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Assessing sequence and relationship of regional maturation in corpus callosum and internal capsule in preterm and term newborns by diffusion-tensor imaging

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ABSTRACT

Background: Diffusion-tensor imaging (DTI) can be used to investigate water diffusion in living tissue.
Objective: To investigate sequence and relationship of regional maturation in corpus callosum (CC) and internal capsule (IC) in preterm and term.
Methods: DTI was performed on 11 preterm infants at less than 37 weeks of corrected gestational age (group I), 21 preterm infants at equivalent-term (group II), 11 term infants during neonatal period (group III). Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were measured in: anterior limb of IC (ALIC), posterior limb of IC (PLIC), genu and splenium of CC.
Results: FA in splenium was more than that in other regions except genu of group I. Differences of FA between genu and PLIC were significant only in group III. ADC in genu was more than that in other regions but in splenium of groups I and II. Differences of ADC between splenium and ALIC were insignificant except group II. Higher FA and lower ADC in PLIC were gotten compared with those in ALIC. Correlations of FA and of ADC existed in CC and IC.
Conclusion: Maturation sequence was splenium followed by genu, then by PLIC and last by ALIC in term at neonatal period. Genu's maturation in preterm at equivalent-term was hindered. Regional maturation's correlations existed in CC and IC.

1. Introduction

White matter injury (WMI) is an important problem in premature infants of between 24 and 34 weeks of birth gestational age (GA) (Jensen, 2006), which results in disrupted white matter (WM) maturation and chronic myelination disturbances (Volpe, 2008). To understand WMI in preterm infants requires continued efforts on understanding the underlying microstructural changes in brain development, especially the maturation of white matter, in preterm. The development of white matter myelination in the preterm has been described qualitatively by conventional MRI (Counsell et al., 2002). To assess accurately the microstructural changes during maturation in preterm brain needs a non-invasive, "in vivo" assessment of white matter development quantitatively. Diffusion-tensor imaging (DTI) offers great potential to fulfill the need. DTI can be used to investigate diffusion properties of water in living tissue (Mathur et al., 2010), which is a useful tool of studying white matter maturation and injury during childhood (Jiao et al., 2010; Welker and Patton, 2012). Fractional anisotropy (FA) describes the degree to which water diffusion is restricted in one direction relative to others, ranging from 0 to 1, with 0 being completely isotropic diffusion and 1 being diffusion constrained in one direction only. In mature white matter, water diffusion is highly anisotropic in that water molecules move less freely perpendicular to fibers than parallel to them. During development, the increase of FA in white matter appears to occur in three stages (Dubois et al., 2008). First stage, fiber organization occurs, during which anisotropy exists in white matter in late intrauterine and premature infants (Kostovic and Jovanov-Milosevic, 2006). The increase of anisotropy seems to correlate with the developmental expansion of immature oligodendrocytes during the premyelination period (Drobyshevsky et al., 2005). Second stage, maturation of pre- and immature oligodendroglial cells, as well as the development of the cytoskeleton and various intracellular structures. Third stage, myelination, which is associated with histological appearance of myelin and its maturation around axons (Wozniak and Lim, 2006;

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Taki and Kawashima, 2012). So the increase of FA is closely related to the maturation of white matter. We used FA as an indication of white matter maturation just like that Klingberg et al. (1999) and Colby et al. (2011) did.

Apparent diffusion coefficient (ADC), which reflects the rate of microscopic water motion in a regional tissue, is used to evaluate water content and to a lesser degree to evaluate white matter myelination (Provenzale et al., 2007).

We designed this study to detect and analyze FA and ADC in corpus callosum (CC) and internal capsule (IC) of three groups' infants, who were preterm infants at less than 37 weeks of corrected GA, at equivalent-term, and term infants at neonatal period. Our aims were: (1) to study differences of regional maturation in CC and IC in preterm and term, (2) to study whether FA and ADC in CC and IC in preterm at equivalent-term can catch up with those in term, (3) to investigate relationships of regional FA and ADC in CC and IC.

2. Materials and methods

2.1. Subject selection

From October of 2010 to January of 2013, we collected 32 cases of preterm babies, who were hospitalized in neonatal department of the first affiliated hospital of Nanjing Medical University, whose parental consents were gotten, whose birth GA was from 27.4 weeks to 34.5 weeks (median: 32.3 weeks), among whom 15 cases' birth GA was from 27.4 weeks to 32 weeks and 17 cases' birth GA was between 32.2 weeks and 34.5 weeks. There were 22 boys and 10 girls, whose birth weight (BW) was from 840 to 2900 g (median: 1550 g). During this period, there were 11 cases of hospitalized term babies, who should be examined MRI for clinical diagnoses and whose parental consents were gotten, among whom 3 cases were because of cephalohematoma, 3 cases because of SGA, 2 cases because of meconium aspiration syndrome, 2 cases because of newborn sepsis, 1 case because of benign familial neonatal seizures, 4 girls and 7 boys, whose BW was between 2050 and 4000 g. Inclusion criteria: (1) parental consents were gotten, (2) infants needed to receive conventional MRI for clinical diagnoses, (3) conventional MRI imaging of brain were normal (if the babies' parental consents were not gotten, they just received conventional MRI). Exclusion criteria: (1) infants were suffered from severe intracranial hemorrhage, white matter injury, brain infarct, neonatal meningitis, or congenital anomaly, (2) infants need not receive conventional MRI for clinical diagnoses, (3) parental consents were not gotten. GA was calculated from the date of last menstrual period and was confirmed with early prenatal ultrasound scanning. The research ethics committee of the first affiliated Hospital of Nanjing Medical University approved the study, and the informed parental consents were obtained.

