Regional Microstructure And Volume Abnormalities In The Corpus Callosum Of Neonates With Transposition Of The Great Artery Undergoing Cardiopulmonary By Pass Surgery.

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Purposes: Newborn infants with congenital heart disease (CHD) have brain injury and impaired neurodevelopmental and behavioral outcome [1,2]. White matter injury is the predominant brain injury pattern in these infants [3] and they show delayed brain maturation [4,5]. Abnormal corpus callosum has been associated with neurodevelopmental outcome in preterm infants (6,7).The aims of this study is to use DTI and volumetric images to (i) assess myelin maturation of 5 segments of the corpus callosum (genu=Ge, rostral body=Ro, body=Bo, isthmus=Is and splenium=Sp); (ii) to quantify the volume of each of theses segments and (iii) to compare the microstructure and volumetric changes in neonates with transposition of the great arteries (TGA) pre-surgery (Ppre) and post-surgery (Ppos) to that of age matched healthy controls (HC).

Materials and Methods: 15 term infants with d-TGA, who had both pre and post surgical MRI scans with DTI and 3D-T1W volumetric sequences. They were scanned at postnatal age of a minimum of 3 days to a maximum of 11 days (mean = 8 ± 6, median = 8). They were scanned under natural sleep.. In addition 20 healthy term infants (mean GA 40 ± 1 weeks, age at MRI 24 ± 11 days, range from 8 to 60 days, median = 22) were recruited from the postnatal ward at the University Hospital of Zurich. This study was approved by the local ethical committee and all parents were consented. MPRAGE was performed for 3D volumetric measures (3T scanner, TI=450 ms, flip angle = 12°, FOV=256 mm^2, matrix=256x256, slice thickness 2 mm and zip factor 2 to achieve an isotropic $1mm^3$ voxel). For DTI we used 35 gradient diffusion directions and b value of 700 s/mm^2 and a set of reference T2W volume (b=0). The slice thickness was 2.5 mm, FOV=22 cm^2, matrix size of 128x128 reconstructed in 256x256. The between-two-groups (Ppre vs HC, Ppos vs HC, and Ppos vs Ppre) DTI and volume statistical comparison was carried out separately for each region (Ge, Ro, Bo, Is, Sp) with a post-hoc repeated measures MANCOVA using post-conception age at MRI as covariate. Correlation of volume and DTI indices (parallel diffusion E_1, perpendicular diffusion E_{23}, apparent diffusion coefficient ADC and fractional anisotropy FA for each group (HC, Ppre and Ppos) was tested with a partial correlation controlling for post conception age at MRI. ROI were manually drawn on directionally color-encoded maps for each segment and were assessed for each index. Volume segmentation was manually performed on sagittal plane on the basis of the length of the corpus callosum: genu = 1/6, rostral body= 1/3, body=2/3, isthmus = 4/5.

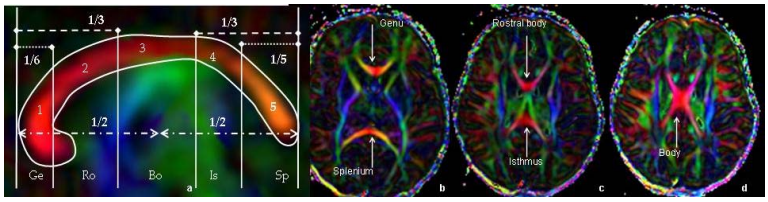

Figure 1: (a) a sketch showing the 5 segments of the corpus callosum (1:genu, 2:rostral body, 3:body, 4:isthmus, 5:splenium). Direction encode color map views (b-d) of axial plane showing the 5 segments.

Results:

Volumetric measures: The Sp was significantly smaller in the Ppre compared to HC ($p<0.001$). Examination of Ppos showed that each segment was smaller than that of HC (Ge: 0.004, Ro: 0.012, Bo: 0.002, Is: 0.006 and Sp: < 0.001). Ppos *vs* Ppre did not show any significant difference in term of volume in any segment. Diffusion measures (Table 1): Compared to HC, Ppre showed higher E_1 and ADC in the Ro and higher E_{23} and ADC and lower FA in the Sp. In Ppos we observed higher E_1, and ADC in the Ge, higher E_1, E_{23}, and ADC in the Ro, higher E_1, E_{23}, and ADC and lower FA in the Bo, higher E_{23} and ADC and lower FA in the Is and Sp compared to HC. The Ppos group had higher E_{23}, and ADC and lower FA compared to Ppre.

Volume vs diffusion measures: Partial correlation controlling for age showed no correlation between DTI indices and volume in any segment.

Table 1: Statistical results of parallel (E_1) and perpendicular (E_{23}) diffusions, apparent diffusion coefficient (ADC) and fractional anisotropy (FA) in patients pre-surgery (Ppre) and post-surgery (Ppos) compared to healthy control (HC)

	Ge	Ro	Bo	Is	Sp
Ppre vs HC					
E_1	--	↑0.024	--	--	--
E_{23}	--	--	--	--	↑0.004
ADC	--	↑0.015	--	--	↑0.025
FA	--	--	--	--	↑0.002
Ppos vs HC					
E_1	↑0.018	↑0.035	↑ 0.034	--	--
E_{23}	--	↑0.002	↑<0.001	↑<0.001	↑0.003
ADC	↑0.007	↑<0.001	↑<0.001	↑<0.001	↑0.026
FA	--	--	↓0.006	↓0.007	↓0.001
Ppos vs Ppre					
E_1	--	--	--	--	--
E_{23}	--	--	--	↑0.003	--
ADC	--	--	--	↑0.034	--
FA	--	--	--	↓0.026	--

Summary: Pre-surgery imaging showed smaller volume in the splenium in infants with TGA compared to healthy term infants. Post-surgery, smaller volume of all CC segments was found in infants with TGA compared to healthy term infants. Altered microstructure was already seen pre-surgery in the rostral body and the splenium compared to healthy term infants. Isthmus showed higher mean and radial diffusivity and lower FA in the isthmus pre-surgery compared to post-surgery imaging. Altered microstructure was not associated with abnormal volume.

Discussion: These findings might suggest delayed fetal maturation or altered fetal development of the CC, consistent with previous reports [8]. The isthmus seems to be the selectively vulnerable during the postnatal period and surgery. The lack of correlation between diffusion and volumetric measures might be explained by the short time period between pre-and postsurgery. In preterm infants, thin corpus callosum has been associated with abnormal neurodevelopmental outcome, especially cognitive outcome. The observed altered development of the CC in this study might explain the abnormal neurodevelopmental outcome observed in children and adolescents with CHD [9].

References: [1] Edgin et al. *J Int Neuropsychol Soc.* (2008); [2] Woodward et al. *Dev Neuropsychol* (2011); [3] Mahle et al. *Circulation* (2006); [4] Miller et al. *J Pediatr* (2005); [5] McQuillen et al. *Stroke* (2007); [6] Hart et al. *Dev Med Child Neurol* (2008); [7] Jo et al. *Neuroradiol* (2012); [8] Makki et al., *AJNR* (2013); [9] Schaefer et al. *Dev Med Child Neurol* (2013)