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MRI perfusion findings in patients with tuberculous meningitis

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Abstract

Background & Objectives: Tuberculous meningitis (TBM) is a devastating infection in the world. The primary objective of the study was to evaluate magnetic resonance imaging (MRI) perfusion cerebral changes in the patients with TBM before and after anti-tuberculous therapy, with normal appearing contralateral brain in the same patient, and with control subjects. M*ethods:* MRI perfusion of brain (Dynamic susceptibility contrast-enhanced) was performed at diagnosis and repeated one month after treatment. The study was conducted on both TBM patients and age-matched control subjects. Perfusion parameters were obtained by placing the region of interest (ROI) at the cerebral infarcts, normal appearing contralateral brain and TBM without infarction group. Relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV) and mean transit time (MTT) were assessed. Perfusion parameters pre-treatment and post-treatment were compared. *Results:* Eighteen TBM patients and 6 age-matched control subjects were recruited. Acute cerebral infarctions were demonstrated in 10 (55.6%) patients. Comparison of pre-treatment MRI perfusion studies showed significantly reduced rCBF of the infarcted regions compared to the normal appearing contralateral brain (279.0ml/100g/min vs 615.2 ml/100g/min, $p < 0.05$), and age-matched control subjects (279.0 ml/100g/min vs 754.1 ml/100g/min, $p < 0.05$). There was significantly reduced rCBV of the infarcted regions compared to the normal appearing contralateral brain (45.0ml/100g vs 96.8ml/100g, $p < 0.05$), and age-matched control subjects (45.0ml/100g vs 82.9ml/100g, $p<0.05$). There was significantly increased MTT of the infarcted regions compared to age-matched control subjects (9.8sec vs 6.7sec, $p< 0.05$). There was also significantly reduced rCBF of the normal appearing contralateral brain (615.2ml/100g/min vs 754.1ml/100g/min, $p<0.05$) and TBM patients without cerebral infarction (554.9ml/100g/min vs 754.1ml/100g/min, $p<0.05$) compared to age-matched control subjects. Increased MTT was significantly present in the normal appearing contralateral brain (9.6sec vs 6.7sec, $p<0.05$) and TBM patients without cerebral infarction (7.8sec vs 6.7sec, $p<0.05$) compared to age-matched control subjects. Comparison of pre and post-treatment MRI perfusion study showed significant increased rCBF (501.4ml/100g/min vs 279.0ml/100g/min, $p<0.05$) and rCBV (104.0ml/100g vs 45.0ml/100g, $p<0.05$) in the infarcted regions. -Significant increased in rCBV (104.2ml/100g vs 77.1ml/100g, $p<0.05$) and MTT (9.0sec vs 7.8sec, $p<0.05$) were also demonstrated in TBM patients without cerebral infarction following treatment. *Conclusion:* Perfusion parameters of the infarcted regions were consistent with infarcted tissue. Perfusion parameters of the normal appearing contralateral brain of TBM showed ischaemic changes.

Keywords: Tuberculous meningitis, MRI perfusion, infarct, vasculitis, MRA

INTRODUCTION

Tuberculosis (TB) is a major health problem with an enormous burden.[1] Extra-pulmonary TB involvement can occur in isolation or as disseminated TB.[2] Infection of the central nervous system (CNS) caused by *Mycobacterium tuberculosis,* which includes TB meningitis (TBM) is a devastating clinical manifestation of TB.[3] TBM has high mortality and morbidity.[3] Non-invasive imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brainn are routinely used in the diagnosis of TBM.[4,5]

Advanced magnetic resonance imaging (MRI)

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such as MRI perfusion yields information on the haemodynamic state (impaired tissue perfusion) of the cerebral tissue.[6] MRI perfusion provides information about hypoperfused cerebral areas before actual structural brain tissue damage takes place.[6] Furthermore, MRI perfusion gives insights into the cerebral circulation (including capillary bed status), and the presence of angiogenesis.[7] In addition, MRI perfusion allows more superior and faster perfusion measurements than PET scan or SPECT scan.[8]

There were few studies conducted on MRI perfusion abnormalities in TBM. The primary objective of this study was to evaluate magnetic resonance imaging (MRI) perfusion cerebral changes of the patients with TBM before and after anti-tuberculous therapy, using relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV) and mean transit time (MTT) quantifications map in the patients with tuberculous meningitis (TBM) before and after antituberculous therapy. We aimed to compare the MRI changes between areas of cerebral infarcts in TBM patients with normal appearing contralateral brain in the same patients. The secondary objective was to compare MRI perfusion changes in TBM patients with/without infarcts with control subjects.

METHODS

This study was a prospective study involving clinically diagnosed TBM patients referred from the Neurology Unit of University Malaya Medical Centre (UMMC). A total of 6 healthy volunteers without neurological symptoms or co-morbidities were age-matched control subjects. The study was approved by the Institutional Ethics Committee of UMMC (Ethics No: 907.20). Written informed consent to participate in the study was obtained from all the study subjects or legally authorized representatives.

The patients were recruited from March 2012 to November 2014. TBM was defined as "definite" when cerebrospinal fluid (CSF) acid-fast bacilli (AFB) direct smear, mycobacterial culture or polymerase chain reaction (PCR) for mycobacteria tuberculosis was positive.[9] TBM was categorised as "probable" if the patient had one or more of the following features: active pulmonary tuberculosis (PTB) on chest X-ray, AFB direct smear or culture in any specimen other than CSF such as sputum, bronchoalveolar lavage, and clinical evidence of extrapulmonary tuberculosis.[9] TBM was considered as "possible" when the patients had at least four of the following criteria: history of TB, CSF pleocytosis with lymphocyte predominance, duration of illness of > 5 days, a ratio of CSF glucose to plasma glucose of < 0.5, absence of Cryptococcus in CSF, altered mentation, turbid CSF or focal neurological signs.[9]

The conscious level of TBM patients was evaluated with Glasgow Coma Scale (GCS) at the time of hospitalisation. Detailed medical history including patients' demographic, fever, headache, vomiting, duration of illness and concurrent medical conditions were recorded. The severity of TBM at presentation was graded based on modified British Medical Research Council criteria into[10]: Stage 1: GCS 15/15 with no focal neurological signs; Stage II, GCS 11-14/15 or 15/15 with focal neurological signs; Stage III: GCS ≤ 10/15.

