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Original scientific paper

Changes of the Corpus Callosum in Children who Suffered Perinatal Injury of the Periventricular Crossroads of Pathways

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A B S T R A C T

There is a high incidence of periventricular leukomalacia, caused by hypoxia-ischemia, in preterm infants. These lesions damage the periventricular crossroads of commissural, projection and associative pathways, which are in a close topographical relationship with the lateral ventricles. We explored to what extent abnormalities of echogenicity of the periventricular crossroads correlate with changes in size of the corpus callosum. Our study included nine infants (gestation from 26–41 weeks; birth weight between 938–4450 grams) with perinatal brain injury. Periventricular areas, which topographically correspond to the frontal, main and occipital crossroad, were readily visualized by cranial ultrasound scans, performed during the first two weeks after birth. Corpus callosum mediosagittal area measurements were performed using magnetic resonance images, acquired between the first and sixth postnatal month (postmenstrual age 40–49 weeks). We found a statistically significant correlation between the increased echogenicity in the crossroad areas and the decrease of the corpus callosum midsagittal area ($p<0.05$). This supports the hypothesis that callosal fibers can be damaged, during growth through the periventricular crossroads of pathways.

***Key words**: human, development, magnetic resonance, ultrasound*

Introduction

Periventricular lesions caused by hypoxia-ischemia are the major cause of motor, sensory and cognitive deficits[1–4] in infants, who were born prematurely. Two basic forms of periventricular leukomalacia were described: focal and diffuse[5,6]. The focal lesions affect the fetal »white matter« in the strategic periventricular zones[7]. Judas et al. 2005[8] have proposed that damage of the crossroads of periventricular projection, associative and commissural pathways may explain frequent occurrence of combination of motor, sensory and cognitive deficits (for detailed description of periventricular crossroads see Judas et al. 2005[8]). Diagnosis of periventricular lesions can be performed by magnetic resonance imaging (MRI) and ultrasound (US) examination. It was shown that US was not a completely reliable method in diagnosis of periventricular leukomalacia[9,10]. However, US is still the basic clinical method for screening preterm infant brain. In order to evaluate the potential of the ultrasound method for analysis of periventricular crossroads, we have compared early ultrasound findings with postnatal values of mediosagittal area of corpus callosum. This initial study will allow us to develop a new approach to test the hypothesis whether corpus callosum can be damaged while passing through the periphery of periventricular crossroads. The additional goal was to determine the developmental window of vulnerability of developing corpus callosum.

Materials and Methods

Nine preterm and term infants, who suffered perinatal brain injury, were included in the research. The gestational age ranged from 26 to 41 gestational weeks

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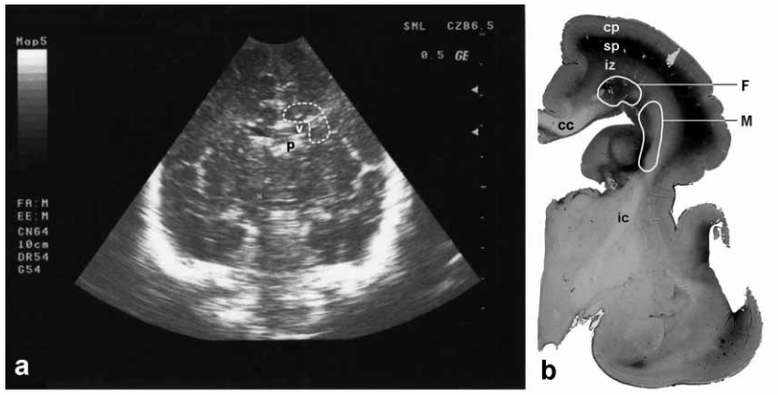

Fig. 1. a) Coronal section on an ultrasound image of a 2 month- old infant. The area that encompasses both the frontal and the main crossroads is indicated by the dotted line. v – lateral ventricle; p – plexus choroideus. b) Coronal section through the telencephalon of 20 week-old fetus, as revealed by fibronectin immunocytochemistry. The position of the frontal crossroad, situated dor- sally to the anterior horn of the lateral ventricle, and the main crossroad, situated laterally to the lateral ventricle, is indicated. The Zagreb Neuroembryological Collection. cp – cortical plate; sp – subplate; iz – intermediate zone; cc – corpus callosum; ic – internal capsule, F – frontal crossroad, M – main crossroad.

(GW), median 38 GW (Table 1). They were treated in the Intensive Care Unit of the University Hospital Center Zagreb, and underwent a series of US examinations and MRI procedures. The Internal Review Board of the Ethical Committee at the School of Medicine, University of Zagreb, gave ethical approval for the research, and parental consent was obtained for each infant.

