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Role of Oxidative Stress in Tuberculous Meningitis: a Clinico-Radiological Correlation

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Abstract

Central nervous system infection may be associated with oxidative stress and may influence clinical severity and outcome. We report oxidative stress markers in the patients with tuberculous meningitis (TBM) and correlate these with clinico-radiological severity and outcome. Fifty-six patients with TBM diagnosed on the basis of clinical, cerebrospinal fluid (CSF), and magnetic resonance (MRI) were included. Plasma glutathione (GSH), total antioxidant capacity (TAC), and malondialdehyde (MDA) were measured in the patients and 55 matched healthy controls. Hospital death was noted. Disabilities at 3 and 6 months were categorized using the modified Rankin Scale (mRS) as poor (mRS > 2) or good (mRS ≤ 2). The patients had lower levels of GSH (1.49 ± 0.49 vs 2.57 ± 0.39 mg/dL, $p < 0.001$) and TAC (0.25 ± 0.17 vs 2.20 ± 0.31 mmol Trolox Eq/L, $p < 0.001$), and higher level of MDA (6.61 ± 1.72 vs 3.09 ± 0.38 nmol/mL, $p < 0.001$) compared to controls. Total antioxidant capacity correlated with cranial nerve palsy and CSF pleocytosis. Patients with tuberculoma had lower GSH compared to those without. Six patients died in the hospital, and they had lower GSH ($p < 0.01$) and TAC ($p = 0.02$) levels compared to those who survived. Thirty-one and 36 patients had a good outcome at 3 and 6 months respectively. The patients with good outcome had higher GSH level.

Keywords Tuberculous meningitis · Oxidative stress · Glutathione · Total antioxidant capacity · Malondialdehyde · MRI · Tuberculoma

Introduction

Tuberculosis is a global health problem, and there is a resurgence of tuberculosis even in the countries where it has become rare (WHO 2016). The annual incidence of tuberculosis varies from 9 cases/100,000 populations in the USA to 110–165 cases/100,000 population in the developing countries (Raviglione et al. 1995). About 10% of the patients with extra pulmonary tuberculosis have central nervous system (CNS) involvement. Tuberculous meningitis (TBM) is the most severe form of tuberculosis resulting in high mortality (20–30%) and neurological sequel in 25–50% (Misra et al. 2011; Kalita et al. 2007, 2009; Thwaites and Hie 2005; Marais et al. 2010). Computerized tomographic (CT) scan and magnetic resonance imaging in TBM reveal exudates, stroke, hydrocephalous, tuberculoma, or tubercular abscess in isolation or in various combinations (Misra et al. 2011; Gupta et al. 1994). In experimental studies on bacterial meningitis, there have been growing evidences of oxidative stress-mediated brain injury and neurological complications. Leucocytes and macrophages migrate to the site of bacterial infection to destroy the microorganism. The activated macrophages including central nervous system (CNS) immune cells consume more oxygen thereby liberating reactive oxygen species (ROS), which in turn produce toxic superoxide anions, H_2O_2, and hydroxyl radicals. In a normal situation, ROS is neutralized by cellular enzymatic (superoxide dismutase and catalase) and non-enzymatic antioxidants (glutathione, uric acid, etc.). Inability to neutralize excess production of ROS leads to an imbalance in oxidative and antioxidant activity resulting in lipid peroxidation and DNA breakdown (Sies 1997; Levonen et al. 2014). Central nervous system infection and stroke are regarded

Highlights
- The patients with tuberculous meningitis have increased oxidative stress.
- The lower level of antioxidant is associated with death and poor outcome.
- Role of augmenting antioxidant or reducing stress may be explored in the outcome of tuberculous meningitis.

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as severe stress, and likely to result in oxidative stress-mediated brain injury. There are reports of increased oxidative stress markers in the patients with bacterial meningitis especially in pyogenic meningitis (Miric et al. 2013; Kastenbauer et al. 2002; Awodele et al. 2012). In a study on TBM patients, CSF and serum malondialdehyde (MDA) were higher, which gradually increased following treatment until 6 weeks, then returned to normal (Miric et al. 2013). The children with acute bacterial meningitis had higher MDA level compared to TBM (Ray et al. 2000). Some authors reported the status of vitamins C, A, and E as well as lipid peroxidation and thiol status in pulmonary tuberculosis (Plit et al. 1998; Kumar et al. 1994). Most of these studies have not correlated oxidative stress markers with clinical severity, MRI findings, and long-term outcome. In this communication, we report oxidative stress markers in patients with TBM and correlate these findings with clinical severity, MRI findings, and 6-month outcome.