2.2. Groups and methods

2.2.1. Groups

Preliminarily, we designed to divide the enrolled preterm babies into two groups, but some babies lived too far from our hospital and some babies' parents had no time to come back to our hospital by the due date, so we let the enrolled babies' parents choose when the babies came back. Finally we were not able to randomly separate the preterm babies into two groups. Group I, 11 preterm infants were done DTI at less than 37 weeks of corrected GA (BW: 1568 ± 308 g, GA: 30.9 ± 1.5 weeks), group II, 21 preterm infants, on whom DTI was performed at equivalent-term age (BW: 1680 ± 555 g, GA: 32.0 ± 2 weeks); There was no difference in GA ($p = 0.174$) and BW ($p = 0.54$) between groups I and II. Group III, 11 term infants were done DTI during the neonatal period.

2.2.2. Preparations for infants

DTI was performed on the infants when their vital signs were stable. Infants were sedated with orally administered chloral hydrate (50 mg/kg). Before sedating infants, we checked whether there was metal on the infants or not, and took measurements of hearing protection. Patients should be wrapped snugly in 1–2 sheets.

2.2.3. Imaging parameters

A MRI protocol was performed on the subjects with a 3.0-Tesla MRI scanner (Trio, Siemens, Germany). The MRI protocol included a T1-weighted sequence, a T2-weighted sequence, a FLAIR sequence, and a DTI sequence. As the number of gradient directions increases, the quality of FA maps becomes better, while imaging needs longer time and the number of artifacts increase for newborn babies. Basser et al. reported that minimum of six gradient directions are necessary to assess diffusion anisotropy fully (Basser and Pierpaoli, 1996). Some researchers just used 6 directions in their studies (Colby et al., 2011; Provenzale et al., 2012; Cheong et al., 2009). In this study, DTI images were acquired in the axial plane with a 12-direction diffusion weighted multi-slice echoplanar spin-echo imaging protocol, TR = 3000 ms, TE = 93 ms, slice thickness = 4 mm, inter-slice gap = 0.4 mm, voxel size 1.9 mm × 1.8 mm × 3.0 mm, average = 1, b-value = 1000 s/mm^2. All images were processed on workstation of Syngo MR1317 (Siemens, Germany).

Using Functional software, the analysts blinded to any clinical material drew regions of interest in anterior limb of IC (ALIC), posterior limb of IC (PLIC) of the left and the right, genu and splenium of CC on ADC and FA maps with reference to corresponding T2-weighted images, and measured ADC and FA.

In group II, there were artifacts on ALIC of the left in one case (the data in ALIC of this case were deleted).

Table 1
Regional ADC and FA values in CC and IC of three groups.

	I	II	III
Genu of CC			
ADC	1.542 ± 0.159	1.416 ± 0.164	1.329 ± 0.147
FA	0.435 ± 0.080	0.513 ± 0.105	0.589 ± 0.064
Splenium of CC			
ADC	1.504 ± 0.427	1.336 ± 0.303	1.163 ± 0.073
FA	0.518 ± 0.137	0.673 ± 0.126	0.694 ± 0.071
ALIC (right)			
ADC	1.330 ± 0.089	1.171 ± 0.100	1.137 ± 0.063
FA	0.263 ± 0.040	0.331 ± 0.057	0.320 ± 0.050
PLIC (right)			
ADC	1.138 ± 0.102	1.032 ± 0.069	1.002 ± 0.041
FA	0.397 ± 0.059	0.477 ± 0.070	0.477 ± 0.065
ALIC (left)			
ADC	1.328 ± 0.073	1.151 ± 0.090	1.122 ± 0.052
FA	0.390 ± 0.051	0.481 ± 0.082	0.503 ± 0.053
PLIC (left)			
ADC	1.121 ± 0.091	1.028 ± 0.074	1.009 ± 0.049
FA	0.226 ± 0.039	0.298 ± 0.048	0.302 ± 0.042

Mean ± SD (ADC × 10^{-5} mm^2/s).

2.3. Statistical analyses

Data were analyzed with SPSS16 software (StatsDirect, Sale, United Kingdom). ADC and FA values were showed up with equivalence ± SD for groups. Comparisons of regional FA and ADC values and of different group's FA and ADC were analyzed by independent-samples t test. Relationship of regional FA and ADC was analyzed by correlation analysis. The results were significant at a level of $p < 0.05$.

3. Results

3.1. ADC and FA values

ADC and FA values (mean ± SD) in genu and splenium, in ALIC (of the right and of the left) and PLIC (of the right and of the left) of three groups were showed in Table 1. Fig. 1 showed the images of CC and IC on DTI in three groups.

3.2. Comparisons of regional FA in three groups

FA values in splenium were the highest among those in all measured regions in each group, and the differences of FA were significant statistically between splenium and other regions except genu of group I ($p = 0.098$). The differences of FA between genu and PLIC (of the right and of the left) were not significant statistically in groups I and II, but in group III. The differences of FA between PLIC (of the right and of the left) and ALIC (of the right and of the left) were significant statistically in three groups (p values see Table 2). We rebuilt 3-dimensional images of fiber bundles in CC and IC of three groups, respectively, from which we can see that the density and the number of fiber bundles in splenium were more than those in genu in three groups, and that the density and the number of fiber bundles in PLIC were more than those in ALIC in three groups (see Fig. 2).

3.3. Comparisons of regional ADC in three groups

ADC in genu was more than that in other regions measured in each group, except splenium of group I ($p = 0.781$) and of group II ($p = 0.298$). The differences of ADC between splenium and ALIC (of