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MAGNETIC RESONANCE IMAGING REVEALS DYSFUNCTION OF BLOOD BRAIN BARRIER IN CEREBRAL MALARIA ALONE AND WITH MULTI ORGAN DYSFUNCTION SYNDROME.

Medical Science

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ABSTRACT

Introduction: The underlying mechanism of cerebral malaria alone or with multiple organ dysfunction (MOD) among patients with falciparum malaria is not clearly understood. Though autopsy studies showed various types of pathological changes, during life Magnetic Resonance Imaging (MRI) can identify structural and functional modification of brain during the disease process. There have been few MRI studies of brain among adult patients with cerebral malaria (CM) but none with CM and MOD. Therefore, we have conducted this study to find out and to compare the MRI abnormalities among patients of CM and CM with MOD.

Methods: This prospective study has been conducted at VSSIMSAR, Burla in which 138 consecutive patients of severe falciparum malaria were enrolled. 119 patients after exclusion were subjected to MRI within 10 hours of admission and it was repeated as per the protocol. The diagnosis of P.falciparum malaria was done by peripheral smear or Rapid diagnostic test. The diagnosis of sever malaria was done by WHO criteria. Patients of CM were grouped into Group-1 and of CM with MOD to Group-2.

Results: In the study CM and CM with MOD constituted 29 (24.4%) and 90 (75.6%) patients. MRI showed increased brain volume, vasogenic oedema, and cortical thickening in all patients of severe malaria. Cytotoxic oedema also found in 37.9% of cases of CM and 75.5% of MOD ($p<0.001$). Infarction and haemorrhage were found in less percentage of cases. Predominant posterior swelling consistent with posterior reversible encephalopathy syndrome (PRES) is found in majority of cases of CM (48.3%) compared to frontal swelling (0.0%) ($p<0.001$). With treatment MRI findings improved within 72 hours of treatment. Patients who died did not show any improvement in MRI finding.

Conclusion: Different type of MRI findings at different areas of brain is possible in CM and CM with MOD. It is due to dysfunction of blood brain barrier (BBB) and it can be reversible with treatment. Therefore, intervention with drugs improving BBB may be beneficial for survival.

KEYWORDS

INTRODUCTION:

Cerebral malaria is a rapidly progressive potentially fatal complication caused by *Plasmodium falciparum*. The patients present with features of diffuse reversible encephalopathy along with symmetrical motor signs The onset of coma may be sudden often following a generalized seizure, or gradual with initial drowsiness, confusion, disorientation, delirium or agitation followed by unconsciousness[1].

Various hypotheses have been suggested for the pathogenesis of cerebral malaria. Cytoadherence of parasitized erythrocytes to the vascular endothelium, rosette formation and decreased deformability of the infected erythrocytes and injury to neuronal tissue by chemokines and malarial toxin is thought to be the major contributing factors for neurological dysfunction in cerebral malaria[2]. However, these hypotheses are unable to explain the mechanism of reversibility of coma. Because, unlike viruses and bacteria, malaria parasites do not infiltrate and infect the brain parenchyma. Instead, the parasites sequestration occurred in the capillaries. Microvascular obstruction leads to congestion and dysfunction of blood-brain barrier that lead to neurological alterations[3].

Evidence of blood-brain barrier (BBB) alteration leading to cerebral oedema among patients with cerebral malaria (CM) have been observed by computed tomography (CT) of brain. But the cerebral edema was unable to explain the depth of the coma or high mortality[4]. Further CT scan cannot differentiate vasogenic from cytotoxic edema. This distinction can be made by diffusion-weighted Magnetic Resonance Imaging (MRI) of brain[5].

