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Original Research Article

Quantitative Evaluation of the Blood–Brain Barrier Integrity in Tuberculous Meningitis: An Observational Study

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Abstract

Objective: The aim of the study was to quantitatively evaluate blood–brain barrier (BBB) perfusion changes in TBM patients using dynamic contrast-enhanced (DCE) MR perfusion.

Methods and Material: Fifty untreated patients of TBM and 10 healthy controls were prospectively evaluated by conventional imaging and DCE MR perfusion. Mean permeability indices— *K* trans and Ve—were calculated from multiple regions of interest (ROIs) placed in basal cisterns and comparison was done between the patients and controls.

Results: The basal cisterns showed variable enhancing exudates in 21 patients. Tuberculomas were seen in 24 patients. Hydrocephalus was seen in 20 patients. Cerebral infarction was seen in 17 patients. There was also statistically significant difference in the permeability indices ($p < 0.001$) between "enhancing cases" versus "non-enhancing cases," and no statistically significant difference as observed in any of the permeability indices between "non-enhancing" cases versus the controls. Statistically significant positive correlation was seen between clinical staging and *V*e mean (where $p < 0.05$). No significant correlation was seen between clinical staging and *K*trans mean in our study.

Conclusion: DCE MR perfusion is useful in the quantitative measurement of disruption of BBB and perfusion alterations in patients of TB meningitis.

Keywords: Gallstones, Epithelial lesions, Histopathological examination.

Introduction

Tuberculous (TB) meningitis is the most severe complication of human *Mycobacterium tuberculosis* infection. TB meningitis causes death in 10% of cases with advanced disease and severe neurologic sequelae in as many as 80% of survivors. [1,2] The current human immunodeficiency virus pandemic has increased the overall tuberculosis incidence, and human immunodeficiency virus infection predisposes to the development of TB meningitis in children and adults. [3, 4]

In TB meningitis, the host inflammatory response is an important factor in pathogenesis and clinical deterioration.The precise mechanisms underlying this inflammatory reaction are poorly understood. The inflammatory process causes disruption of the blood-brain barrier

(BBB) with resultant vasogenic edema. The inflammatory exudate obstructs cerebrospinal fluid (CSF) flow and produces adhesions leading to the development of hydrocephalus. Furthermore, vasculitis can cause diffuse cerebral ischemia and infarction. [3,5,6]

Meningeal inflammation in TB is attributed to inflammatory cytokines and chemokines as well as factors released by the infectious organisms which lead to disruption of blood– brain barrier (BBB). [7-9] Methods to quantitatively measure the disruption of BBB and the ongoing inflammation have been limited in the past, owing to the complexity of the techniques involved. Hitherto, MRI in meningitis is used to demonstrate meningeal enhancement and other intracranial complications associated with the disease.[10,11] dynamic contrast-enhanced magnetic resonance (DCE MR) perfusions and their physiological indices of permeability (*K*trans) and leakage (*Ve*) give information related to the integrity of BBB and changes in the extravascular extracellular space and help in the quantitative measurement of BBB disruption, which is not possible by routine post-contrast T1-weighted MRI.[12-15]We have tried to highlight MRI's capability to provide quantitative data on BBB functionality in patients of TB meningitis by acquiring quantifiable permeability parameters. We hypothesize that leakiness of BBB in TBM leads to perfusion changes which can be measured quantitatively using DCE perfusion MR imaging.

Materials and Methods:

This was a prospective study performed in a Department of Radiology, SSIMS Medical College, Bhilai, Chhattisgarh, India for 10 months. which 50 consecutive patients with clinical diagnostic criteria of TB meningitis were included.

The criteria included clinical picture of meningitis like fever, headache, vomiting, neck stiffness, altered mentation, etc., along with supporting CSF evidence of the disease (high protein, low glucose and raised lymphocytes, and acid fast bacilli), and presence of extra neural site of tuberculosis as evidenced by appropriate mycobacterial tests and radiology, along with response to antituberculosis therapy (ATT). The gold standard for confirmation in our study was TB PCR of CSF samples and only those patients who tested positive were included in the final study. Informed and written consent was taken from all the patients or guardians before the study.

