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Corpus callosum in preterm infants and patients with cerebral palsy

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Abstract

Midsagittal magnetic resonance images of the brain of 25 infants (16 preterm vs 9 term) and those of 100 children of age between 2 and 11 (50 cerebral palsy patients vs 50 healthy peers) were analyzed in order to reveal morphometric differences in the corpus callosum between those groups. The MRI and clinical findings were analyzed retrospectively. For morphometric measuring the midsagittal area of the corpus callosum was divided into seven segments (CC1 - CC7) using the Witelson's method. The ratio of the areas of the anterior and posterior segments of the corpus callosum, described by self-designed formula $KCC = (CC2 + CC3) \times CC6/CC7$ proved to be a reliable indicator of differences between the brain of preterm and term infants, and of children with cerebral palsy and their healthy peers respectively.

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Keywords: Magnetic resonance imaging; Morphometry; Corpus callosum; Preterm infants; Cerebral palsy.

1. Introduction

Cerebral palsy (CP) is a non-progressive disorder with clinical manifestations such as motor dysfunction accompanied by cognitive impairment due to lesions of the developing brain. Etiological factors contributing to pathogenesis are still not defined completely, suggesting the polyetiologic nature of the disease. Among preterm children the rate of CP patients varies from 40 to 150 cases per 1000 preterm newborns [1]. MRI-studies suggest

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that the cerebral white matter and corticospinal pathway are among the most affected areas of the cerebral palsy brain [2]. However up to 32% of patients with clinical manifestation have no pathological findings on MRI [3].

Therefore there isn't much consensus in terms of factors causing cerebral palsy. Among others, the prenatal lesions or genetic factors could be involved in the pathogenesis [4]. Wallerian degeneration of corticospinal tract fibers in children with hemiplegia allows to suggest that the deficit of white matter may be partly due to the death of cortical neurons [5]. According to the results of our previous immunohistochemical research with (MAP2) antibody, in the second half of gestation the differentiation of cortex-to-cortex projecting neurons follows the differentiation of subcortically projecting neurons. Labeling cells in progress by MAP2 immunostaining reveals the heterochronic character of subcortically projecting and the associative neuronal population formation and in fact detects the critical period of cell development. It is worth that, areas where immunopositive cell were dense are detected in local groups in the medial, ventral prefrontal, precentral and postcentral, posterior temporal and occipital areas [6]. These findings consequent with literature data on prenatal MRI [7] let us to postulate the crucial role of time coincidence of premature birth or teratogenic factors with the critical period of morphogenesis. This results in affecting different cortex areas and specific callosal hypoplasias provoked by abnormal transcallosal pathways initiated by injured neurons.

The goal of present study is analyzing the corpus callosum on brain MRI-images of term versus preterm infants and of cerebral palsy children versus their healthy peers by measuring it with corpus callosum coefficient elaborated on the basis of heterochronic corticogenesis study.

2. Materials and methods

In this study we used a retrospectively identified MRI-database of male and female neonate infants and children, imaged at Saint-Petersburg State Pediatric Medical University from January 2010 to December 2012. All MRI scans were obtained using a 1.5T GE Sigma HDxt scanner with the use of conventional echo-planar sequence. A series of sagittal and axial T1- and T2-weighted images (FOV 24 cm, 5 mm section thickness, 2.5 mm intersection gap, 256×192 acquisition matrix) were carefully selected and subjected of morphometric analysis with the use of Image J free software and DICOM Viewer. Technical details of neonatal brain imaging were the same apart from 2 mm section thickness, 1 mm intersection gap, use of FLAIR/FSE sequence.

The first group consisted of neonates born at 37-42 weeks of gestation (subgroup of term infants), and born at 27-36 weeks of gestation (subgroup of preterm infants). Neonatal patients were not subjects of repeated follow-up, and in the present study results of a one-time examination conducted on 7-21 postnatal days were used. The inclusion criteria for the study were the absence of demonstrated by radiological analysis periventricular leucomalation, or ischemic lesions and a sufficient contrast level, which enabling to differentiate gray and white matter of the brain. The 25 series were selected of images of the neonatal brain with mild signs of external hydrocephaly and moderate hypomyelination detected by professional radiologists. These abnormalities are not associated with neurological implications as was shown by follow-up neonatal brain MRI-study with a reference to the psychomotor status of 2 years old patients [8]. Thus, a valid comparative analysis of normalized MRI-series allowed to reveal specific CC structural hallmarks associated exclusively with shortened gestation, but not with hypoxic ischemic lesions.