MRI study of brain with 0.2 Tesla scanner among patients of CM in adults showed increased brain volume and swelling[6]. Paediatric patients with CM, with 0.35 Tesla MRI also showed brain swelling which was reversed to normal with treatment. The increased brain volume has been implicated in the pathogenesis of death and it has also been correlated with retinopathy[7]. In uncomplicated malaria high-field (3.0) MRI also revealed restricted water diffusion in the splenium of corpus callosum in 4 of 10 patients, indicating that acute cerebral injury can also occur in falciparum malaria without neurological syndrome[8]. Brain swelling due to vasogenic and cytotoxic oedema gas been observed in CM among nonfatal CM in both adult and paediatric Cm[9].

However, complicated malaria is no longer limited to cerebral form, but is as well extended to other clinical forms of the disease like renal failure, anaemia, acute respiratory distress syndrome (ARDS), etc. and at present multi-organ dysfunction (MOD) has been encountered more often that CM alone and the constellation of CM with jaundice and renal failure (RF) is very common[10]. But there is dearth of information regarding MRI finding in patients with CM with MOD.

Therefore, we have undertaken this study to assess the brain with high-field MRI scan to understand the pathophysiology of CM with and without MOD and to correlate with severity.

MATERIAL AND METHODS:

The present study was a hospital based prospective study, conducted in

V.S.S Institute of Medical Science and Research, Burla, Sambalpur, Odisha from October 2014 to September 2018. Sambalpur is situated between the geographical coordinates of 21.5°N 83.87°E. Malaria is hyperendemic in this region, and transmission occurs throughout the year with a seasonal peak from July to October. Ethical approval was obtained from the Institutional Ethics Committee. Because CM patients are comatose, written informed consent was obtained from the families of all patients before enrolment in the study.

In this study, consecutive adult patients (18-65 years) of severe falciparum malaria who tested positive for asexual stage of parasite were enrolled. The diagnosis of falciparum malaria was made with detection of asexual form of the parasite in the Giemsa stained peripheral blood smears or through RDT test. The parasitic count per L was calculated by multiplying number of asexual form of parasites per 200 leukocytes with total leukocyte count. Smear was taken daily to know the parasite clearance with treatment. Severe malaria was defined according to the WHO criteria[1]. Organ dysfunction has been defined according to the criteria developed at our center, and patients with cerebral malaria, renal failure, ARDS, jaundice, anaemia with or without thrombocytopenia and leukopenia, shock have been considered as neurologic, renal, hepatic, hematologic, and circulatory (cardiac) organ dysfunction respectively [11]. Patients with more than one organ dysfunction have been categorized to MOD.

Patients who are clinically unstable for transportation and having RF, were excluded from the study. Other exclusion criteria included were presence of co-infection by other species of *Plasmodium*, documented allergy to MRI contrast media, other causes of febrile encephalopathy and in female patients with pregnancy or lactation.

On admission, a detailed medical history was taken, and physical examination was conducted and all data were recorded on a standardized clinical record form. Blood samples were collected for complete blood count, parasite count, haemoglobin, haematocrit, glucose, blood urea, creatinine, liver function tests. Other investigations, including ECG and blood culture, were performed when clinically indicated. Blood gases were monitored frequently in patients receiving ventilatory support until they recovered. Retinal examination was done by direct and indirect ophthalmoscopy within 6 h of admission.

MRI of the brain was performed using a 1.5-Tesla (T) GE Healthcare, USA, initially within 10 h of admission and then again at 72 h after admission. Sagittal T1-weighted images, axial T2-weighted and fluid-attenuated inversion recovery (T2/FLAIR) turbo spin echo, axial trace diffusion-weighted imaging (DWI) (b values, indicative of the degree of diffusion weighting applied, of 1,000 s/mm^2), and axial T1 spin echo (T1-SE) after contrast (469 mg/ml gadopentetate dimeglumine [Gadoview]; Arco Lifesciences). The pulse sequences included T2, FLAIR, T1, and gradient echo. Apparent diffusion coefficient (ADC) maps were generated and used to confirm restricted diffusion.

Perfusion parameters, such as cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT), were calculated to locate the lesions in the brain and to describe their physiological features.