Cranial US scans were obtained using a GE Medical Systems Logiq™ a 200 machine, with 6.5 and 5 MHz transducers. Paper copies of the images were made using a Sony UP-895 MDV printer on Mitsubishi K 65 HM-CE high-quality paper, for later analysis.

The US scans were performed through the anterior fontanel using the standard five coronal and five sagittal and parasagittal sections. The second and third coronal sections were used for the analysis. The US scans used were performed in the first two postnatal weeks. Two observers performed the analysis of the US scans, and a consensus was reached concerning the analysis.

The degree of echogenicity of white matter on US scans was analyzed as follows. The intensities were scored on a linear analog scale[9] from 0 to 3 compared to the echogenicity of the plexus choroideus, the grade 3 being given to the areas with the same echogenicity as the plexus (0 – normal echogenicity, 1 – mild increase in echogenicity, 2 – moderate increase in echogenicity, 3 – severe increase in echogenicity). The grade 3 was also given to areas that had cysts in the white matter. The three crossroad areas were analyzed, according to topographical criteria given by Judas et al. 2005[8]. The frontal crossroad area, situated dorsally and the main, situated laterally to the angles of the frontal-central portion of the lateral ventricles, and the occipital situated laterally to the trigonum of the lateral ventricle (Figure 1b and 2c).

TABLE 1
CHARACTERISTICS OF INFANTS INCLUDED IN THE STUDY

Infants	GW	Weight (g)	Chronological age at US scan	Chronological age at MRI scan	Postmenstrual age at MRI scan	Scores of crossroad echogenicity		CC area (mm^2)
						Main	Combined	
K.D.	41	3800	1 d	1m 2w	47 w	4	NA	165.98
R.T.	41	4450	6 d	1m	45 w	5	12	141.54
Č.M.	39	3190	9 d	3w	42 w	5	8	183.16
K.A.	39	3050	1 d	1m 3w	45 w	4	NA	150.91
T.J.	37	2800	1 d	1m 1w	42 w	5	8	156.82
P.N.	33	2210	5 d	1m 3w	40 w	3	10	175.02
B.M.	31	2240	10 d	2m 2w	41 w	6	14	128.94
V.M.	27	970	2 d	3m 3w	42 w	5	11	156.51
D.E.	26	938	1 d	5m 3w	49 w	1	6	180.52

GW – gestational weeks, CC – corpus callosum, m – month, w – week, d – day

Two scales were calculated from these grades. The first one was the scale for the main crossroad areas, which was calculated by adding the intensity grade of the right and left main crossroad areas, thus giving the range for this scale from 0 (normal echogenicity of the main crossroad areas on both sides) to 6 (severely increased echogenicity of the main crossroad areas on both sides). The second scale was calculated by adding the ultrasound intensity grades of all three crossroad areas of both sides, thus giving the range for this scale from 0 (normal echogenicity in all three crossroad areas on both sides) to 18 (severely increased echogenicity in all the crossroads on both sides). It was possible to determine the echogenicity of the main crossroad areas in all nine infants included in the study. We were able to determine the echogenicity of all the crossroad areas of both sides in seven of the nine infants (Table 1).

The MR images used for the measurements of the mediosagittal cross-section of the corpus callosum, were 3D spoiled gradient-echo (3D-GRE) T1-weighted MR images obtained with the high-field 2T MR imaging system (Gyrex Prestige, GEMS/Elscint, Haifa, Israel) and the following parameters: repetition time (TR) 650 ms, echo time (TE) 12 ms, number of excitations (NEX) 1, flip angle 180°, and section thickness of 5 mm. The matrix size and the field of view were adjusted to obtain a spatial resolution of at least 0.898 x 0.898 mm^2. The MR scan was performed between 40–49 postmenstrual weeks, at the

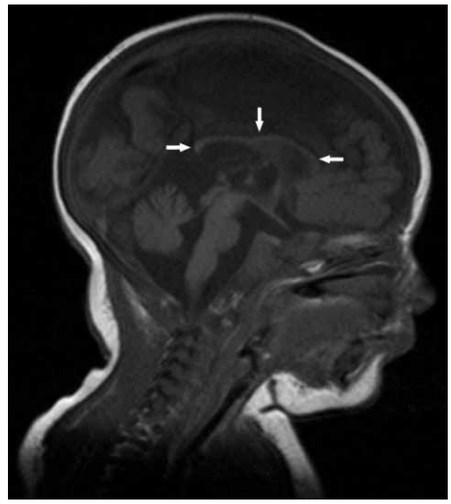

Fig. 3. The mediosagittal slice of a T1-weighted image of a 1 month-old infant, acquired with a 2T imaging system. The corpus callosum (arrows) in the picture is of reduced size.

