Serial Dynamic Contrast Enhanced MR Imaging to Quantify Treatment Induced Temporal Changes in Brain Tuberculomas

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Introduction: Conventional magnetic resonance (MR) imaging scores over computed tomography in better characterization of brain tuberculomas (BT)[1]. Combined use of in vivo proton MR spectroscopy (PMRS) and magnetization transfer (MT) MR imaging further improved its characterization[2]. The medical treatment of BT is however largely empirical and is based on very few publications and individual experiences[3]. The response to treatment is judged by the reduction in size of the lesion on imaging which may show a decrease between 3-6 months and complete disappearance by 12 months of therapy. Still it is not clear which tuberculoma responds and which one does not to the specific treatment and is finally removed on surgery. Dynamic contrast enhanced (DCE) MR imaging has been widely used to predict and monitor the response to therapy in gliomas[4]. Here for the first time we used DCE MR imaging to predict the response to therapy in BT patients.

Materials and Methods: Seventeen patients (age 5 to 45 years) with BT were examined with specific anti-tubercular treatment (ATT). 15 patients were examined up to the 12 months at a time interval of 4 months. Remaining two were excised due to non-response to the treatment. Non-response to the treatment was based on the no clinical improvement in the condition of patients after 4 months of treatment. Initial diagnosis was based on the characteristic imaging features on MT and PMRS while final diagnosis was confirmed after response to the treatment (n=15) and histopathology (n=2). With informed consent DCE MRI was performed using sequential multi-section multiphase (n=32) three dimensional spoiled gradient recalled echo sequence (TR/TE-5/1.4, flip angle-15º, (FOV)-360×270mm, slice thickness-6mm, matrix size-128×128) with a temporal resolution of 5.2s for 12 slices covering the lesion[5]. The contrast (Gd-DTPA, 0.2 mmol/kg) was injected at the 4th acquisition. Fast Spin echo T_1W and fast double spin echo PD and T_2W imaging was performed to quantify voxel wise pre-contrast tissue T_{10}. Images were registered for voxel wise analysis and de-scalped manually. The absolute tissue T_{10} value was used to generate concentration time curve from signal intensity-time curve[5]. Quantitative analysis of concentration time curve was performed for calculation of cerebral blood volume (CBV) and cerebral blood flow (CBF)[5]. Pharmacokinetic model was implemented for permeability (k^{trans}) and leakage (v_e) calculation[5]. Corrected CBV map was generated by removing the leakage effect of the disrupted blood brain barrier (BBB)[5]. Region of interest (ROI) analysis was done for the calculation of all perfusion indices separately for cellular and necrotic fractions. Relative quantification of CBV (rCBV) and CBF (rCBF) was performed by placing the ROI on normal contra-lateral portion of the brain. The cellular and necrotic fraction volumes of the lesion were calculated from the MT MR images[6] using in house developed software. One way ANOVA was performed to see the changes in perfusion metrics along with changes in different volume fraction of tuberculoma. Pearson correlation was performed between perfusion metrics and different volume fraction at each time interval.

Results: The k^{trans}, v_e, rCBV and rCBF decreased significantly ($p<0.001$) with significant reduction in cellular components over four time study period (Table 1). Only rCBV correlated significantly ($p=0.001$) with cellular components. We did not found any correlation of k^{trans} and v_e with rCBV, rCBF and cellular components. The perfusion indices were not significantly correlated with necrotic components. There was no significant reduction in necrotic components up to the four time study period. The two excised BT showed increase quantitative perfusion indices after 4 month of treatment without any change in the volume of the lesions. Out of fifteen, three cases showed almost complete disappearance of lesion after 12 month of treatment; consist of mostly cellular fraction with very small fraction of necrotic components.

Discussion: rCBV is measure of angiogenesis in BT which governed by the high expression of vascular endothelial growth factor (VEGF)[7]. VEGF is also responsible for the short term increased permeability[8]. Expression of various cytokines and cell adhesion molecules (CAMs) is reported in intracranial infections and is associated with the large opening of BBB[9]. We suggest that increase permeability (k^{trans}) and leakage (v_e) in case of BT is due to the high expression of these cytokines and CAMs. Reduction in both hemodynamic (rCBV, rCBF) and physiological indices (k^{trans}, v_e) was found in these patients in response to the ATT. We suggest that decrease in hemodynamic indices is primarily due to the low expression of VEGF from macrophages in response to the ATT which result in decrease angiogenesis. While decrease in physiological indices is due to the less expression of cytokines and CAMs both on leukocyte and endothelial cell surface and result in less opening of BBB. It was found that only cellular component respond to the ATT and almost disappear after 12 month. No significant reduction in necrotic component over time suggests that this fraction does not respond to ATT. Our data suggest that the DCE MR imaging may be useful in understanding the therapeutic response in different components of BT.

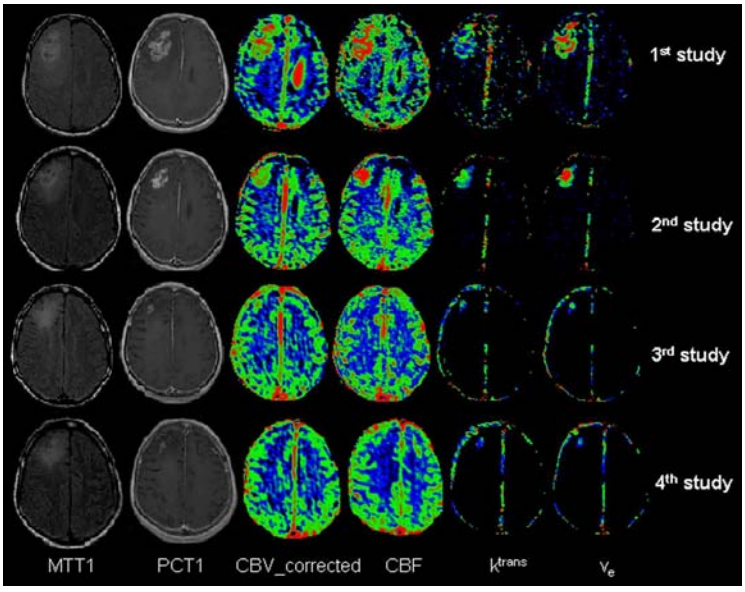

Table-1

Quantitative parameters	Study (mean±SD)			
	1st	2nd	3rd	4th
rCBV	3.35 ± 0.78	2.29 ± 0.89	1.43 ± 0.58	1.14 ±0.49
rCBF	4.07 ± 0.72	2.76 ± 0.98	2.01 ± 0.74	1.52 ± 0.58
k^{trans} (min^{-1})	2.10 ± 0.57	1.56 ± 0.72	1.03 ± 0.41	0.74 ± 0.32
v_e	0.60 ± 0.14	0.43 ± 0.17	0.28 ± 0.11	0.21 ± 0.09
Cellular volume (cc)	7.16 ± 3.73	4.69 ± 3.77	2.30 ± 2.71	1.21 ± 1.20
Necrotic volume (cc)	6.15 ± 5.27	6.23 ± 5.05	5.74 ± 4.69	6.23 ± 4.14

Figure 1: A case of right frontal tuberculoma patients on follow up study. MT T_1 and PC T_1 weighted image show that it consists of mostly cellular components which almost disappear after 12 months of treatment. Both hemodynamics (CBV and CBF) and physiological indices (k^{trans} and v_e) are also decreasing during the treatment.

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