Vasogenic oedema was defined as an increased DWI signal with markedly increased diffusion coefficients compared to white matter. Cytotoxic oedema was defined as DWI hyperintensity associated with decreased diffusion coefficients compared with those of white matter (DWI/ADC mismatch). The degree of generalized brain swelling was semi-quantified as mild (just apparent), moderate (clear without mass effect), or marked (extensive with mass effect).

All patients were treated with intravenous artesunate (2.4 mg/kg of body weight). The first dose was given immediately after diagnosis and the second and third at 12-h intervals, for a minimum of 3 doses. Subsequent doses were administered daily. Once the patients were conscious and able to take medication orally, the treatment was switched to an artemisinin-based combination therapy: oral artesunate (4 mg/kg of body weight) once daily for 3 days together with a single dose of oral sulfadoxine-pyrimethamine (25 and 1.25 mg/kg of body weight) on the first day of oral therapy. A single gametocidal dose of primaquine (0.75 mg/kg of body weight) was given on the second day of oral therapy[12].

RESULTS:

Clinical Features:

During the study period 138 patients of severe falciparum malaria were admitted, out of which, MRI could not be done in 19 patients due to death within 24 hours (n=5) and difficulty in transportation due to low clinical and hemodynamic condition, which made them unfit for the procedure (n=14). Thus 119 patients were subjected to MRI within 10 hours of admission. Out of them 29 (24.4%) had CM i.e. neurologic dysfunction. Thirty (25.2%) patients had neurologic and hepatic dysfunction . Neurologic, hepatic, and renal dysfunction constituted majority of patients (39, 32.8%). Rest 9 (7.6%), 7 (5.9%) ,5 (4.2%) patients had neurologic and haematologic, neurologic +hepatic + renal + cardiac dysfunction, neurologic +hepatic + renal + respiratory organ dysfunction respectively. We have grouped all the patients in two Groups, Group-1 CM, Group-2 CM with MOD. The biochemical and other parameters were mentioned in Table-1. Total number of deaths were 12 (10.1%) of which 2 (6.8%) from Group-1 and 10 (11.1%) from Group-2 ($p<0.001$).

MRI Findings:

The MRI findings are described in Table-2 and from Fig. 1 to 6. All patients showed generalised swelling involving more than 2 lobes and cortical thickening. The distribution of swelling was predominantly in posterior part of brain involving occipital, parietal, and temporal lobe. Frontal lobe has been spared. Only 8 (8.8%) patients of Group-2 had frontal lobe involvement. All patients of Group-1 showed complete or near complete resolution of cortical thickening within 72 hours, whereas 71 (78.8%) patients of Group-2 showed recovery within by 72 hours and 19 (21.1%) patients did not show recovery till 7 days and all 9 patients of death were among those 19 patients constituting (9 of 19) 47.4% of death. All had cortical thickening, which was either unilateral 7 (24.1%) or bilateral 22 (75.9%) of Group-1 and 12 (13.3%) and 78 (86.6%) among Group-2.

Evidence of vasogenic oedema was found in all cases with variable severity among both the Groups. In Group-1, 8 (27.5%), 17 (58.6%), 4 (13.7%) had mild, moderate, and severe brain swelling respectively, where as in Group-2, 10 (11.1%), 55 (61.1%), 25 (27.7%) patients had mild, moderate, and severe brain swelling respectively. On total, 18 (15.1%), 72 (60.5%), and 29 (24.4%) patients had mild, moderate, and severe brain swelling respectively. Vascular engorgement was found in all cases as evidenced by increased cerebral blood volume (CBV), delayed cerebral blood flow (CBF), and slow mean transit time (MTT). MRI features of ischaemia and cytotoxic oedema was found in 11 (37.9%) cases of Group-1 and 68 (75.5%) cases of Group-2 cases making total 79 (66.3%) cases. It was determined from patchy areas of diffusion-weighted imaging (DWI) / apparent diffusion coefficient (ADC) (DWI/ADC mismatch).

