Increased cortical anisotropy in Neonatal Meningitis-An indicator of meningeal inflammation

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Introduction: The most common cause of death in neonatal period is infections, including septicemia, meningitis, respiratory infections, diarrhea, and tetanus. Neonatal mortality rate associated with meningitis can be as high as 33-48 % in the developing countries (1). Tumor necrosis factor- α (TNF-α) produced in response to the bacterial pathogen mediates the up-regulation of adhesion molecules like selectins, intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) (2). Although conventional magnetic resonance imaging (MRI) is more sensitive than computerized tomography (CT) in detecting inflammatory vasculitis, it is insensitive to subtle changes in tissue microstructure. Diffusion tensor imaging (DTI) of brain abscess has shown high fractional anisotropy (FA) in the abscess cavity and it has been suggested that expression of various cell adhesion molecules on inflammatory cells is responsible for their orientation on principle eigen vector in the abscess cavity (3). The hypothesis of this study is that the FA value in the cortical region in pediatric patients with bacterial meningitis is higher compared to age/sex matched healthy controls and that in antibiotic treated neonates the FA approaches the control value with time.

Materials and Methods: The present study was carried out on fourteen term babies [8 males] with neonatal meningitis and 10 age/sex matched controls. The diagnosis of bacterial meningitis was based on clinical manifestations, meningeal enhancement on post contrast T1 images as well as biochemical analysis of CSF. The microorganisms cultured were E. coli (n=6), S. pneumoniae (n=2) and Group B streptococcus (n=1). In the remaining five patients CSF was termed sterile. The patients were treated with standard antibiotics protocol for neonatal meningitis. 5 neonates with meningitis had repeat imaging after 2 weeks of antibiotic treatment. Of the remaining 9 patients, 4 died and other 5 subjects were lost for follow up. Whole brain conventional MRI (T2, T1) and DTI were performed on a 1.5-Tesla GE MRI system. DTI data were acquired using a single-shot echo-planar dual spin-echo sequence with ramp sampling. The acquisition parameters were: TR=8sec/TE=100ms/number of slice =30-34/slice thickness=3mm/interslice gap=0/FOV=240mm/image matrix=256×256 (following zero-filling)/NEX=8/ diffusion weighting b-factor=700 s mm^{-2}. The DTI data were processed as described in detail elsewhere (4). Post-contrast T1-weighted images were also obtained in patients, after injecting Gadodiamide (Gd-DTPA-BMA, Omniscan, Amersham Health, Oslo, Norway) intravenously at a dose of 0.1 mmol/ kg- body weight. For the quantitation of FA and MD values in patient group and controls elliptical ROIs were placed on the cerebral cortical regions (Fig 1C). The ROIs were positioned on the diffusion weighted imaging (DWI) images (b=700) to ensure the absence of CSF contamination. A student's independent t-test was performed to evaluate the regional differences in the DTI metrics between meningitic patients and healthy controls. Student's paired t-test was applied to detect the effect of antibiotic treatment on FA and MD values in the cortical region.

Results: Abnormal meningeal enhancement on post contrast T1 images was noted in all the neonates with clinically diagnosed bacterial meningitis (n=14). One neonate also showed ependymitis on post contrast T1 images (Fig 1F). On follow-up MRI studies in 5 neonates, after 2 weeks of antibiotic treatment meningial enhancement though less intense than before treatment, was observed in three neonates.
At the time of initial study, cortical FA values were significantly higher in neonates with meningitis (frontal cortex=0.127±0.027, parietal cortex=0.114±0.014, occipital cortex=0.110±0.016, temporal cortex=0.106±0.015) compared to healthy controls (frontal cortex=0.068±0.011, parietal cortex=0.069±0.009, occipital cortex=0.068±0.010, temporal cortex=0.069±0.009). A significantly decreased FA (Fig 2) and MD values were observed in the patients after 2 week of antibiotic treatment compared to the initial study in the entire cerebral cortical region except for the parietal cortex.

Discussion: There is a general agreement that grey matter has low anisotropy relative to the white matter. The small grey matter anisotropy arises from coherent spatial organization of axons, dendrites, or glial processes would generate deviations from isotropy among the diffusion tensor eigenvalues. This phenomenon has previously been shown in the developing human cerebral cortex in fetal brain (5) and preterm infants (6). Gupta et al showed high FA in the abscess wall as well as cavity and suggested that the inflammatory cells in the abscess cavity become oriented and organized; resulting in high diffusion anisotropy (3). We propose that the high FA values in the cortex are actually due to the adhered inflammatory cells on the surface of pia-arachnoid because of the presence of cell adhesion molecules that are known to be up-regulated in the presence of bacteria. Because of the fairly close alignment of cerebral cortex with pia mater, the cerebral cortex can not be separated from the pia-arachnoid membrane on MRI. Therefore, the oriented inflammatory cells arranged in the pia-arachnoid interface give an impression of high FA values in the cerebral cortex. Significant decrease in FA values in cerebral cortical region after the administration of antibiotic in patients group suggests positive treatment response in meningitic patients. In conclusion, increase in FA with no significant changes in MD values in neonatal pyogenic meningitis suggests presence of inflammatory molecules, which are the marker of disease activity.

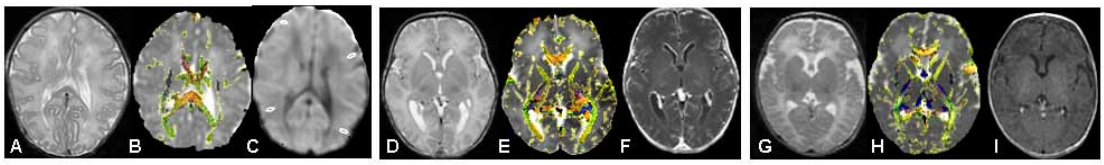

Figure 1. T2 (A), color coded FA (B), and exponential ADC (C) image from an 11-days-old healthy neonate through the lateral ventricles shows normal grey matter and white matter. The small arrows (yellow) in color coded FA modulated by the principal eigenvectors (B) image indicate the direction of the principal tensor eigenvector. The cut off value for the color-coded FA for display is kept at 0.15. T2 (D) from a pre-antibiotic treated 15 days old neonate with pyogenic meningitis does not show any visible abnormality. Color coded FA (E) shows increased FA values in cortical grey matter region compare to control. Post contrast T1-weighted (F) image shows meningeal and ependymal enhancement consistent with meningitis along with ependymitis. Following two weeks of antibiotic treatment, there is reversibility of abnormalities on T2 (G), color coded FA (H) and post contrast T1 (I). Color coded FA map (H) shows decreased FA values in cortical region compared to pre-antibiotic treated images.

References:

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Figure2: Bar diagram shows reversal of FA values in neonates with bacterial meningitis following 2 weeks of antibiotic treatment. * denotes p values less than 0.05.