The findings of CSF analysis which included CSF glucose, CSF protein, CSF leukocyte count, CSF AFB smear, CSF AFB culture, and sensitivity;sputum AFB direct smear and AFB culture; tracheal aspirate, pleural fluid and pus (from abscess) AFB smear and culture were recorded. Human immunodeficiency virus (HIV) serology and chest radiographs were performed in all the study patients.

All patients received standardised anti-tuberculous treatment regime between 9 and 18 months. The intensive phase consists of daily oral dose of ethambutol (25mg/kg, maximum dose 2000mg), isoniazid (5mg/kg, maximum dose 300mg), rifampicin (10mg/kg, maximum dose 600mg) and pyrazinamide (30mg/kg, maximum dose 2500mg). The maintenance phase consists of isoniazid and rifampicin. All severe TBM patients received steroids. Anti-epileptic drugs were given if the patients had seizures.

The patients were followed up between 3 and 6 months to determine the clinical outcome. The outcome was categorised as improved, residual neurological sequelae or death.

All patients were above 18 years of age. All newly diagnosed patients with TBM who had no underlying previous clinical meningitis or previous documented neurological deficits were included. The patients who were excluded from this study were the patients who had undergone surgery for any intracranial problem (e.g. shunt placement for hydrocephalus), patients with central nervous disorders with various neurological deficits, female patients who were pregnant, and those with contraindication for MRI examination (e.g., MR incompatible metal implant, cardiac pacemaker and neurostimulator).

MRI scan of the brain

The MRI scans of the brain using stroke protocol and MRI perfusion were performed at the same setting within one to two weeks of admission in all the patients. Repeat MRI examination was done at four weeks of treatment or earlier if the patient deteriorated. All the age-matched control subjects also underwent MRI examination using the same imaging protocol.

MRI examination was performed using 3.0 TESLA SIGNA HDX MR systems (GE healthcare) and using High Definition NeuroVascular (HDNV) head coil (8 channels). The paramagnetic agent used was gadopentetate dimeglumine (Magnevist) with dosage of 0.2 mmol/kg body weight. Informed consent for MRI examination and MRI checklist was obtained from the patients or next-of-kin and control subjects before MRI examination.

Dynamic susceptibility contrast imaging: Measurement of perfusion parameters

Dynamic susceptibility contrast (DSC) imaging was used in this study. DSC is based on transient changes in the local magnetic field of the surrounding tissue induced by a bolus of paramagnetic tracer passing through the brain capillary network.[11] This is measured as signal changes on MRI.[11] DSC involves an exogenous, intravascular, nondiffusible contrast agent, usually a gadolinium-based contrast agent, which emphasizes the susceptibility effects of gadolinium-based contrast agents on the signal echo.[12]

The first pass of a bolus of gadolinium-based contrast agent through cerebral tissue is monitored by a series of T2- weighted MR images. The susceptibility effect of the paramagnetic contrast agent leads to a signal loss in the signal intensity–time curve. Signal intensity–time course data is converted to relative tracer tissue concentration-time-course data to obtain CBV, CBF, MTT and bolus arrival time.[11,12] Regional CBF and CBV values can be obtained by region-of-interest (ROI) analysis.[12]

Cerebral blood volume (CBV) is defined as the volume of blood in an area of cerebral tissue.[11] CBV is determined by the area below the tracer concentration-time curve.[11] Cerebral blood flow (CBF) refers to blood volume per unit time passing through a region of cerebral tissue.[11] CBF is determined by the height of the ideal tissue concentration-time curve.[11] Mean transit time (MTT) is the average time for blood to pass through the brain tissue area.[11] MTT reflects the start of contrast injection to the peak enhancement within a region of interest.[11] MTT is calculated by dividing are under tissue response function by its height (MTT= CBV/CBF).[11]

In general, tissue at risk of cerebral infarction has normal or reduced CBF, normal or raised CBV, and increased MTT/TTP.[11] Cerebral infarct has reduced CBF and CBV as well as increased MTT/TTP.[11]

The MRI perfusion protocol

Pre Gadolinium MRI perfusion (Scan time: 1 minute 4 seconds): Axial 2D Gradient Echo Echo planar imaging (EPI) sequence. 1,500/30 (repetition time msec/echo time msec). After the review of diffusion weighted (DW) images, 25 axial sections with 40 phase (thickness 5mm,gap 1.0mm, field of view 220mm, matrix size 128x128) were obtained at the positions containing the largest diffusion defects on diffusion weighted imaging (DWI).

Post gadolinium MRI perfusion (Scan time: 1 minute 4 seconds): After one set of baseline images were collected, a bolus of gadopentetate dimeglumine (Magnevist) 0.2mmol/kg was injected into antecubital vein using 18G cannula at injection rate of 3mls for 15 mls of Magnevist using MR compatible power injector. The bolus of contrast was followed by 3mls/sec for 15mls of saline at the same injection rate.

The MRI images were reviewed by two neuroradiologists with 15 and 7 years of experience respectively by consensus method, utilizing the imaging Workstation AW 3.0T and software by GE Medical system. The locations of basal meningeal enhancement, hydrocephalus, tuberculoma and infarction were recorded. The TBM patients with cerebral infarction without signs of neurological deficit were classified as having silent infarcts.

Vascular pathologies in the circle of Willis were assessed based on the MRA time of flight (TOF) images. The vascular changes such as beaded appearance, stenosis and signal attenuation were considered abnormal.

