Dynamic Contrast Enhanced (DCE) Perfusion Indices as a Measure of Blood Brain Barrier (BBB) Disruption in Different Stages of Neurocysticercosis

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Introduction

Neurocysticercosis (NCC) is a parasitic infection, caused by establishment of cysticercus larva of *Taenia solium* in the central nervous system of its host (man or pig). Single cyst is found in 20-53% of cases[1], while when multiple, few cysticerci are usually found[2]. The signs and symptoms depends upon the number, topology and stage of the cyst as well as the host immune response[3,4].; and include seizures, signs of elevated intracranial pressure, movement disorders and hydrocephalus[5,6,7]. In most cases symptoms appear years after the initial invasion, either by inflammation around the parasite, mass effect, or residual perilesional scarring[8,9]. Morphologically 3 stages of the NCC are recognized[10,11] 1) viable, or vesicular stage 2) colloid, or granular stage 3) fibrocalcified nodule stage. Different stages of NCC show a heterogeneous pattern on conventional MR imaging[12], making these difficult to be precisely classified. Earlier studies have shown contrast enhancement with or without perifocal edema in degenerating cysts[13]. We performed dynamic contrast enhanced (DCE)-MRI in patients with different stages of the cysts to see the relationship between the perfusion indices and the degree of perifocal oedema. This is the first preliminary study describing the perfusion indices in different stages of NCC.

Materials and methods

Subjects*:** A total of thirty cysts from 15 patients with a definitive diagnosis of NCC on conventional MRI (scolex demonstration) were included in the study. All these were classified into ***group1: Cysts without post contrast enhancement and without oedema. (n=10); ***group2:*** Cysts with post contrast enhancement but without oedema (n=10); ***group3:*** Cysts with post contrast enhancement and surrounding oedema (n=10). Informed consent was obtained before DCE-MRI.

***Data acquisition*:** All patients underwent both conventional and DCE-MRI on a 1.5 Tesla scanner (Echo-speed plus, General Electric, Milwaukee, USA) using quadrature transmit–receive head coil. The institutional ethical as well as the research committee approved the study protocol. DCE-MRI was performed using a three dimensional spoiled gradient recalled echo (3D-SPGR) sequence [TR/TE/flip angle/ number of excitation(NEX)/slice thickness/ field of view (FOV)/matrix size=5.0ms/1.4ms/15°/0.5/6mm/360×270mm/128×128mm, number of phases=32]. At the fourth acquisition, Gd-DTPA-BMA (Omniscan, GE Healthcare, USA) was administered intravenously with the help of a power injector (Optistar™ MR, Mallinckrodt, Liebel-Flarsheim, Ohio) at a rate of 5ml/sec, followed by a bolus injection of 30ml saline flush. A series of 384 images in 32 time points for 12 slices were acquired with a temporal resolution approximately of 5.25sec. Prior to 3D SPGR, fast spin echo (FSE) T_1-weighted (TR/TE/NEX/slice thickness/FOV/matrix size= 375ms/9.4ms/1/6mm/360×270mm/256×256mm) and fast double spin echo PD and T_2 weighted (TR/TE1/TE2/NEX/slice thickness/FOV/matrix size= 3500ms/25ms/85ms/1/6/360×270mm/256×256mm) imaging were performed for the same slice position to quantify voxel wise pre-contrast tissue T_{10}.[14]

***MRI data processing and quantitative analysis*:** Voxel wise tissue T_{10} was calculated from FSE T_1, T_2 and PD weighted images. Quantitative analysis of concentration time curve was performed for calculation of cerebral blood volume (CBV) and cerebral blood flow (CBF). Pharmacokinetic model was implemented for permeability (k^{trans}) and leakage (v_e) calculation. Corrected CBV map was generated by removing the leakage effect of the disrupted BBB[14]. For the calculation of perfusion indices ROIs ($10mm^2$) were drawn on the region with the highest value as defined by the CBV color-coded map on each slice. Relative quantification of CBV (rCBV) and CBF (rCBF) were quantified by placing the ROI on normal contra-lateral portion of the brain.