Methodology

All patients were evaluated for their demographical profile (age and sex), clinical symptoms (seizure, fever, signs of meningitis, etc.) and laboratory findings. Only those cases of TBM were included in the study who had either not been started on ATT or were in early stage of empirical treatment (< 2 weeks) on the basis of clinical findings, on the assumption that short period of treatment would not alter the permeability characteristics. Apart from the patients, we also included 10 controls in our study who underwent brain MRI for nonspecific complaints and were found to have normal structural brain MRI findings. These were patients who underwent MRI brain for other clinical conditions like headache, vertigo, and neuropsychiatric illnesses; and were found to have normal structural brain MRI findings. Informed and written consent was taken from all the controls as well.

MRI Protocol:

All patients underwent DCE MRI using a dedicated 16 element head coil at1.5T MR Unit (Siemens, Magnetom Essenza; Siemens Healthcare, Erlangen, Germany). DCE was performed after acquiring routine brain sequences. DCE imaging was performed using a three-dimensional-

spoiled gradient recalled echo (3D-SPGR) sequence (repetition time or TR: 4.65 milliseconds; echo time or TE: 1.6 seconds; field of view (FOV): 230 × 100; matrix: 230 × 230; flip angle of 12 degrees; slice thickness: 3.6). At the fourth acquisition, gadolinium contrast agent gadodiamide (Gd-DTPA-BMA), at a dose of 0.1 mmol/kg of body weight was administered intravenously at a rate of injection of 2.5 to 3 mL/s (using an MR compatible power injector, MEDRAD, Spectris Solaris EP), followed by a bolus injection of 15 to 20 mL saline flush. A total of three series were acquired. To calculate the baseline T1 relaxation time per pixel (baseline T1 map), two T1 reference series with different flip angles (2 and 15 degrees, respectively) were acquired. The two-reference series were identical to the DCE series in terms of field of view, orientation, resolution, slice thickness, number of slices with a TR of 3.79 milliseconds and TE of 1.38 milliseconds. A DCE series was acquired with 40 dynamics, with high temporal resolution and flow artifact reduction.

Statistical Analysis:

Analysis was conducted using IBM SPSS statistics (version 22.0). All statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. Mann–Whitney test for comparison of permeability indices between two groups (cases vs. controls, basal enhancement vs. controls, and no basal enhancement vs. controls) was made for each ROI. **Results:**

There were 20 males and 10 females with age ranged from 21 to 60 years (mean age: 25.7 years). Nine patients in their early stages of the disease presented with fever, headache, neck stiffness, vomiting, etc. Thirteen patients showed focal neurological deficits in addition to the abovementioned symptoms while eight cases were brought in comatose state (**Table 1** showing clinical findings in the patients). Distributions of structural MRI changes are shown in **Table 2.** The basal cisterns showed variable enhancing exudates in 21 patients. Tuberculomas were seen in 24 patients. Hydrocephalus was seen in 20 patients. Cerebral infarction was seen in 17 patients. Convexity/leptomeningeal enhancement was seen in only ten patients.Twenty four cases showed basal exudates in interpeduncular cistern, thirteen in suprasellar cistern, and nine in ambient cistern. Four cases showed basal exudates in the sylvian fissures. (**Table 3**) The mean cisternal permeability indices analyse among the cases as well as the controls are summarized in **Table 4**. Statistically significant difference in the permeability indices was observed ($p < 0.001$) between "enhancing cases" versus the controls. There was also statistically significant difference in the permeability indices ($p < 0.001$) between "enhancing cases" versus "non-enhancing cases," and no statistically significant difference as observed in any of the permeability indices between "non-enhancing" cases versus the controls. Statistically significant positive correlation was seen between clinical staging and *V*e mean (where $p < 0.05$). No significant correlation was seen between clinical staging and *K*trans mean in our study. **(Table 5)**.