The MRI perfusion was analysed by the radiologists utilizing the imaging Workstation AW 3.0T. The MRI perfusion analysis software used was gamma variate analysis (brainstat GVF). Brainstat GVF is an automated processing tool for the generating parametric maps from a dynamic post-contrast series. Comparison (relative quantification) requires the placement

of regions of interest (ROI) in the infarction area with a midline axis of symmetry. The system then automatically places a similar ROI on the contralateral side of the brain to derive the relative values of CBF, CBV and MTT.

The perfusion maps in the normal subject are presented in Figure 1. The perfusion parameters of infarcted area were compared with the normal appearing contralateral brain and age-matched control subjects. In TBM patients with leptomeningitis evidence but without cerebral infarction, the ROI was placed at the basal ganglia, thalamus, internal capsule, corona radiata and occipital region. The relative perfusion values of these regions were compared with age-matched control subjects. The perfusion parameters at diagnosis were compared with perfusion parameters at one month after treatment.

Statistical analysis

The data were analysed using STATA version 13. Univariate analysis was performed using Chi-square test (or Fisher Exact Test) for categorical data and Wilcoxon Rank Sum (Mann Whitney U) test for continuous variables as the data was non-parametric. Logistic regression was used for multivariate analysis.

Normality tests of all perfusion parameters namely rCBF, rCBV and MTT showed most of the data do not meet the normality assumption. Therefore, non-parametric statistical analyses were used for pre-treatment and post-treatment perfusion analysis. MRI perfusion analysis pre-treatment was performed using Wilcoxon Rank Sum (Mann Whitney U) test comparing the 2 independent groups. Whereas MRI perfusion analysis comparing pre-treatment and post-treatment was performed using Wilcoxon Sign Rank Test comparing the 2 dependent groups. Statistical significance was defined at the p-value of <0.05.

RESULTS

Eighteen patients fulfilling the criteria of TBM were recruited in this study. Out of the 18 TBM patients, 12 (67%) had complete repeat MRI examination after one month. Three patients (33%) passed away, and three (33%) other patients did not complete the full examination protocol due to other reasons. Nine (50%) TBM patients

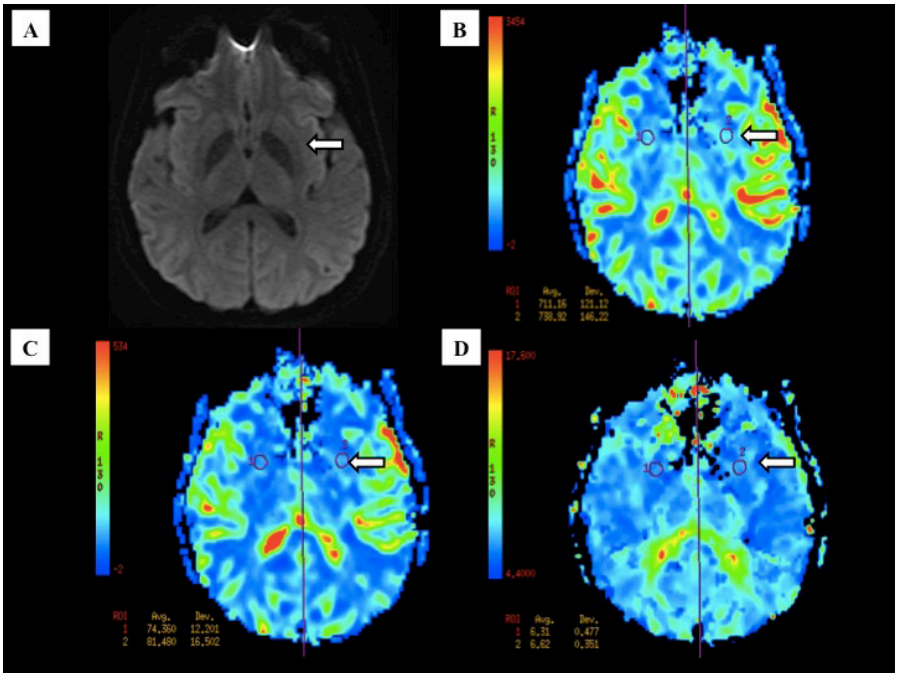

Figure 1: Perfusion maps in the age matched control subject. ROI is placed at the basal ganglia (white arrows) to derive the relative perfusion values. Axial MRI image in DWI of a normal patient (A). Brain perfusion is represented as 3 color-coded maps that consist of CBF (B), CBV (C) and MTT (D), which shows symmetrical perfusion in both brain hemispheres. Blue colour, which is the bottom of colour scale, indicates lowest perfusion value. Red colour, which is in the top scale of colour scale, indicates highest perfusion value.

Table 1a: **Pattern of infarction in TBM patients at clinical presentation**

Pattern of infarct (n, %)	Number of patients (n = 10)
Unilateral infarct	5 (50%)
Bilateral infarct	5 (50%)
Anterior circulation territory	10 (100%)
Posterior circulation territory	3 (30%)
Anterior and posterior circulation territories	3 (30%)

were men and 9 (50%) were women. There were 7 (39%) Malay, 4 (22%) Indian , 2 (11%) Chinese, and 5 (28%) from other ethnic groups. The age-matched control subjects consisted of all females and were all Malays. The mean age of the TBM patients was 38.8±13.3. Nine (50%) patients within the age range of 30-39, while 3 (16.6%) patients were within age groups of 20-29 and 40-49 years respectively. For age-matched control subjects, 3 (50%) subjects were ranged between 30-39 years and 3 (50%) subjects were ranged between 40-49 years.

Majority of the patients presented at stage 2 meningitis (n = 12, 66.6%). Three (16.7%) patients presented with stage 1. Three (16.7%) patients presented with stage 3. The mean GCS score at presentation was 13 ± 2. Eleven (61.1%) patients were classified as "definite" TBM. There was one (5.6%) patient with "probable" TBM. Six (33.3%) patients had "possible" TBM.