We found infarction in 10 (34.4%) patients in Group-1and 59 (65.5%) in Group-2 with total 69 (57.6%) cases. Basal ganglia are mostly affected. Micro-haemorrhage was found in 15(16.6%) cases among Group-2 ($p<0.001$). Corpus Callosum and thalamus were also involved in both groups. Posterior reversible encephalopathy syndrome (PRES) characterized by vasogenic oedema in the posterior part of cortex with complete recovery after treatment was found in 14(48.3%) cases of Group-1 and 54 (60.0%) cases of Group-2 with total 68 (57.1%) cases.

Table-1. Base line Characteristics of the study Population

Characteristics	Group-1 CM n=29	Group-2 CM +MOD n=90	p Value
Male *{n (%)}	20/9	60/30	0.88
Age (Median /Years)	32	31	0.77
Severe malaria* {N(%)}	29	90	<0.001
Mal Severity Score	4.53±0.8	14.7±2.6	<0.001
Admission Interval (Days)	3.2±1.3	5.8±2.8	<0.05
Parasitic Count (N/ µL)	4300.7±180.5	8756.3±256.3	<0.001
Gametocyte Count (N/ µL)	70.8 ±13.9	55.5 ± 15.5	<0.01
Temp. (°F)	101.0±3.8	104.6±2.8	0.28
Pulse rate (N/mt.)	110.2±10.5	117.4±13.7	0.11
Mean BP (mm Hg.)	103.4±8.9	90.8.8±5.5	0.40
Resp.rate (N./mt)	27.5±6.5	3.3±5.2	0.36
GCS	6.5 ±2.2	4.9±2.2	<0.05
Hb.(gm/dl)	8.4±2.2	6.8±3.5	0.82
TLC(10^9/L)	9.8 ±2.4	10.6±1.2	0.12
Platelet (10^9/L)	120.8 ± 80.5	90.7±50.9	0.01

B.glucose (gm/dl)	87.4±32.5	79.5±12.5	0.14
S. Sodium (mEq/L)	136.8±8.5	129.6±4.5	0.21
S.potassium (mEq/L)	4.1±1.1	3.8±1.2	0.16
S.bilirubin (mg/dl)	3.1±2.7	11.9±2.8	<0.001
SGOT (IU/L)	45.8±10.2	61.8±12.2	<0.01
SGPT (IU/L)	55.8±9.8	63.8±12.8	<0.01
Alk.Phosphatase (IU/L)	125.9 ±19.2	278.9±28.2	<0.01
Urine output (ml/24 hrs.)	1100.8±99.7	908.8±96.2	<0.01
B.urea (mg/dl)	25.2±12.8	76.4±24.9	<0.001
S.creatinine(mg/dl)	1.8±0.3	4.2±1.4	<0.001
Number of Death	2 (6.8%)	10 (11.1%)	<0.001

* Comparison made using X^2 test

Rest characteristics: mean (standard deviation), comparison made using t test.

