Cerebellar White Matter Development Lags Supratentorial White Matter

S. Saksena[1], R. K. Gupta[1], G. K. Malik[2], N. Husain[3], R. Trivedi[1], D. K. Rathore[4], A. Purwar[4], R. K. Rathore[4], and P. A. Narayana[5]

[1]Department of Radiodiagnosis, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [2]Department of Paediatrics, King George's Medical University, Lucknow, Uttar Pradesh, India, [3]Department of Pathology, King George's Medical University, Lucknow, Uttar Pradesh, India, [4]Department of Mathematics and Statistics, Indian Institute of Technology, Kanpur, Uttar Pradesh, India, [5]Department of Diagnostic and Interventional Imaging, University of Texas, Medical School at Houston, Houston, Texas, United States

Introduction: Brain development is a complex and orderly process throughout the postnatal phase that continues into adulthood[1]. The cerebellum is one of the first brain structure that begins to differentiate but one of the last to mature, and its cellular organization continues to change many months after birth[2]. Triulzi et al[3], using conventional MRI, have shown that fetal cerebellar development is gradual, steady, and grossly comparable to supratentorial brain development. Diffusion tensor imaging (DTI) has the potential to provide crucial information about the organization and architecture of white matter fibers *in vivo*. DTI has been applied to study normal cerebral white matter (WM) maturation from infancy to adulthood[4]. The aim of this study is to demonstrate the developmental lag in cerebellar WM relative to supratentorial WM in normal children using DTI.

Materials and Methods: ***Subjects:*** Our cohort includes five healthy neonates (mean age: 0.44 months; range: 0.16-1 month), six infants (mean age: 4.66 months; range: 1.5-9 months) and fifteen children (mean age: 64.53 months; range: 12-144 months). Inclusion criteria were normal brain imaging, and absence of neurologic deficits. All the subject's parents gave their informed consent and the study was approved by the institutional review board. The subjects were classified into two groups on the basis of age: Group I, from birth to 2 years and Group II, from 3 to 12 years.
Image Acquisition: Conventional MRI and DTI were acquired on a 1.5 Tesla MRI scanner using standard quadrature head coil. DTI data were acquired using a single-shot echo planar dual spin echo sequence with ramp sampling. The acquisition parameters were: TR=8sec, TE=100msec, number of axial slices=30-34/slice thickness=3mm with interslice gap=0/FOV=200×200mm^2 to 240×240mm^2, depending on size of infant's head, image matrix=256×256, NEX=8, and diffusion weighting b-factor=700 s mm^{-2}. All the children were sedated using oral chloral hydrate.
Data Processing: The DTI data was processed and evaluated using JAVA based in-house developed program[5]. For fractional anisotropy (FA) and mean diffusivity (MD) quantification, regions of interest (ROI's) were placed on the cerebellar peduncles, internal capsule and corpus callosum (CC). Elliptical ROI's were placed at the mid point of the cerebellar peduncular fibers. For inferior cerebellar peduncles (ICP), a coronal plane passing obliquely through it was selected while the ROI's for middle cerebellar peduncles (MCP) were placed at the level of mid pons in the axial plane. For superior cerebellar peduncles (SCP), the parasagittal planes were selected. Elliptical ROI's were placed at the level of third ventricle to obtain FA and MD values in posterior limb of internal capsule (PLIC). Rectangular ROI's were placed on the seven segments of CC based on a single midsagittal slice to obtain the FA and MD values in genu and splenium of CC. The size of the ROI varied from 2 × 2 and 6 × 6 pixels.