Frequency of cerebral infarctions

MRI examinations revealed the presence of acute cerebral infarction in 10 (55.6%) patients. Clinically silent infarcts were demonstrated in 5 (50%) patients while 5 (50%) patients presented with focal neurological deficits,

The occurrence of unilateral and bilateral infarctions was 50/50. Three (30%) patients with bilateral infarction showed almost symmetrical involvement of both sides of the brain. All patients with acute infarction showed involvement of the anterior circulation territory (Table 1a). The most common location was in the lentiform nucleus (Table 1b).

Among the patients who had undergone repeat MRI examination (n = 12, 66.7%), new parenchymal infarctions were observed in 2 (16.7%) patients. Both of the patients showed involvement in posterior circulation territory involving the cerebellum and cerebellar vermis.

Table 1b: **Locations of infarct in TBM patients at clinical presentation**

Location of infarcts (n, %)	Number of patients (n = 10)
Lentiform nuclei	7 (70%)
Internal capsules	4 (40%)
Corona radiata	4 (40%)
Medial temporal lobe	4 (40%)
Cerebral cortices	4 (40%)
Caudate nuclei	3 (30%)
Corpus callosum	2 (20%)
Thalamus	2 (20%)
Cerebral peduncle	1 (10%)
External capsule	1 (10%)
Occipital lobe	1 (10%)
Cerebellar vermis	1 (10%)
Brainstem (midbrain and pons)	2 (20%)

MRA findings

On admission, MRA abnormalities which included vessel irregularity, beaded appearance and stenosis were demonstrated in nine (50%) patients. All these patients showed involvement in the anterior circulation. Only two (11.1%) patients showed involvement in the posterior circulation with concomitant anterior circulation involvement.

The most frequently affected arterial segments were M1 (n =7, 38.9%) and M2 (n = 6, 33.3%) segments of middle cerebral artery (MCA) as well as A1 (n = 7, 38.9%) segment of anterior cerebral artery (ACA). The intracranial portion of internal carotid artery (ICA) involvement was demonstrated in 3 (16.7%) patients. Two (11.1%) patients with posterior circulation artery involvement showed abnormality in the posterior cerebral artery (PCA). One (10%) patient had involvement of P1, P2 and P3 segments respectively.

Infarctions with corresponding MRA abnormalities were demonstrated in 6 (60%) patients. Only one (10%) patient with infarct did not show corresponding MRA abnormality. Two (20%) patients with infarction did not have vascular abnormalities. Only one (10%) patient with vascular abnormality did not have infarction.

Among 12 patients who had undergone repeat MRI, only 2 (16.7%) patients showed complete resolution of vascular changes following treatment. Partial response was demonstrated in 3 (25.0%) patients, and 2 (16.7%) patients had vessels which remained abnormal following treatment. Only one (8.3%) patient showed new vessel involvement on the repeat MRI examination after anti-tuberculous treatment.

Univariate analysis showed that only infarct was significantly associated with MRA abnormality ($p<0.05$) (Table 2). Multivariate

Table 2a: The association of various clinical data, MRI findings and CSF analysis with MRA abnormalities in TBM patients using univariate analysis

Parameters	MRA abnormal (n = 9)	MRA normal (n = 9)	p-value
Infarct, n (%)			***0.015***
No	1 (11.11)	7 (77.78)	
Yes	8 (88.89)	2 (22.22)	
Age			0.48
Mean (SD)	36.78 (9.90)	40.78 (16.32)	
Duration of symptoms			0.26
Mean ((SD)	11.78 (8.74)	15.78 (9.38)	
Focal neurological deficit, n (%)			0.64
No	4 (44.44)	6 (66.67)	
Yes	5 (55.56)	3 (33.33)	
Severity of meningitis, n (%)			0.37
Stage 1	0 (0.00)	3 (33.33)	
Stage 2	7 (77.78)	5 (55.56)	
Stage 3	2 (22.22)	1 (11.11)	
CSF glucose, n (%)			0.58
Low	6 (66.67)	8 (88.89)	
Normal	3 (33.33)	1 (11.11)	
High	0 (0.00)	0 (0.00)	
CSF protein, n (%)			NA
High	9 (100.00)	9 (100.00)	
CSF leucocytes, n (%)			1.00
Negative	1 (11.11)	1 (11.11)	
Normal	1 (11.11)	1 (11.11)	
High	7 (77.78)	7 (77.78)	

analysis showed that only infarct was significantly associated with MRA abnormality (p<0.05).

Univariate analysis showed that only MRA abnormality was significantly associated with infarction (p<0.05) (Table 2b). Multivariate analysis showed that only MRA abnormality was significantly associated with with infarction (p<0.05).

After 3 to 6 months follow- up, 8 (44.5 %) patients improved and 2 (11.0%) had neurological sequelae. Death were recorded in 8 (44.5%) patients.

MRI perfusion findings

Statistical analysis of MRI perfusion were carried out in 8 patients with acute infarction at the time of diagnosis (admission). Another 2 patients with MRI findings of acute infarction were not analysed due to poor perfusion graph. Among 8 patients who had undergone MRI perfusion at inclusion, only 6 patients underwent repeat MR perfusion and were analysed. Repeat MRI perfusion was not carried out in another 2 patients. One patient passed away before repeat MRI and another one patient did not complete the MRI examination protocol. Analysis of MRI perfusion in 5 TBM patients without infarct, was also carried out at the time of diagnosis (admission). Only 2 of these patients had repeat MRI perfusion at one month after treatment and were analysed.