Table 2- MRI brain findings in CM and CM with MOD

Characteristics	Group-1 CM (n=29)	Group-2: CM +MOD (n=90)	Total (n=119)	p Value
Increased Brain Volume	29 (100.0%)	90(100.0%)	119 (100.0%)	
Vasogenic oedema	29 (100.0%)	90(100.0%)	119 (100.0%)	
Cytotoxic oedema	11 (37.9%)	68 (75.5%)	79 (66.4%)	<0.001
Posterior Swelling (PRES Syndrome)	14 (48.3%)	54 (60.0%)	68 (57.1%0	<0.01
Frontal Swelling	0 (0.0%)	8 (8.8%)	8 (8.8%)	<0.01
Infarction	10(34.4%)	59(65.5%)	69(57.9%)	<0.01
a) Basal ganglia	4(13.7%)	28 (31.1%)	32(26.9%)	<0.01
b)Hippocampus	0 (0.0%)	4 (4.4%)	4(4.4%)	<0.01
c)Temporal lobe	2 (6.8%)	5(5.5%)	7(5.9%)	NS
d)Parietal lobe	2(6.8%)	9(10.0%)	11(9.2%)	<0.01
e) Thalamus	1(3.4%)	5(5.5%)	6(5.1%)	NS
f)Corpus Callosum	1 (3.4%)	8 (8.8%)	9(7.6%)	<0.01
Micro Haemorrhages	1 (3.4%)	15(16.6%)	16 (13.4%)	<0.001
Cortical Thickening	29(100.0%)	90(100.0%)	119(100.0%)	<0.001
a) Unilateral	7 (24.1%)	12 (13.3%)	19 (15.9%)	<0.01
b) Bilateral	22(75.8%)	78(86.6%)	100(84.1%)	<0.01

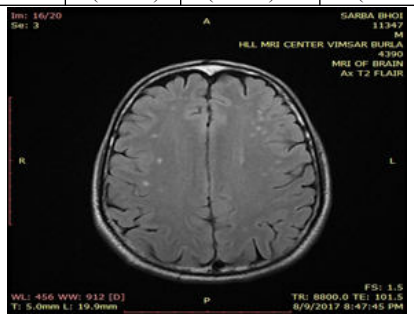


Fig.1.T2 Axial image showing altered signal intensity areas without any restricted diffusion on diffusion weighted images in bilateral frontal and parietal lobes infarction.

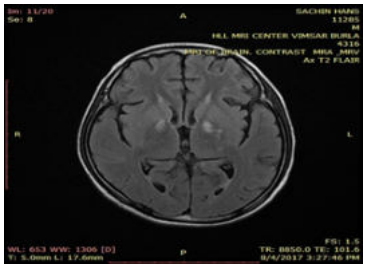


Fig.2.T2 axial image showing hemorrhagic lesions in left thalamus, bilateral basal ganglia.

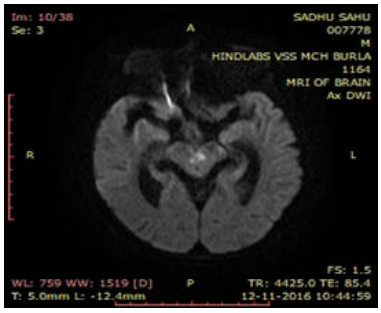


Fig.3. .Diffusion weighted images (in axial view) showing tiny patchy area of restricted diffusion with low ADC value noted in midbrain (acute infarcts). Cytotoxic oedema

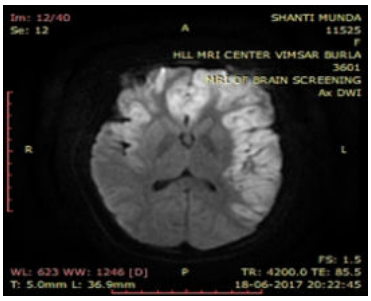


Fig.4. Diffusion weighted images (in axial view) showing cerebral oedema.

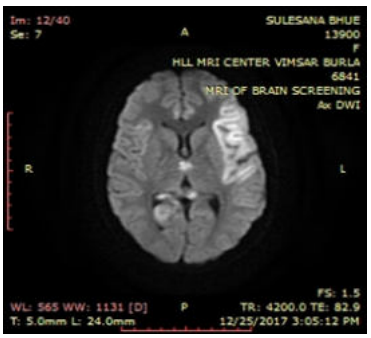
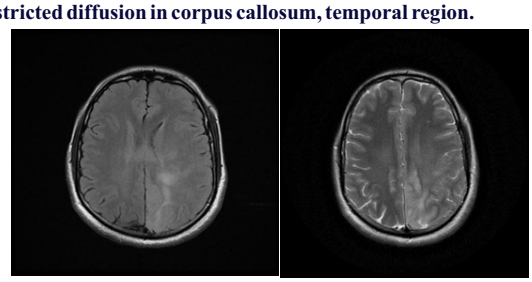


Fig.5. Diffusion weighted images (in axial view) showing areas of restricted diffusion in corpus callosum, temporal region.