The second group consisted of CP subgroup and control subgroup. The CP subgroup consisted of 50 children of both sexes between the ages of 2 to 11 with spastic tetraplegia, diplegia, and hemiplegia CP, no history of trauma or brain operation, the same diagnosis stated after the first physical and radiologic examinations in the age of one year. Control subgroup consisted of 50 healthy peers of both sexes, who underwent medical examination due to otorhinolaryngological problems or head injuries. All subjects were free from neurological or psychiatric diseases, had normal intellectual development and their brain MR-scans were normal.

Non-parametric Mann–Whitney test (U-test) was applied for statistical analysis of significant difference between subgroups (preterm vs term, CP vs healthy control).

3. Results

Comparative morphological analysis of the CC segment areas was performed on midsagittal MRI of brain of term and preterm neonates, CP children and their healthy peers. All images were oriented to the genu – splenium line. The boundary contours of the corpus callosum were outlined manually on adjusted images and the midsagittal area of the corpus callosum was divided into seven segments (CC1 – CC7) using a Witelson’s method [9] consistent with anatomic landmarks (Fig.1b). A standardized way of corpus callosum segmentation is crucial of our study keeping in mind the high order of CC topographic organization: interhemispheric prefrontal pathways are located within rostrum, genu and anterior part of body, premotor and supplementary motor pathways are located within middle and posterior part of CC, precentral and postcentral interhemispheric pathways are located within the isthmus, temporal and occipital interhemispheric pathways are located within splenium [10]. Four out of seven CC segments are initiated by cortex areas with accelerated development: CC2 and CC3 of the frontal area, CC6 of the pre- and postcentral area, and CC7 of the temporal and occipital areas. Taking this into consideration we have derived coefficient which closely reflects CC development status:

$$kCC = (CC2 + CC3) \times CC6 / CC7.$$

The values of kCC in the preterm subgroup are significantly lower than the values for term subgroup. Furthermore, the kCC value of 60 is a preterm subgroup threshold. By this indicator the preterm brain could be differentiated from term brain in 14 cases out of 16 (Fig.1a). Lower kCC rate of preterm neonates versus term born are due to altered proportion of anterior and posterior segments of CC (Table 1).

Table 1. Comparison of term infants vs preterm infants. The ratio of corpus callosum segment area to the total midsagittal callosal area

Group	Percentage midsagittal area CC segment, %			k CC
	CC2+CC3	CC6	CC7	
Term	35.3	11.2	28.9	79.4
Preterm	28.7	9.7	30.8	43.3

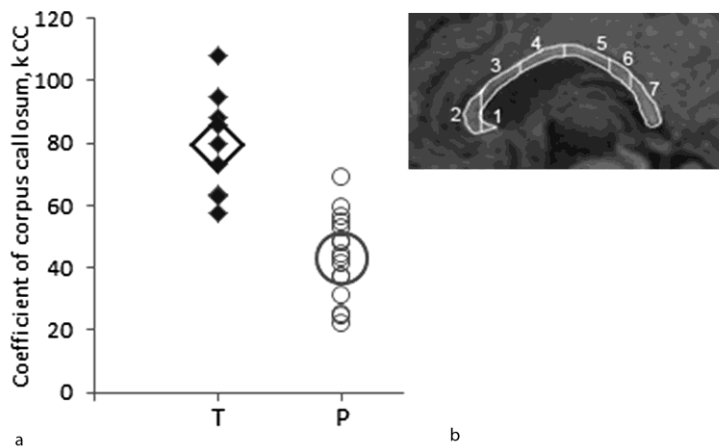


Fig. 1. (a) corpus callosum coefficient (kCC) at term (T) and preterm (P) neonates; small marks - individual coefficient values; big marks - average coefficient value per group; (b) corpus callosum division scheme into seven segments (CC1-CC7)

The kCC in the CP subgroup is significantly decreased ($p \leq 0.01$) comparing to the control subgroup in all age categories. A threshold value of kCC, which enables to differentiate CP brain from healthy brain, is 200. The exclusion consists of 12 cases (5 CP children out of 50 had a kCC value higher than 200 and 7 healthy children had kCC less than control (Fig.2). Decreased values of kCC in CP children comparing to control subgroup values are due to altered proportion of anterior and posterior segments of CC (Table 2). The relative size of CC segments in control group shows no significant age-related dynamics. In contrast the CP subgroup demonstrates the age-related decrease of relative size of genu, and the relative size of isthmus is significantly decreased compared to its control value regardless the age (Table 2). For all age categories the midsagittal area of CC was significantly decreased in patients with spastic cerebral palsy.