Pre-treatment MRI Perfusion

The MR perfusion analysis on admission showed significantly reduced rCBF (279.0ml/100g/

Table 2b: **The association of various clinical data, MRI findings and CSF analysis with infarcts in TBM patients using univariate analysis**

Parameters	Infarct (n = 10)	Non Infarct (n = 8)	p-value
MRA abnormal, n (%)			***0.015***
No	2 (20.00)	7 (87.50)	
Yes	8 (80.00)	1 (12.50)	
Age			0.7216
Mean (SD)	37.5 (9.60)	40.38 (17.40)	
Duration of symptoms			0.86
Mean (SD)	14.4 (10.77)	13 (6.91)	
Focal neurological deficit, n (%)			0.66
No	5 (50.00)	5 (62.50)	
Yes	5 (50.00)	3 (37.50)	
Severity of meningitis, n (%)			0.15
Stage 1	0 (0.00)	3 (37.50)	
Stage 2	8 (80.00)	4 (50.00)	
Stage 3	2 (20.00)	1 (12.50)	
CSF glucose, n (%)			0.59
Low	7 (70.00)	7 (87.50)	
Normal	3 (30.00)	1 (12.50)	
High	0 (0.00)	0 (0.00)	
CSF protein, n (%)			NA
High	10 (100.00)	8 (100.00)	
CSF leucocytes, n (%)			1.00
Negative	1 (10.00)	1 (12.50)	
Normal	1 (10.00)	1 (12.50)	
High	8 (80.00)	6 (75.00)	

Table 3a: **The median values of perfusion parameters comparing the infarcts and normal appearing contralateral brain**

Perfusion Pre-Treatment	Infarcts (n = 25)	Normal Appearing Contralateral Brain (n = 21)	p-value
rCBF (ml/100g/min)			
Median (IQR)	279.0 (200.0, 553.6)	615.2 (473.5, 694.6)	***0.0043***
rCBV (ml/100g)			
Median (IQR)	45.0 (31.7, 80.3)	96.8 (70.0, 142.8)	***0.0026***
MTT (second)			
Median (IQR)	9.8 (9.0, 11.0)	9.6 (8.8, 10.7)	0.53

IQR = Inter-quartile range

min vs 615.2 ml/100g/min, p<0.05) and rCBV (45.0ml/100g vs 96.8ml/100g, p<0.05) of the infarcted regions compared to normal appearing contralateral brain. The rCBF and rCBV of the infarcted regions compared to the age-matched control subjects were also significantly reduced (p<0.05), with median of 279.0ml/100g/min vs 754.1ml/100g/min and 45.0ml/100g vs 82.9ml/100g respectively.

The MTT of the infarcted regions were significantly increased compared to the age-matched control subjects (p<0.05) with median 9.8sec and 6.7sec respectively. The median perfusion parameters comparing the infarcts with normal appearing contralateral brain and infarcts with age-matched control sucjects are presented in Table 3a and Table 3b. Figure 2 illustrates an example of perfusion maps in a TBM patient comparing the infarcted regions and normal appearing contralateral brain. Although the normal appearing contralateral brain showed normal colour map with normal diffusion on DWI, it showed significantly reduced rCBF (615.2ml/100g/min vs 754.1ml/100g/min, p<0.05) and increased MTT (9.6sec vs 6.7sec, p<0.05) compared to ag-e matched control subjects as presented in Table 3c. The rCBV was increased compared to the age matched control subjects however it was not statistically significant (p>0.05). These perfusion findings were suggestive of tissue ischaemia.

Similar findings as presented in Table 3d, were also observed in TBM patients without infarction comparing with the age-matched control subjects showed significantly reduced rCBF (554.9ml/100g/min vs 754.1ml/100g/min, p<0.05) and increased MTT (7.8sec vs 6.7sec, p<0.05) suggestive of tissue ischemia. The box plot showing the pre-treatment perfusion parameters that consist of rCBF, rCBV and MTT in infarct, normal appearing contralateral brain, meningitis patients and age matched controls subject were presented in Figure 3a, Figure 3b and Figure 3c.

Post-treatment MRI Perfusion

MR perfusion analysis comparing the infarcted regions before and after treatment showed significantly increased rCBF (501.4ml/100g/min vs 279.0ml/100g/min, p<0.05) and rCBV (104.0/ml/100g vs 45.0/ml/100g, p<0.05) of infarcted regions after treatment. All perfusion parameters in the normal appearing contralateral brain did not show significant difference before

Table 3b: **The median values of perfusion parameters comparing the infarcts and age matched control subjects**

Perfusion Pre-Treatment	Infarcts (n = 25)	Age-Matched Controls (n = 101)	p-value
rCBF(ml/100g/min)			
Median (IQR)	279.0 (200.0, 553.6)	754.1 (583.7, 1047.8)	***0.0000***
rCBV(ml/100g)			
Median (IQR)	45.0 (31.7, 80.3)	82.9 (64.1, 120.7)	***0.0013***
MTT(second)			
Median (IQR)	9.8 (9.0, 11.0)	6.7 (6.2, 7.5)	***0.0000***