(a) (b)

Fig.6. Fluid attenuated inversion recovery (FLAIR), T2 axial image showing ill defined hyperintensity in in left posterior region causing effacement of adjacent sulci suggestive of vasogenic edema.

DISCUSSION:

The present study showed that patients of CM and CM+MOD had increased brain volume, predominant vasogenic oedema involving the posterior part of the brain predominantly and cytotoxic oedema. The oedema disappeared remarkably with antimalarial treatment within 72 hours among patients of CM. Reversibility took longer time among patients of CM with MOD and associated with death.

Variable MRI findings affecting different parts of brain have been reported by various authors and are limited to case reports. Those included focal or diffuse signal changes in centrum semiovale, corpus-callosum, thalamus, insular cortex, central pontine myelinolysis, myelinolysis in the upper medulla, cerebellar syndrome with demyelination, microinfarcts in cerebellum, bi-thalamic infarction

with or without haemorrhage, acute haemorrhagic infarction in brain stem, cerebellum, cerebral white matter, and insular cortex. There can be multiple sites of brain involvement in a single patient[13-17]. Study from Thailand showed that out of 24 patients 17 showed gross swelling of brain which has been attributed to increased intracerebral blood volume due to sequestration but not cerebral oedema[6]. One patient of this series also showed foramen magnum herniation. In another series, consisting of 43 adult severe falciparum malaria from Bangladesh showed that in 79% cases abnormal MRI finding was present at various anatomical sites. Diffuse brain swelling was (22 of 43) common without vasogenic oedema[18]. In a recent study from Odisha, India it was found that brain swelling, vasogenic oedema, cytotoxic oedema and predominant posterior involvement of brain like PRES are found in both adult and paediatric CM[9]. It is worth mentioning that clinic-pathologically paediatric CM is different from adult malaria and variable types of involvement at various anatomical sites of brain. Abnormalities in the basal ganglia was found in >80% of cases and there are abnormalities in splenium. These were important because lesions at these sites may be responsible for neurological sequel observed in paediatric patients. These abnormalities are more found in patients with retinal abnormalities with CM. The present study showed that increased brain volume, vasogenic oedema, and PRES like syndrome affecting the posterior part of the brain in CM and CM with MODS. Patients with MODS showed infarcts, ring haemorrhages, corpus callosum, basal ganglia more than without MODS. Diffuse and multiple site involvement in MODS suggest that multiple complications in FM contributed to biochemical and physiological alterations of brain that impaired BBB and subsequent cerebral dysfunction. As there was no study to define organ dysfunction of severe malaria, we developed a scoring system in our centre and according to it we found that patients with high MSS are associated with multiple MRI findings[11]. It has been postulated that MODS may lead to systemic changes affecting MRI findings[5].

Apart from brain oedema, changes in basal ganglia, white matter, pons, and brain stem are detected by autopsy among patients of CM. One patient in our series had restricted diffusion in corpus callosum. In the present study, there were infarctions in tectum, parietal lobe, hippocampus, temporal lobe, parieto-occipital region, corpus callosum, and microhaemorrhages in inferior gangliocapsular region. Isolated corpus callosum abnormality, which has been attributed to intramyelinic oedema have been described with seizures, viral infections, and in paediatric CM. This is associated with atypical and sometimes reversible DWI abnormalities[7]. In agreement with a recent study from Odisha, we found that brain swelling, vasogenic oedema, and cytotoxic oedema was found in CM and mostly the vasogenic oedema was found in posterior part of brain like PRES[9]. However, evidence for a generalized increase in BBB dysfunction giving rise to cerebral oedema is controversial, hence mannitol therapy in CM is not found beneficial[19,20].