Results:
Figure 1 illustrates the difference of maturation process among the white matter tracts in both groups. In Group I, the highest FA values (around 0.43) were found in the splenium, genu and MCP. There was a slight change in the first 0-3 months that continued until 24 months in splenium, genu and MCP. However, SCP, PLIC and ICP had lower FA values (around 0.26) but there was a rapid rise in FA values in the first 0-3 months, (around 0.35) which increased to intermediate values (around 0.4) during the first 24 months. Deep white matter structures such as the splenium, genu and PLIC showed a continuous decrease of MD values until the age of 24 months. However, there was an increase in the MD values in the SCP, ICP and MCP until the age of 24 months. In Group II, higher FA values were found in the splenium, genu, MCP, PLIC, SCP and ICP compared to Group I. However, a decrease in MD values was observed in the cerebellar peduncular fibers, splenium, genu and PLIC over this 3-12 years life span.

Discussion: In this study, we demonstrate for the first time a period of developmental delay in cerebellar WM relative to supratentorial WM with age using DTI. The human cerebellum changes its histologic morphology in utero and after birth[2]**.** Our study showed increased patterns of FA values in the cerebellar peduncles in both Group I and Group II. This could be due to differentiation of the dendritic processes of Purkinje cells of cerebellum and decrease in synaptic density during postnatal years[6], which imparts strong tissue orientation. The proliferation and migration of granule cells and WM maturation postnatally may also account for increased FA. However, the increase in FA in splenium, genu and PLIC with the splenium displaying the highest FA values in both groups reflects increasing organization and compacity of the fiber bundles. The cerebellar layers displayed a somewhat delayed, maturation pattern compared to supratentorial WM. It has been demonstrated that in human fetal cerebellar cortex, there is a fall in the water content from 40-60 days gestation (88%) to (79%) at term and then further decreases to (77%) at over 5 years of age or adult stage[6], which might explain increased MD values in cerebellar peduncles from birth to 2 years (Group I). However, decreased MD values in cerebellar peduncles in Group II and supratentorial WM in both Group I and Group II could be related to increased myelination and brain maturation. This study will provide a normative database of cerebellar WM development from neonates to late childhood.

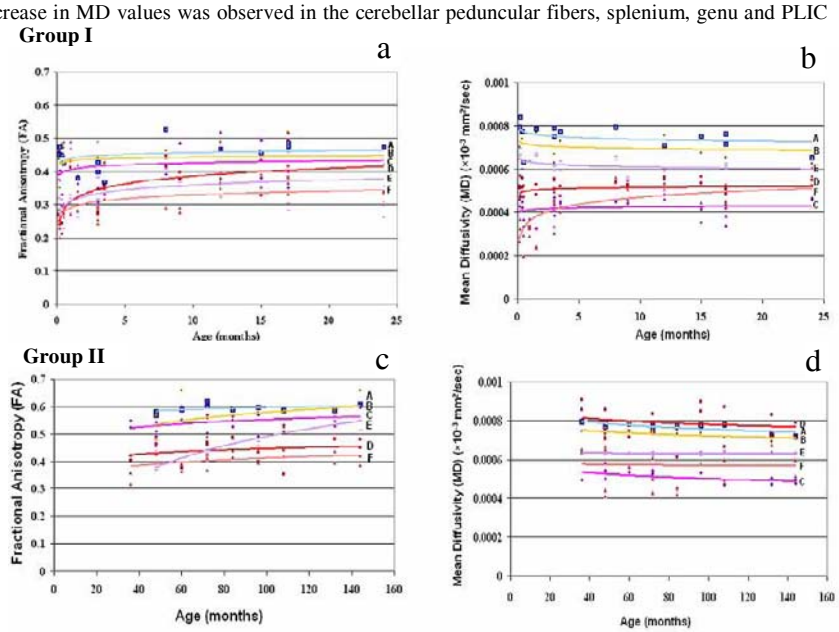

Figure 1. Variation of FA (a, c) and MD (b, d) with age at birth to 2 years (Group I) and from 3 to 12 years (Group II), respectively in all regions of interest.

A = Splenium of corpus callsoum
B = Genu of corpus callsoum
C = Middle cerebellar peduncle
D = Superior cerebellar peduncle
E = Posterior limb of internal capsule
F = Inferior cerebellar peduncle

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