IQR = Inter-quartile Range

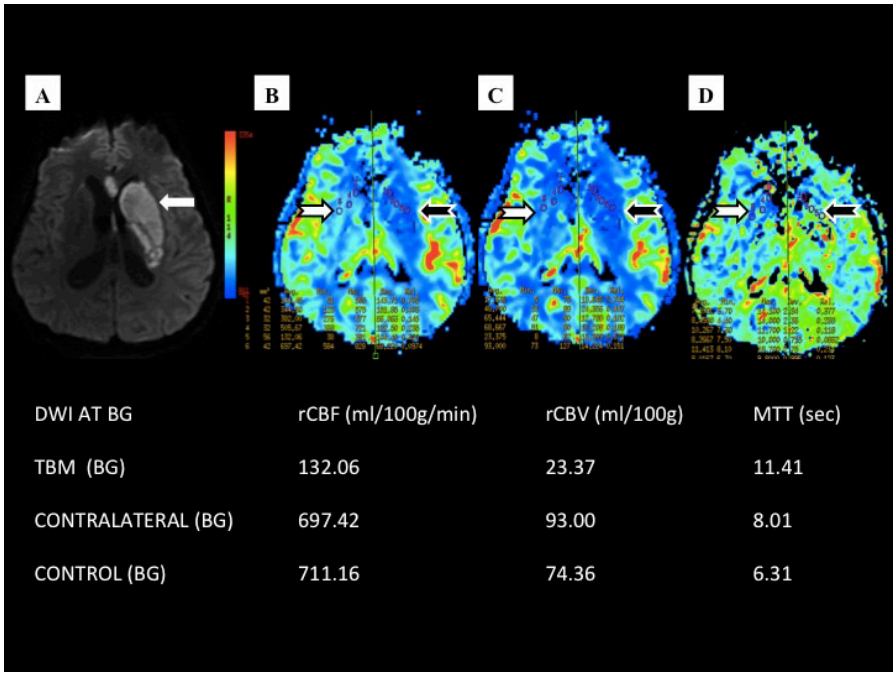

Figure 2: Axial MRI brain image in DWI (A) showed acute infarction involving the left basal ganglia, anterior limb of the left internal capsule and left thalamus (white arrow). MRI perfusion maps in rCBF (B), rCBV (C) and MTT (D) showed reduced rCBF and rCBV with increased MTT of the infarcted regions (notched black arrows) compared to the normal appearing contralateral brain (notched white arrows). The blue colour (bottom of colour scale) indicate lowest perfusion value and the red colour (top of colour scale) indicate highest perfusion value.

Table 3c: The median values of perfusion parameters comparing the normal appearing contralateral brain and age-matched control subjects

Perfusion Pre-Treatment	Normal Appearing Contralateral Brain (n = 21)	Age Matched Controls (n = 101)	p-value
rCBF(ml/100g/min)			
Median (IQR)	615.2 (473.5, 694.6)	754.1 (583.7, 1047.8)	***0.0429***
rCBV(ml/100g)			
Median (IQR)	96.8 (70.0, 142.8)	82.9 (64.1, 120.7)	0.2854
MTT(second)			
Median (IQR)	9.6 (8.8, 10.7)	6.7 (6.2, 7.5)	***0.0000***

IQR = Inter-quartile range

Table 3d: The median values of perfusion parameters comparing the TBM patients without infarct and age-matched control subjects

Perfusion Pre-Treatment	TBM without infarct (n=60)	Age-Matched Controls (n=101)	p-value
rCBF(ml/100g/min)			
Median (IQR)	554.9 (383.1, 856.8)	754.1 (583.7, 1047.8)	***0.0015***
rCBV(ml/100g)			
Median (IQR)	77.1 (56.9, 105.1)	82.9 (64.1, 120.7)	0.1327
MTT(second)			
Median (IQR)	7.8 (6.4, 9.6)	6.7 (6.2, 7.5)	***0.0006***

IQR = Inter-quartile range.

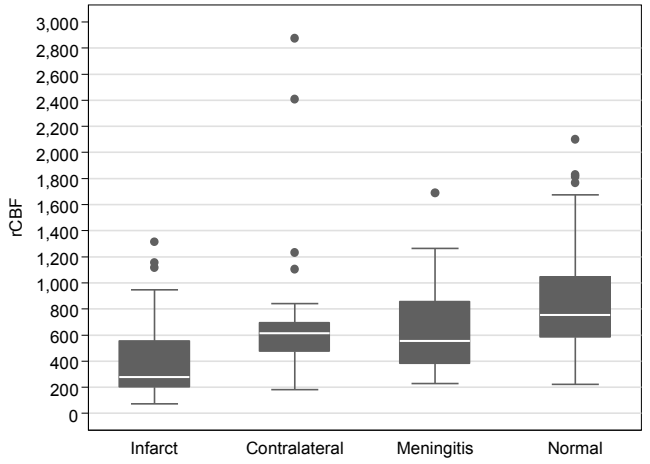

Figure 3a: The box plot represents the pre-treatment rCBF in the infarcts, normal appearing contralateral brain, TBM without infarct (labelled as meningitis), and age matched control subjects.

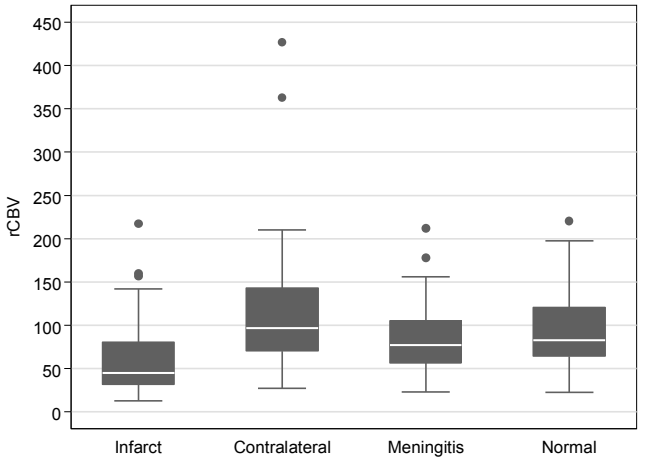

Figure 3b: The box plot represents the pre-treatment rCBV value in the infarcts, normal appearing contralateral brain, TBM without infarct (labelled as meningitis), and age-matched control subjects.

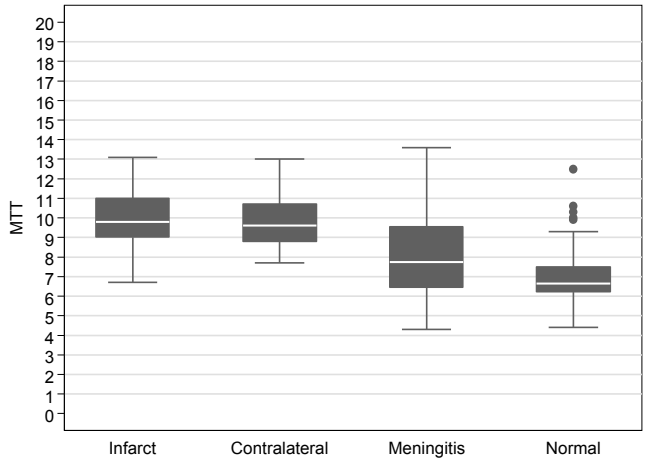

Figure 3c: The box plot represents the pre-treatment MTT in the infarcts, normal appearing contralateral brain, TBM without infarct (labelled as meningitis), and age-matched control subjects.

and after treatment (p>0.05). In TBM without infarct group, there was a significant increase in rCBV (104.2ml/100g vs 77.1ml/100g, p<0.05) and MTT (9.0sec vs 7.8sec, p<0.05) after treatment. However, there was no significant difference of rCBF in meningitis patients before and after treatment (p>0.05). Table 4 represents the median perfusion parameters before and after treatment of the infarcted region, normal appearing contralateral brain and TBM patients without infarct. Figure 4 illustrates an example of perfusion maps in a TBM patient with infarcted regions before and after treatment.