***Statistical analysis*:** One way analysis of variance (ANOVA), using Bonferroni multiple comparisons was performed to compare various perfusion indices among the three groups of cysts. Pearson's correlation was performed to see the correlation between perilesional oedema volume and perfusion indices.

Results: The various perfusion indices obtained by putting regions of interest over the cysts are summarized in table1. Bonferroni multiple comparisons showed that the value of Ktrans ($p < 0.01$), Kep ($p < 0.01$), ve ($p < 0.01$) and vp ($p < 0.01$), was significantly higher in group3 as compared to group1 and group2. Though not significant, the value of Ktrans, Kep, ve and vp was found to be higher in group2 cysts as compared to group1 cysts. The rCBV and rCBF was not significantly different among the three groups. A positive significant Pearson's correlation was observed between volume and Ktrans (r=0.98, p=0.001), volume and Kep (r=0. 89, p=0.01), volume and ve (r=0. 81, p=0.03), volume and vp (r=0. 93, p=0.01).

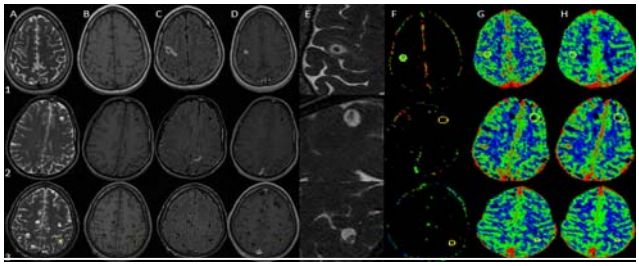

Fig. 1: *Showing A:T2, B:T1, C:FLAIR, D:Post contrast T1, E:Fiesta, F:Kep map, G:CBVcorrected map, H:CBF map of three groups (1-3) of NCC.*

PARAMETERS	GROUP 1	GROUP 2	GROUP 3	ANOVA (p-value)
Ktrans	0.0±0.0	0.04±0.03	0.43±0.06	0.0
Kep	0.0±0.0	0.14±0.01	0.95±0.28	0.0
rCBF	1.82±0.64	1.88±0.53	1.19±0.75	0.2
rCBV	1.85±0.77	1.25±0.18	1.14±0.94	0.3
ve	0.0±0.0	0.04±0.008	0.46±0.13	0.0
vp	0.0±0.0	0.01±0.003	0.13±0.003	0.0

Table 1: *showing the values of perfusion indices for the three groups. Unit of k^{trans} is (min^{-1}).*

Discussion: In this study we have found significantly high value of Ktrans , Kep, ve and vp in cysts with both post contrast enhancement and perilesional oedema (group3), suggesting that these cysts pose maximum inflammatory response as compared to other groups. The positive value of Ktrans, Kep, ve and vp in group2 cysts indicate the opening of BBB but to a lesser extent than group3 cysts. Nil value of Ktrans, Kep, ve and vp in group1 cysts which appears to be innocuous on MRI advocates an intact BBB. We also found significant correlation between oedema volume and with Ktrans, Kep, ve, and vp. Matrix metalloproteinase-9 (MMP-9) plays a key role in the disruption of the BBB and the blood–CSF barrier, which may cause brain edema and tissue damage[15,16]. Vascular endothelial growth factor (VEGF) has also been implicated in the increased BBB permeability in initial phase of acute stroke while in tumors and infection it primarily governs angiogenesis[17]. In a recent study the expression of MMP-9 is proposed as marker of BBB disruption and disease activity in BT, correlated with Ktrans[18]. We hypothesize that the higher perfusion indices and presence of perilesional oedema in group3 cysts may be due to the high activity of MMP-9. Minimally high value of rCBV in group1 cysts may indicate the minimal inflammation in this group and may be indication of the onset of degeneration of the cyst but the absence of significance in rCBV and rCBF values among the groups is probably due to the lack of angiogenesis. We conclude that different stages of NCC show difference in the degree of BBB disruption, which may be correlated with measure of clinical symptoms in future.

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