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The pictures were analyzed using the Analyze 6.0 software package (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). The parameters for recognizing the mediosagittal section were previously established,

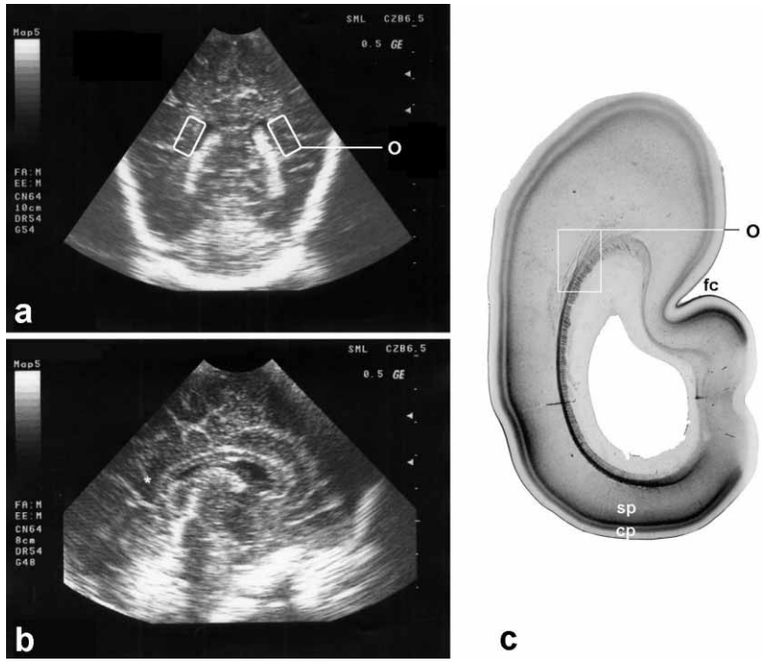

Fig. 2. a) Coronal section on an ultrasound image of a 2 month- old infant. The area of the occipital crossroads, indicated by the square, can be readily visualized on this section, localized lateral to the lateral ventricle, at the level of the trigonum. O – occipital crossroad area. b) Mediosagittal section on an ultrasound image of the same infant. The corpus callosum is easily visualized on this section. The position of the occipital crossroad is indicated by the asterix (*). c) Coronal section through the telencephalon of 26 week-old fetus, AchE-stained. The occipital crossroad is located dorsolateral to the posterior horn of the lateral ventricle, at the level of the trigonum. cp – cortical plate; sp – subplate; fc – fissura calcarina, O – occipital crossroad.

and include a visible interhemispheric fissure, fully depicted corpus callosum and visible cerebral aqueduct[11–14] (Figure 3). The voxel size of the mediosagittal section was reduced to 0.1x0.1x0.1, to minimize the voxelisation effect in order to obtain more precise area measurements. The corpus callosum was manually delineated, and the area size automatically calculated. The procedure was repeated five times by a single observer; the mean value was calculated and used for subsequent statistical analysis.

The histological and immunocytochemical slices used for visualization of the periventricular crossroads, belong to the Zagreb Neuroembryological Collection[15] (Figure 1b and 2c).

Results

We were able to visualize all three crossroad areas of both sides by US in seven of the nine infants included in the study (Figure 1a, 2a and 2b). The combined echogenicity scale was calculated, and the relationship between the corpus callosum midsagittal area and the scale was statistically analyzed. The calculated Pearson's quotient (r) was –0.8574, showing that the higher combined echogenicity of all the crossroad areas is in correlation with the smaller mediosagittal area of corpus callosum, statistical significance of $p<0.05$ (Figure 4).

All the infants included in the study had visible main crossroad areas on both sides on US examination (Figure 1a). The relationship between the scale and the corpus callosum midsagittal area, as measured on MR images, was statistically analyzed using the Pearson's correlation test. The calculated quotient (r) of –0.6541 showed a negative correlation between the main crossroad echogenicity scale and the corpus callosum area**,** with $p=0.056$ (Figure 5), indicating a need for a larger study sample.

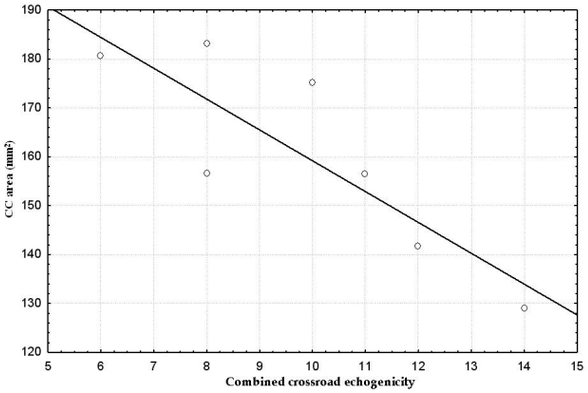

Fig. 4. The graph shows the relationship between the sum of echodensities of the three crossroads of both sides (combined crossroad echogenicity) and the midsagittal cross-sectional area of the corpus callosum. We see that the higher overall echogenicity, indicating greater damage of the crossroads, correlates with the smaller cross-sectional area of the corpus callosum (r=–0.8574, p<0.05). CC – corpus callosum.