Table 1: Clinical findings in the patients

Clinical features	Number of patients (n=50)
Fever, headache, vomiting, neck stiffness (stage 1)	14
Meningeal signs associated with focal neurological deficit (stage 2)	27
Comatose (stage 3)	9

Table 2: Distribution of structural MRI changes

Structural MRI changes	Number of patients
Basal exudates	21
Tuberculomas	24
Hydrocephalus	20
Cerebral infarction	17
Convexity enhancement	10

Table 3: Distribution of location of basal exudates

Location of basal exudates	Number of patients (n=50)
Interpeduncular	24
Suprasellar	13
Ambient	9
Sylvian fissures (right, left)	4

Table 4: Mean Ktrans and Ve values in cases and controls and their statistical significance (*p*-value <0.001 in differentiating between "enhancing" cases and controls as well as between "enhancing" cases and "non-enhancing" cases; Note nonsignificant *p*-value between "non-enhancing" cases and controls)

Patient category	*K*trans mean ± SD	Ve mean ± SD
"Enhancing" cases	0.1761 ± 0.1628	0.3912 ± 0.2189
"Non-enhancing" cases	0.1527 ± 0.0715	0.0592 ± 0.0720
Controls	0.04279 ± 0.0801	0.0418 ± 0.0682

Abbreviation: SD, standard deviation.

Table 5: Diagnostic performance of Ktrans and Ve for differentiation between cases and controls

Variable (mean)	Cut-off	Sensitivity	Specificity
*K*trans	> 0.0927	80.2%	79.7%
*V*e	> 0.0632	87.8%	93.7%

staging and *V*e mean (where $p < 0.05$). No significant correlation was seen between clinical staging and *K*trans mean in our study.

Discussion:

DCE MRI-derived permeability indices provide information about the distribution of contrast in the pathological tissues and thus the functional and structural composition of the tissues and integrity of BBB. BBB disruption and leakiness are increasingly being recognized in various pathological conditions like stroke, multiple sclerosis, dementia, infections, and intracranial tumors. [16-20] Limited literature is available on the role of DCE MRI in assessing the integrity of BBB in infective conditions. We found highly significant difference ($p < 0.001$) in the permeability values of "enhancing cases" and normal controls. Some authors have used permeability indices to distinguish between various intracranial pathologies. Singh et al showed statistical significance between various intracranial space occupying lesions using physiological perfusion indices. [21] They found that the mean *K*trans as well as the mean *V*e values were significantly higher in tuberculomas compared with gliomas.

Although DCE MRI is a useful sequence as it provides quantitative data on BBB functionality, its role needs to be explored

further in cases showing low levels of BBB disruption. Hence, more work needs to be done in this field to determine the role of DCE-derived variables in quantifying perfusion alterations before structural changes are noted in routine MRI imaging. This can be explained by the fact that along with the up regulation of neuroinflammatory markers and recruitment of inflammatory cells during the course of disease, the disruption of the BBB also increases which manifests as perfusion changes in the inflamed meninges. Hence, DCE- derived *Ve* mean can be used as a marker for staging of the disease and can prognosticate the patients with respect to the clinical severity and expected outcome. However, this area needs further exploration as concrete evidence of a positive correlation would have ideally required significant correlations between clinical staging and both the permeability parameters (mean *K*trans and *Ve* mean) rather than with *Ve* mean alone. One major limitation of our study is its small sample size. As the prevalence of tuberculosis is high in our country, a larger population size would have enabled us to validate our results with greater accuracy and confidence. There is also lack of histopathological confirmation of the final diagnosis. In our study, we also recruited patients who were in early stage of treatment (< 2 weeks), based on assumption that short period of treatment would not alter the permeability characteristics of the inflamed basal meninges.

Conclusion:

DCE MR perfusion is useful in the quantitative measurement of disruption of BBB and perfusion alterations in patients of TB meningitis.

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