The infected erythrocytes adhere to the microvasculature through *Plasmodium falciparum* erythrocyte membrane protein-1(*Pf*EMP1) and knob associated histidine rich protein to intracellular adhesion molecule-1(ICAM1), platelet endothelial cell adhesion molecule 1 and cellular differentiation antigen 36(CD36), known as sequestration[2]. Sequestration leads to capillary obstruction, reduced perfusion of the brain parenchyma and reduced delivery of necessary nutrients to neurons leading to coma. Further, parasitized RBCs clumped together by autoagglutination and non-parasitized erythrocytes by resetting aggravating the microcirculatory flow[3]. This plugging of micro vessels causes microvascular congestion, local hypertension which increases pressure on tight junctions and breaks the tight junction leading to the rupture of the BBB, causing oedema, haemorrhage, and other abnormalities[21]. In addition, recent study showed that toxic metabolites from parasitized RBCs are transferred to and endocytosed by the endothelial cells. This is associated with the opening of the intercellular tight junctions and breakage of BBB[22]. It is a notable fact that the anatomical substrate of the BBB is the cerebral microvascular endothelium, which together with pericytes, astrocytes, and the extracellular matrix form a neuro-vascular unit. Tight junctions between the endothelial cells restrict paracellular diffusion. The tight junction is an intricate complex of transmembrane protein i.e. occludin & caudins and cytoplasmic proteins like Zonula occludens-1,2 7 cingulins. These protein concentrations are found reduced in CM suggesting BBB dysfunction [3,23].

Therefore, different types of cerebral lesions are possible at different areas of brain depending on the site of involvement and duration of disease.

Increased blood volume in brain following sequestration of intraerythrocytic parasites, accumulation of intra-cellular fluid due to impaired cellular metabolism (cytotoxic oedema), and of interstitial fluid in the brain tissue following disruption of blood brain barrier (vasogenic oedema). All these 3 mechanisms are interlinked since cytoadherence of parasites to endothelial cells compromised the functional integrity of BBB[19]. However, distinction between vasogenic and cytotoxic oedema can be done by diffusion-weighted MRI scanning but not by CT scan. Hence, MRI is a powerful diagnostic tool understanding and monitoring CM pathology. The vasogenic oedema resulted from parenchymal hypoperfusion, augmented filtration pressure at capillary beds to overcome vascular endothelium and tight intercellular junction of BBB, and BBB dysfunction due to hypoxia[9].

We found a predominant vasogenic oedema in the cortex, subcortex, and white matter of bilateral parietal and occipital lobe which is also known as PRES. The pathogenesis of PRES is due to impaired cerebral autoregulation that increases cerebral perfusion, endothelial dysfunction, and breakdown of BBB resulting in vasogenic oedema. Normally, sympathetic stimulation is vaso-protective in both hypertension and inflammation. The sympathetic neural network is sparse in posterior circulation territories of brain. Therefore, PRES occurred in hypertension and other inflammatory causes[24]. Hence, due to diminished sympathetic innervation, parasite sequestration and subsequent inflammation causes BBB dysfunction giving rise to PRES.

There was indication of cytotoxic oedema and vascular engorgement as evidenced by DWI and ADC mismatch and perfusion parameters in 79 (66.4%) cases. The microvascular blockage is the cause of stasis and vascular engorgement. The sequestration of parasitized RBC may explain microvascular dilatation and engorgement. The penetrating arteries may be affected by the parasites causing perivascular ring-like haemorrhages, white matter necrosis, and lacunar infarct[9].

In conclusion, the present study showed that different types of neurological lesions can be detected by MRI in CM. Increased brain volume, vasogenic oedema, and predominant involvement of posterior part of brain are important abnormalities. All types of pathological changes are reflection of severity of BBB dysfunction.

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