Correlation of Neuroinflammatory Molecules Quantified from CSF with Fractional Anisotropy in the Neonatal Meningitis

R. K. Gupta[1], R. Trivedi[1], G. K. Malik[2], A. Yadav[1], K. N. Prasad[3], and R. K. Rathore[4]

[1]Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [2]Pediatrices, Chhatrapati Shahuji Maharaj Medical University, Lucknow, India, [3]Microbiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [4]Mathematics and Statistics, Indian Institute of Technology, Kanpur, Uttar Pradesh, India

Introduction: Meningitis is a severe acute infectious disease caused by a wide range of bacteria (1). In developing countries, neonatal mortality from all causes is about 34 per 1,000 live births; most of these deaths occur in the first week of life (2). Bacterial lysis in the CSF leads to the release of bacterial components into the cerebrospinal fluid (CSF). Lipopolysaccharides, teichoic acid, and peptidoglcans are formidable stimuli for the release of cytokines and other proinflammatory host proteins (3). The cytokines including tumer necrosis factor-α (TNF-α) and interleukin-1 (IL-1) trigger a cascade of inflammatory mediators (4). Gadolinium (GD)-DTPA magnetic resonance imaging (MRI) can detect abnormal meningeal enhancement (5). Diffusion tensor imaging (DTI) provides information about microstructural organization by enabling the measurement of fractional anisotropy (FA) and mean diffusivity (MD). A recent DTI study in neonatal meningitis has shown high FA in the laptomeningeal cortical region and it has been suggested that the presence of various cell adhesion molecules on inflammatory cells is responsible for their orientation on the principle eigenvector in the subarachnoid space (6). The aim of this study was to demonstrate a correlation between FA in cortical regions, as measured by *in-vivo* DTI, and various NMs in the CSF from 15 neonates with bacterial meningitis.

Materials and Methods: The present study was carried out on 15 term babies with neonatal meningitis and 10 age/sex matched controls. Neonatal meningitis was diagnosed by clinical manifestations, culture of cerebrospinal fluid (CSF) in BACTEC culture media (BD BACTEC Plus) as well as meningeal enhancement on post contrast T1 images. Enzyme linked immunosorbent assay kit (R&D Systems, Minneapolis, USA) was used to quantify human soluble intra-cellular adhesion molecules (sICAM), tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) cytokines in CSF collected on lumber puncture of meningitic neonates. Conventional MRI (T2, T1) and DTI were performed in patients as well as controls 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 (7). Post-contrast T1 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. Because of the thin cortical ribbon during the neonatal period, and close alignment of pia-arachnoid membrane to the cortex, the ROI placed in the cortical region included the leptomeninges, cortex, and adjoining subcortical white matter. We used the term "leptomeningeal corticosubcortical white matter" (LCSWM) to define the region where the ROIs were placed for the quantitation of FA and MD values in patient group and controls. A student's independent t-test was performed to evaluate the differences in the FA values between meningitic neonates and healthy controls. Bivariate analysis of correlation was performed to study the relationship between the FA values in LCSWM and NMs extracted from CSF, with the assumption that there was no correlation between DTI measures and NMs (Ho = 0). Alternatively if a correlation > 0.00 was observed at α = 0.05 and 90% power of test, the null hypothesis was rejected.

Results: All neonates with bacterial meningitis showed abnormal meningeal enhancement on post contrast T1 images. The significantly high FA values in LCSWM were observed in the neonates with bacterial meningitis (0.11±0.02) as compared to the controls (0.07±0.01). No significant change in MD values in LCSWM was observed in neonates with bacterial meningitis [(0.85±0.09) $\times 10^{-3}$] compared to controls [(0.91±0.05) $\times 10^{-3}$]. Significant direct correlation was observed between neuroinflammatory molecules (sICAM, TNF-α, and IL-1β) quantitated from CSF of patients and FA values in LCSWM. No correlation was observed between MD values in LCSWM and neuroinflammatory molecules.

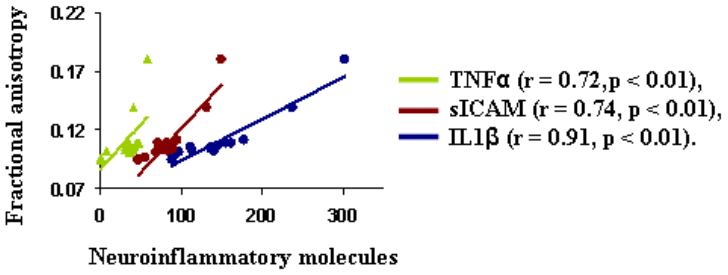

Figure 1

Fig.1: Plot showing relationship between fractional anisotropy (FA) values from LCSWM and neuroinflammatory cytokines [interleukin1- β (IL1-β, blue), tumor necrosis factor- α (TNF- α, green) and soluble intercellular cell adhesion molecules-1 (sICAM-1, red)] quantified from CSF if patients with neonatal meningitis.

Discussion: There are growing bodies of evidences showing high FA values in non-white matter fibers. The increased FA in non-white matter fibers has been shown previously in brain abscess lesions as well as in LCSWM of neonates with bacterial meningitis and suggest that the presence of inflammatory molecules are responsible for high FA in abscess cavity and subarachnoid space respectively. In the brain abscess they have demonstrated a significant positive correlation between the neuroinflammatory molecules from pus aspirate and FA values inside abscess cavity (8). In this study, we have shown the significant positive correlation of FA in LCSWM of neonates with bacterial meningitis and neuroinflammatory molecules and suggest that the high FA in LCSWM in neonates with bacterial meningitis reflects the extant of inflammatory response. *In-vivo* detection of activity of neuroinflammatory molecules may help in more precise assessment of the activity of the disease and thus may be helpful in clinical management of these patients in future.

References:

(1) Neuman HB, et al. *Clin Pediatr*; 2001, 40: 595-600.
(2) Costello A, et al. save the children fund, Washington; 2001.
(3) Nau R, et al. *J Antimicrob Chemother*; 199, 39:781.
(4) Tauber MG, et al. Blackwell Science; p-124, 1997.
(5) Kastrup O, et al. *Neuro Rx*; 2005; 2:224-332.
(6) Trivedi R, et al. *Neuroradiology*; 2007, 49: 767-775.
(7) Purwar A, et al. Proceedings of ESMRMB, 2006, 21-23, Abstract #644.
(8) Gupta, et al. *AJNR* (in press).