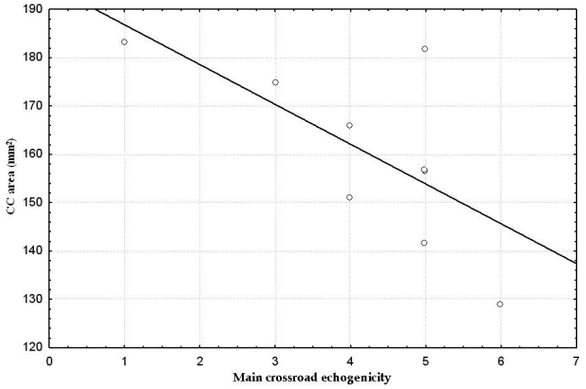

Fig. 5. The graph shows the relationship between the sum of echodensities of the main crossroad areas of both sides and the midsagittal cross-sectional area of the corpus callosum. We see that the higher overall echogenicity, indicating greater damage of the crossroads, correlates with the smaller cross-sectional area of the corpus callosum (r=–0.6541, p=0.056). CC – corpus callosum.

Discussion

The results presented in this study have shown that areas of the periventricular crossroads of pathways as described by Judas et al.[8] can be readily located on conventional US scans in infants. Areas of frontal, main and occipital periventricular crossroads, which contain a periventricular contingent of growing callosal fibers[8,16], in our material frequently show hyperechodensities. These abnormal changes of the periventricular crossroads were frequently associated with a significant reduction of callosal cross-sectional area compared with normal infants[17,18]. Previous studies of infants, who suffered perinatal hypoxia-ischemia during preterm period, have also demonstrated significant reduction of callosal cross-sectional area[19–25], which was associated with marked cognitive deficit[20,21]. All authors agree that the final measurements of callosal cross-section area should be performed after myelinization is finished, after 10 years of age. However, these studies did not explain why corpus callosum is damaged in lesions located lateral to the angle of the ventricles. We are inclined to accept the explanation of previous studies[8,16] that callosal fibers grow through the frontal crossroad, the periphery of the main crossroad and through the occipital crossroad. Judas et al 2005[8] proposed that developmental vulnerability of periventricular crossroads is related to the disturbance of axonal guidance molecules and extracellular matrix. This pathogenetic mechanism may explain the lesion of corpus callosum. Our data supports the hypothesis that corpus callosum can be damaged during growth through the periventricular crossroad of pathways. Namely, corpus callosum fibers in preterm infants show intensive growth and remodeling[26–29] and increased requirement for axonal guidance with extracellular matrix molecules[26]. Therefore, late gestation and preterm period are very likely vulnerable periods of callosal growth. Our findings are in accordance with this possibility.

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PROMJENE KORPUSA KALOZUMA U DJECE S PERINATALNIM OŠTEĆENJEM U ODNOSU NA EHOGENOST PERIVENTRIKULARNIH KRIŽANJA PUTOVA

SAŽETAK

Kod nedonoščadi postoji visoka incidencija periventrikularne leukomalacije, uzrokovane hipoksijom-ishemijom. Ove lezije oštećuju periventrikularna križanja asocijatvnih, komisuralnih i kalozalnih putova, koji su u bliskom topografskom odnosu sa postraničnim komorama. Istražili smo u kojoj mjeri abnormalnosti ehogenosti periventrikularnih križanja putova koreliraju sa promjenama veličine korpusa kalozuma. Naša je studija obuhvatila devetoro djece (trajanje gestacije od 26–41 tjedana, težina pri rođenju od 938–4450 grama) s perinatalnom ozljedom mozga. Područja oko postraničnih komora, koja topografski odgovaraju frontalnom, glavnom i okcipitalnom kružanju putova, su prikazana pomoću kranijalnog ultrazvuka, obavljenog u prva dva tjedna nakon rođenja. Mjerenja mediosagitalne površine korpusa kalozuma su izvršena na slikovnim prikazima magnetske rezonance glave u dobi između prvog i šestog mjeseca poslije rođenja. Pronašli smo statistički značajnu povezanost između povećane ehogenosti područja periventrikularnog križanja putova i smanjene mediosagitalne površine korpusa kalozuma ($p<0.05$). Naši rezultati podupiru hipotezu da kalozalna vlakna mogu biti oštećena za vrijeme rasta kroz periventrikularna križanja putova.