DISCUSSION

Advanced neuroimaging techniques are now available in TBM. In particular, MRI perfusion using spin echo (SE) and dynamic contrast enhanced (DCE) method have been used in two studies on tuberculomas in TBM.[13,14] Magnetization transfer (MT) imaging has been performed in two previous studies in the assessment of exudates in TBM.[15,16]

However, to the best of our knowledge, there were no studies on MRI perfusion using DSC in TBM with cerebral infarction conducted to date. One previous study described the cerebral blood flow changes in TB meningitis using single-photon emission computed tomography (SPECT).[17] In this study involving 17 TBM patients, SPECT studies were abnormal in 88 percent of the patients.[17] The study showed that there were basal ganglia hypoperfusion in 82 percent, cortical hypoperfusion in 59 percent, and midbrain hypoperfusion in 6 percent.[17] Corresponding infarction with basal ganglia hypoperfusion were observed in 29 percent, whereas only 6 percent with cortical hypoperfusion had corresponding infarction.

MRI perfusion in the present study showed significant reduction of rCBF and rCBV and increased MTT of the infarcted regions compared to age matched control subjects and normal appearing contralateral brain. Interestingly, normal appearing contralateral brain and vasculitis patients without evidence of infarction showed ischaemic changes with reduced rCBF and increased MTT. This findings may be related to the inflammatory changes in the vessels particularly at the Circle of Willis from the basal exudates that results in strangulation, vasculitis and vasospasm.[18] Raised intracranial pressure (ICP) also contributes to reduced cerebral perfusion and CBF.[19,20] Cerebral infarction can contribute to raised ICP.[20]

In a recent study on arterial spin labeled (ASL) MRI perfusion in TBM patients, a significant difference was reported in the CBF in the basal ganglia area of TBM patients compared to control subjects.[15] In this same study, reduction in CBF was observed in one TBM patient without infarction.[15]

In both human and animal studies, post-ischaemic hyperperfusion was reported to occur in acute cerebral ischaemia following vascular recanalisation.[21-23] In the previous study using animal model, post-ischaemic hyperemia was defined as an increase in rCBV of more than 20% compared to the value on the contralateral normal side.[21] In addition, post-ischaemic hyperperfusion in the human model following recanalisation by intra-arterial thrombolytic therapy occured in about 40% of patients within hours and about 50% of patients at seven days.[23] Post-treatment MRI perfusion in our study showed improvement of perfusion of the infarcted region as evidenced by an increase in rCBF and rCBV. Post-treatment MRI perfusion in vasculitis patient without infarction also showed an increase in rCBV and MTT. These findings were important in the management of TBM, particularly in the treatment of vascular complications that can influence patients' prognosis.

Vasculitis is a feature of TBM, and it affects the large, medium and small vessels of the Circle of Willis.[24] Vasculitis causes arterial stenosis or occlusion.[24] Vasculitis leads to ischaemia or infarction from regional hypoperfusion.[24,25] In the present study, arterial irregularity, beaded appearance and stenosis were observed in half of the study patients. Two studies had reported 50% occurrence of intracranial abnormalities on MRA in their TBM patient cohorts, which were similar to the results in our study.[26,27] In another study on digital subtraction angiography (DSA) in TBM patients, 46% had abnormal vascular findings.[28] 70.2% had abnormalities in the blood vessels in a previous study on CTA in TBM patients.[24]

In this study, all the patients with vascular abnomalities had involvement of the anterior circulation. In a previous study, 91% had involvement of the anterior circulation.[24] 11.1% of our study patients had posterior and anterior circulation involvement. In the study by Singh *et al,* 18.2% had both anterior and posterior circulation involvement.[24] None of our patients had posterior circulation involvement alone compared to a previous study which showed that 27.3% had posterior circulation involvement.[24]

The most frequently involved arteries observed

Table 4: **The median of perfusion parameters with p-values comparing the infarcted regions, normal appearing contralateral brain and TBM without infarct (labelled as meningitis), patients pre-treatment and post-treatment**

Perfusion parameters	Pre-treatment median (IQR)	Post-treatment median (IQR)	p-values
rCBF (ml/100g/min)			
Infarcts (n = 25)	279.0 (200.0, 553.6)	501.4 (310.3, 1493.6)	***0.019***
Normal appearing contralateral brain (n = 21)	615.2 (473.5, 694.6)	951.4 (399.8, 1978.0)	0.11
Meningitis (n = 22)	554.9 (383.1, 856.8)	748.0 (659.1, 836.3)	0.46
rCBV (ml/100g)			
Infarcts (n = 25)	45.0 (31.7, 80.3)	104.0 (40.8, 202.8)	***0.0128***
Normal appearing contralateral brain (n = 21)	96.8 (70.0, 142.8)	120.8 (81.5, 323.3)	0.092
Meningitis (n = 22)	77.1 (56.9, 105.1)	104.2 (86.8, 132.6)	***0.0055***
MTT (second)			
Infarcts (n = 25)	9.8 (9.0, 11.0)	11.2 (7.8, 13.1)	0.43
Normal appearing contralateral brain (n = 21)	9.6 (8.8, 10.7)	11.5 (9.7, 12.7)	0.095
Meningitis (n = 22)	7.8 (6.4, 9.6)	9.0 (8.2, 10.6)	***0.0005***

