Diffusion Tensor Imaging of Developing Human Cerebrum

R. K. Gupta[1], K. M. Hasan[2], R. Trivedi[3], B. Kanabar[4], M. Pradhan[5], V. Das[6], N. A. Parikh[7], P. A. Narayana[4]

[1]Radiodiagnosis, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, UP, India, [2]Departments of Radiology, University of Texas, Houston, Texas, United States, [3]Radiology, SGPGIMS, Lucknow, UP, India, [4]Department of Radiology, University of Texas, Houston, Texas, United States, [5]Medical Genetics, SGPGIMS, Lucknow, UP, India, [6]Gynecology, KGMU, Lucknow, UP, India, [7]Pediatrics, University of Texas, Houston, Texas, United States

Introduction: Diffusion tensor Magnetic resonance imaging (DT-MRI) is a noninvasive modality that provides information about tissue microstructural organization. DTI exploits the anisotropic random translational motion of water molecules within the tissue, which reflects the microstructural organization during brain development[1,2]. Microstructural growth of cerebral gray matter begins with the production of neuronal and glial precursors in the lining of lateral and third ventricles (germinal zones), followed by the neuronal migration from the germinal zone to their destination[3]. The neuron finally organizes into horizontal laminar aggregates and vertical columns, and attains normal cortical cytoarchitectonic patterns. The ability to noninvasively monitor neuronal migration and maturation processes in vivo should greatly improve our understanding of the normal developmental pattern of the cortical gray matter that may help in early diagnosis of developmental disorders like mental retardation, epilepsy, and severe learning disabilities.

Methods: *Subject:* A total of fifteen human fetuses of 15-37 weeks gestational age (GA) and five term normal infants aged 1, 4, 8, 20 and 113 days were studied. The younger fetuses were obtained after spontaneous abortion, while the older ones were obtained after medical abortion, which had intrauterine death due to unknown causes resulting in termination of pregnancy. None had detectable central nervous system malformations on antenatal ultrasound. This was further validated at detailed autopsy. All the MRI studies were performed on unfixed brains. The time delay between MRI scans and delivery was always less than three hours. The age of each fetus was based on a combination of the post-ovulatory age and early ultrasonographic GA estimation. Five term normal infants were included to assess the changes that may extend into the postnatal period.

Image Acquisition and Data Processing: Whole brain conventional MRI and DTI were acquired on a 1.5 Tesla GE MRI scanner using a standard quadrature head coil. DTI data was acquired using a single-shot echo planar dual spin echo sequence with ramp sampling. The acquisition parameters were: TR=8sec/TE=100ms/slice no=30-34/slice thickness=3mm/interslice gap=0/FOV= 160-240mm (varying from depending on the size of the fetal head)/image matrix=256x256 (following zero-filling)/NEX=8/ diffusion weighting b-factor=700 s mm^{-2}. A balanced rotationally invariant dodecahedral diffusion-encoding scheme was used for generating the DTI data[4]. Tensor field for each voxel was obtained by interpolating and decoding of distortion corrected data. The tensor field data were then diagonalized to obtain the eigenvalues (λ_1, λ_2 and λ_3) and the three-orthonormal eigevectors (e_1, e_2 and e_3). The tensor field data and eigenvalues were used to compute the mean diffusivity (D_{av}) and FA for each voxel. Data processing and analysis were performed using an in-house developed DTI-Toolbox implemented under IDL. For quantitative analysis, the DTI-derived maps were displayed and overlaid on images with different contrasts to facilitate the region-of-interest (ROI) placement in the three orthogonal planes for visual inspection (fig a).

Results: The FA values in the cerebral cortex were observed to peak bilaterally around 27-28 weeks and decreased gradually till 32 weeks (FA still above 0.2) Fig b. The value of FA declined to less than 0.2 after 32 weeks. The highest correlation was observed between the right and left frontal regions (r=0.9818, p=0.00001). The FA value of the right frontal cortex was observed to be significantly larger than the left frontal cortex (p=0.007; sign test) (fig c). But this trend was reversed in the late trimester. The frontal cortical FA difference decreased with GA until birth (r= -0.58; p=0.015).

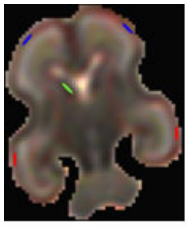

Fig.a

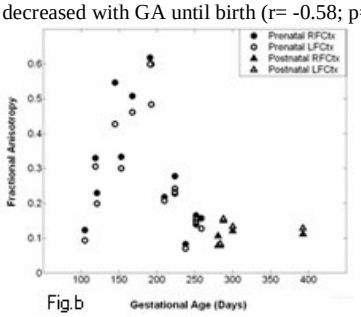

Fig.b

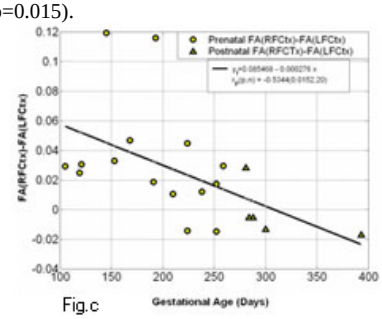

Fig.c

Regional FA values from the germinal matrix (GMx) also showed significant inverse correlation with age (r= -0.8057, p=0.0049). The radial orientation of the germinal matrix was also evident between 17 to 28 weeks GA. At each value of GA between 17 to 30 weeks, the FA values in the subplate and intermediate zones were less than in the cortex and the GMx [2,5]. The FA values in the subplate zone showed an inverse correlation with GA (r= -.55, p=0.06), however this did not reach statistical significance.

Discussion: The main observations of this study are: 1) the FA value, which is a measure of diffusion anisotropy, increases with gestational age (GA) in the cerebral cortex from 15–28 weeks, followed by a decrease through 36 weeks, and 2) significant difference in the FA values in the right and left frontal cortices suggesting cortical gray matter lateralization very early on in the developing brain.Most of the neurons that form the cerebral cortex migrate to their destinations along the specialized radial glial fibers (RGF) that span the entire thickness of the hemisphere from the ventricular surface to the pia, this perhaps explains the continued increase in the FA values in the cerebral cortex up to 27 weeks of GA. After cessation of neuronal production, the radial glial cells retract their ventricular and pial attachments and differentiate into astrocytes. The observed decline in the cortical FA after 27 weeks GA probably reflects an alteration in the radial organization with neocortical maturation.We observed the lateralization as early as 15 weeks of GA. It is likely that the molecular events underlying the brain asymmetry occur sometime between 6-20 weeks[6]. It suggests that the significant cortical FA asymmetry may be related to the differences in neuronal number or the differences in the density of the connecting fibers that are known to influence the FA of the brain tissue The current quantitative DTI studies demonstrate the possibility of noninvasively following neuronal migration, cortical maturation and neocortical lateralization in the developing brain.

References: 1. McKinstry RC et al. Cereb Cortex 12:1237-1243,2002 2. Maas LC et al. Neuroimage 22:1134-1140,20043. Sidman RL, Rakic P. Brain Res 62:1-35,19734. Hasan, KM, et al. J Magn Reson. Imaging 2001;13:769-785. Kostovic I, Judas M, Rados M, Hrabac P. Cereb Cortex 20026. Geschwind DH, Miller BL (2001) Am J Med Genet 101:370