Table 2. Comparison of children with CP vs. children without one (CP/control)

Age group (years)	Percentage midsagittal area CC segment, %			kCC
	CC2+CC3	CC6	CC7	
2-3	46.1 / 41.2	6.5 / 8.2	22.3 / 27.2	129.2 / 255.3
3-4	44.6 / 41.3	5.9 / 8	23.7 / 27.6	120.2 / 245.6
4-5	41.9 / 39.7	6.8 / 8.3	25.3 / 29.5	129.7 / 260.9
5-6	42.7 / 40.5	7.2 / 8.2	25.8 / 30.2	153.0 / 259
6-7	39.3 / 39.7	6.8 / 8.4	29.0 / 29.5	140.4 / 261.9
7-8	35.8 / 40.2	6.9 / 8	25.4 / 30.0	92.0 / 256
8-9	38.3 / 41.7	6.5 / 8	23.5 / 29.8	95.8 / 287.2
9-11	35.2 / 38.6	7.1 / 8.8	28.1 / 29.3	123.9 / 328.1

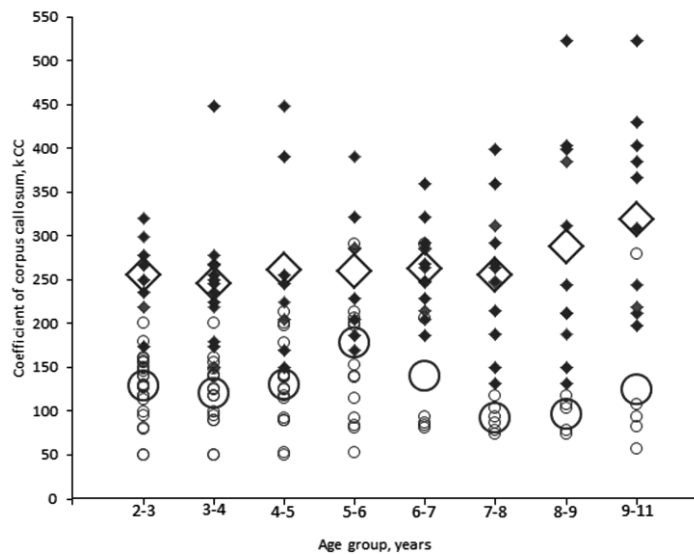


Fig. 2. Corpus callosum coefficient (kCC) at CP children (circles) and their healthy peers (rhomb). Small marks - individual coefficient values; big marks - average coefficient value per group

4. Discussion

Currently, there are no much data on direct effect of premature birth on transcallosal pathways organization. It is known that the CC in preterm infants is less than that volume of term born children, specifically in the anterior part of truncus and isthmus [11]. Some of CC prenatal developmental trends are definite: all the CC segments appear to be formed by the end of the second trimester, and the progressive increase of commissure in the genu-to-splenium direction is shown during the last trimester [12].

Our data suggest that in preterm infants anterior segments of CC tend to decrease relative volume rather than in term born infants. This fact could be explained by heterochronic character of cerebral hemispheres development with areas of accelerated neurogenesis of frontal cortex during the last weeks of gestation [6], [7]. Logically, in preterm infants this period of development could be dramatically influenced by exposure to abnormal environment compared with term born, thus the frontal cortex area and initiated pathways being highly susceptible to perinatal injury.

CP children compared to their healthy peers are often reported to have decreased volumes both of white matter and corpus callosum [13].

Commonly, the CP is associated with perinatal brain injury and a shortened gestational age. The results of our study demonstrate that regardless of the age in CP children compared to their peers the area of genu, containing callosal pathways of prefrontal areas, is significantly decreased. What is more, such patients have decreased midsagittal area of isthmus and the volume of primary motor, somatosensory pathways within it. The decreased rate of kCC in CP children is derived from the above mentioned CC structural alterations.

5. Conclusion

Significantly decreased values of kCC in preterm infants compared to term born and in CP children compared to their healthy peers could result from the perinatal injury of certain cortex areas and the suboptimal volume of transcallosal pathways of anterior and posterior segments of corpus callosum.

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