IQR = Inter-quartile range

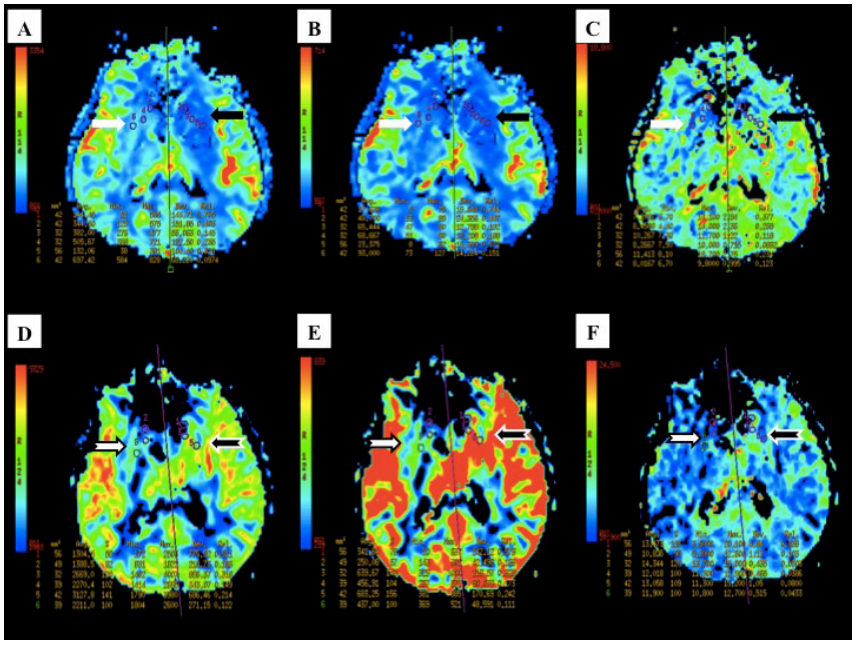

Figure 4: The top row representing the MRI perfusion maps pre-treatment in rCBF (A), rCBV(B) and MTT (C) and the bottom row representing the MRI perfusion maps post-treatment in rCBF (D), rCBV (E) and MTT (F), showed generalised incrased in rCBF and rCBV particularly comparing the infarcted regions pre-treatment (black arrows) and infarcted regions post-treatment (notched black arrows). The MTT maps post-treatment (F) generally showed reduced MTT compared to the MTT pre-treatment (C), however not statistically significant. The blue color (bottom of colour scale) indicate lowest perfusion value and the red color (top of colour scale) indicate highest perfusion value.

in the present study were M1 and M2 segments of middle cerebral artery, A1 segment of the anterior cerebral artery and intracranial portion of the internal carotid artery. These findings were in agreement with the previous studies which showed frequent involvement of the proximal middle cerebral artery, proximal anterior cerebral artery and intracranial portion of the internal carotid artery.[24,26]

Our study also showed infarctions with corresponding MRA abnormalities in 60%, and 10% of the patients with infarcts did not have corresponding MRA abnormality. 20% with cerebral infarction did not demonstrate MRA abnormality. These findings were in agreement with a MRA study in TBM patients in which MRA abnormalities associated with infarction were found in 37 percent of the patients.[27] 31% of the patients with infarcts did not have corresponding MRA abnormality, whereas 6% with cerebral infarction did not have MRA abnormality.[27]

After one month of treatment, the TBM patients with infarcts in our study had increased CBF. In the study by Sukriti Kumar *et al*., several patients had CBF restored to normal in follow-up scans up to nine months.[15] Following repeat MRI at one month after treatment, 16.7% of our study patients demonstrated complete resolution of vascular changes, 16.7% remained unchanged, 25.0% had mixed response (had both unchanged and complete response) and only 8.3% showed new vessel involvement. In the previous study, unchanged abnormal angiogram on follow-up CT angiography was seen in 54% of the TBM patients, with new abnormalities in 4%.[24] New vessel involvement can develop while patients were receiving antituberculous treatment as observed in one patient in our study.[29,30]

Cerebral infarction is a common complication in TBM.[31] This was observed in 55.6% of the patients in the present study. The incidence of cerebral infarcts varies depending on the methods of evaluation. In the recent study on ASL MRI perfusion imaging, cerebral infarcts were seen in 13.3% of the TBM patients.[15] In the autopsy series, infarction was found in 41% of cases.[30] CT scan reveals infarction in 20-40% of TBM patients.[24,32]

Our study finding support the recommendation for an extension of the duration of intensive antituberculous therapy based on the repeat MRI perfusion findings. Currently the duration of intensive phase is two months. We suggest a longer duration if repeat MRI perfusion at two months of therapy is still abnormal. TBM is a neurocritical illness with high mortality, and should be managed in intensive care units.[20] MRI perfusion is valuable because it can help guide the management of TBM patients.

Moreover, we propose a longer duration of dexamethasone administration. Presently, dexamethasone is given for a total of 6-8 weeks.[33] If repeat MRI perfusion at two months of treatment shows an abnormality, we propose a longer duration of dexamethasone. In a previous randomized controlled trial study, treatment with anti-tuberculous therapy improves survival among patients with TBM.[34] Dexamethasone has an anti-inflammatory effect and may favourably affect the outcome of TBM patients.[34] In a randomized double-blind placebo-controlled trial study, the frequencypf infarction in the dexamethasone group was 27% compared to 58% in the placebo group.

This study was limited by a small sample size. In addition, repeat MRI examinations at one month were not carried out in several patients due to deterioration of clinical conditions, death, and patient refusal for repeat MRI examination.

In conclusion, perfusion parameters of the infarcted regions were consistent with infarcted tissue. Perfusion parameters of the normal appearing contralateral brain and meningitis patients without infarction also showed ischaemic changes. Increased perfusion parameters were observed in the infarcted regions and TBM without infarct group following treatment MRI perfusion is beneficial because it guides the management of TBM patients, thus improvimg morbidity and mortality.

DISCLOSURE

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Conflict of interest: None

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