Following the Development of Corpus Callosum (CC) in the Prenatal Period in Humans through Diffusion Tensor Tractography (DTT)

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Introduction: The corpus callosum (CC) is the largest commissural fibers in a human brain that connects two cerebral hemispheres. It is important for the functional integration of the two hemispheres. The development of the CC begins during the fifth week of fetal life with the formation of the primitive lamina terminalis, which thickens to form the commissural plate (1). The growth and changes in configuration of the CC in fixed brain of human fetuses has been described on histopathology (1). Although the normal standards for the appearance and growth of CC in the neonates have been established with magnetic resonance imaging (MRI) (2), no imaging or histopathological data is available on growth of CC in unfixed human fetal brain. Diffusion tensor imaging (DTI) characterizes the apparent diffusion properties of water (3). The popular region of interest (ROI) – based morphometric DTI method is limited to 2 dimensional that does not reflects the whole fiber bundle in 3 dimensional space. In brain white matter, the principle diffusion direction corresponds well with orientation of major fiber in each voxel. Diffusion tensor tractography (DTT) method gives 3 dimensional information of white matter fiber tract. Our aim was to study the normal appearance and development of CC in the freshly aborted human fetal brain from 16 weeks of gestational age (GA) to term, through DTT.

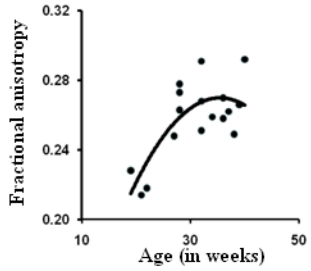
Materials and Methods: Conventional MRI and DTI were performed on 20 normal human fetal brains with age ranging from 16 to 40 weeks of gestational age (GA). The younger fetuses were obtained after spontaneous abortion, whereas the older ones were obtained after medical abortion for incurable renal malformation, osseous dysplasia, or intrauterine death from unknown causes. None of the fetuses had detectable CNS malformations on antenatal ultrasound. The time delay between MRI scans and delivery was 3.8±0.8 hours. The age of each fetus was based on a combination of postovulatory age and early ultrasonographic GA estimation.

All these studies were approved by the Institutional Ethics Committee. Written consent for performing these studies was obtained from the parents.

Imaging protocol: MRI data was acquired on a 1.5-T GE MRI scanner using quadrature transmit–receive head coil. The MRI protocol included T2-weighted, T1-weighted and DTI. DTI was acquired by using a single-shot echo planar dual spin-echo sequence with ramp sampling. The b-factor was set to 0 and 700 s/mm2. The other acquisition parameters were TR=8 sec, TE=100 msec; number of axial sections = 20–34, slice thickness of 3 mm with no gap, FOV varying from 160 mm × 160 mm to 240 mm × 240 mm depending on the size of the fetal head, and image matrix of 256 × 256 (after zero-filling).The diffusion tensor encoding used was a dodecahedral scheme with 10 uniformly distributed directions. Tracking has been done using FACT Algorithm. The software enables to select region of interest (ROI) from the plane orthogonal to the orientation of fiber bundle associated with the thickest part of the fiber bundle. The interface incorporates a number of plug-in for the operations of add/delete selected fibers, morphological trimming operations , adding fibers from another ROI and gathering statistics on the obtained fiber volume or parts of it. The free hand ROIs were placed on mid sagittal T2-weighted image on CC at the level of massa intermedia.

Statistical analysis: To study the exact relationship between GA and FA of the callosal fiber bundle, linear, quadratic, cubic, log-linear, growth and exponential models were applied. For each model, regression coefficients, R^2, 95% confidence interval of mean and other model statistics were computed. R^2 statistics was used to determine the best fit model. Pearson correlation coefficient between FA in CC and GA was performed. p value ≤ 0.05 was considered to be significant.

Results: In this study we observed increasing pattern of callosal bundle FA as well as fiber density (FD) as a function of GA. Quadratic model (R^2=0.64) was considered to examine the trends in callosal FA with increasing GA (Fig. 1). Figure 2 shows the 3D projection of callosal fibers on mid sagittal plane for different GAs. We observed the fibers of genu and splenium of CC from 16 weeks onwards, however, no fibers of midbody were observed till 19 weeks of GA. Beyond 19 weeks of GA, CC formed a shape like adult form only in terms of superficial appearance, that further showed increment in both fiber length and thickness with age. In Fig. 2, red, green, and blue represent left-to-right, anterior-to-posterior, and superior-to-inferior directions, respectively. A significant positive correlation (r = 0.61, p = 0.02) was observed between callosal bundle FA values and GA.



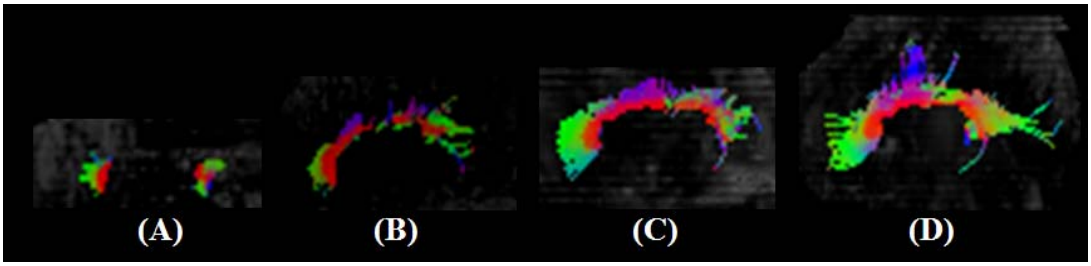


Fig. 1 **Fig. 2**

Fig. 1: Relationship betwen callosal bundle FA and GA in human fetal brain using quadratic regression model.

Fig. 2: Projection of callosal fibers on mid sagittal plane at different GA: (A) 19 weeks, (B) 21 weeks, (C) 32 weeks, and (D) 40 weks shows normal pattern of CC development in human fetal brain.

Discussion: To the best of our knowledge this is the first DTT study showing normal development of CC in fetal brain ranging from 16 to 40 weeks of GA. We observed an increasing trand of callosal bundle FA and FD as a function of age. Beyond 19 weeks of GA we observed that CC attained superficial appearance of CC that is in line with previous study based on histopathological data (1). It has been reported that CC attains its superficial adult shape by the GA of 18 weeks in human fetal brain and further on it increases in thickness with GA. Our observation of CC development in fetal brain. FA can be used to visualize and quantitatively characterize development in immature white matter even before the onset of myelination. This ''premyelinating'' anisotropy has been attributed to nonstructural mechanisms, such as ion fluxes across the axolemma (4) and proliferation of immature oligodendrocytes (5) during this period. The possible mechanisms for the increase in callosal FA with GA during late 2nd trimester and early 3rd trimester could be explained on the basis of premyelinating axonal changes. The myelination in callosal fibers starts during the late 3rd trimester. During this period of time the increase in callosal FA could be attributed to the combination of both premylinating as well as myelinating processes. The ability to noninvasive monitoring of CC development in vivo should greatly improve our understanding of the normal developmental pattern of the CC in human fetal brain that may be used as a reference for the diagnosis of developmental defects of the CC.

References: 1) Rakic et al. J Comp Neurol 1972,132:45-72; 2) Barkovich et al. AJNR 1988,9:487-491; 3) Basser et al. J Magn Reson 1996,111:209–219; 4) Prayer et al. AJNR 2001,45:235-243; 5) Drobyshevsky et al. J Neurosci 2005,25:5988-5997.