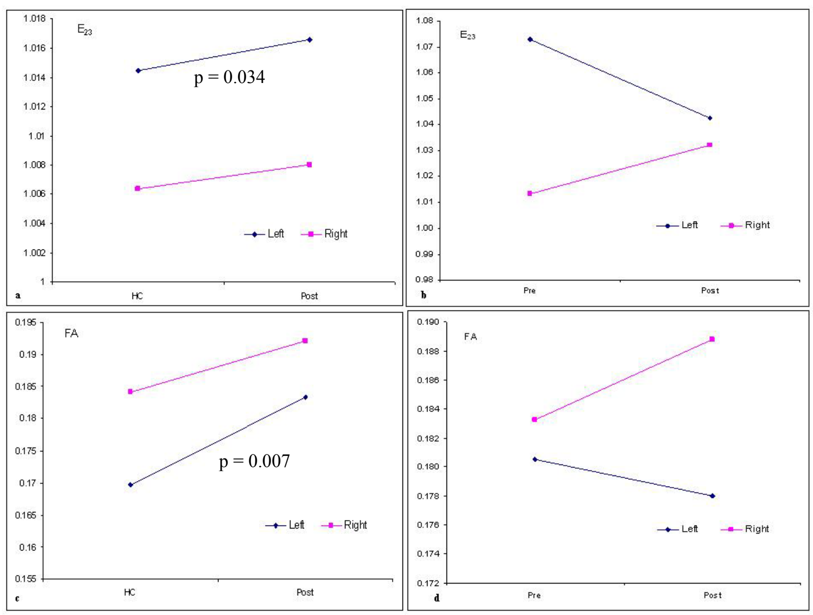

Figure 1: Estimated marginal means of perpendicualr diffusion E_{23} (a - b) and FA (c-d) in both sides for the healthy controls (HC), the pre-surgical (Pre) and post-surgical (Post) groups.

Discussion: Our analysis revealed that the thalamus of neonates with TGA had different asymmetric development before surgery compared to that of health controls. This suggested an existing astrocyte hypertrophy and oligodendrocyte death accompanying the myelin deficit in both sides of neonates with TGA prior to CPB surgery (higher E_{23}). More interestingly following CPB surgery the asymmetric development became similar to that of HC due either to plasticity or recovery. Following surgery an improvement was observed in the right side compared to pre-surgical exams while disorganized fibers in the left (decreased FA compared to pre-surgical group). These impairments may originate from venous outflow, leading to hypoxic injury or hypoxic injury of white matter tracts connected to various thalamic nuclei.

References: [1] Edgin JO et al., *J Int Neuropsychol Soc*. (2008); [2] Woodward LJ et al., *Dev Neuropsychol* (2011); [3] Miller SP et al., *J Pediatr* (2005); [4] McQuillen PS et al., *Stroke* (2007); [5] Mahle WT et al. *Circulation* (2006). [6] Kato T, *Neurotrauma* (2007); [7] Spencer MD, et al., *Neuroimage* (2006).