Materials and Methods

The patients with TBM admitted in the neurology service of a tertiary care teaching hospital in India during 2015–2017 were included. The study was approved by the Institute Ethics Committee.

Diagnostic Criteria of TBM The diagnosis of TBM was based on the following clinical, cerebrospinal fluid (CSF), and MRI/CT criteria:

Essential Criteria

One or more features are suggestive of meningitis: headache, irritability, vomiting, fever, weight loss, neck stiffness, convulsions, focal neurological deficits, or altered consciousness for more than 5 days.

Supportive Criteria

(a) CSF cells of 10–500/μL with > 50% lymphocytes, protein 1 g/L, and sterile bacterial and fungal culture.
(b) Cranial CT or MRI imaging showing evidence of exudates, infarction, hydrocephalus, or tuberculoma in isolation or in combinations.
(c) Evidence of extra CNS tuberculosis on chest radiograph suggestive of active tuberculosis, CT, MRI, or ultrasound evidence of tuberculosis outside the CNS, *Acid Fast Bacillus* (AFB) identified in smear, or *Mycobacterium tuberculosis* cultured from another source such as sputum, lymph node, gastric washing, or urine.
(d) Exclusion of alternative diagnoses (Marais et al. 2010)

Criteria for Definite and Highly Probable TBM

The patients fulfilling essential criteria with two supportive criteria were defined as highly probable TBM, and those with acid fast bacilli in CSF smear, positive CSF culture, or polymerase chain reaction (PCR) for *M. tuberculosis* were considered definite TBM (Kalita et al. 2014).

Exclusion Criteria Patients with septicemia, malignancy, renal failure, pre-existing liver failure, autoimmune disorder, and chemotherapy, immunosuppressant, or radiotherapy, and pregnancy were excluded.

Evaluation The patients were evaluated by two senior neurologists (JK and UKM). Their demographic details, duration of illness, fever, headache, vomiting, focal weakness, seizure, alteration in sensorium, and cranial nerve palsy were noted. Consciousness was assessed by the Glasgow Coma Scale (GCS). Patients were examined for comorbidities such as anemia, diabetes, hypertension, and HIV infection. Presence of extra CNS tuberculosis such as lymph node, pulmonary, abdominal, or bone tuberculosis was noted.

Severity of TBM The severity of TBM was graded as per the Medical Research Council (MRC) criteria (BMRC 1948).

Stage I: Meningitis only.
Stage II: Meningitis with the focal deficit or GCS score 11–14.
Stage III: Meningitis with GCS score < 11.

Investigations Total blood counts, erythrocyte sedimentation rate, hemoglobin, blood sugar, blood urea nitrogen, serum creatinine, sodium, potassium, transaminases, bilirubin, albumin, calcium, and alkaline phosphate were measured. Chest radiograph, electrocardiogram, and HIV serology were done. Cranial CT scan was done using third-generation spiral CT scanner. Cranial MRI was done using a 3T MRI machine (GE medical system, Wisconsin, USA). T1, T2, FLAR, DWI, and T1 contrast images were obtained. Presence of exudate, hydrocephalous, infraction, and tuberculoma was noted. Cerebrospinal fluid was examined for the cell, protein, sugar, AFB in smear and culture, PCR for *M. tuberculosis*, and IgM ELISA for tuberculosis and cryptococcal antigen.

Oxidative Stress Markers Plasma GSH and TAC were measured as markers of antioxidant, and MDA as a marker of lipid peroxidation. Five-milliliter venous blood was collected in an EDTA vial, and plasma was separated and stored at − 80 °C until analysis. Plasma GSH was measured by spectrophotometer at 412 nm as per the method of Tietze et al. (Tietze 1969). Plasma TAC was also measured using spectrophotometer at

532 nm (Koracevic et al. 2001). Plasma lipid peroxidation was estimated by measuring MDA, an end product of lipid peroxidation using spectrophotometer at 532 nm (Janero 1990). Plasma GSH, TAC, and MDA levels were also measured in 55 age (36.8 ± 15.8 vs 32.9 ± 15.0 years, $p = 0.19$) and gender (female 25 vs 24; $p = 1.00$) matched healthy controls.

Treatment and Outcome All patients received 4 drug antitubercular treatment including rifampicin 10 mg/kg/day (~ 450 mg/day), isoniazid 5 mg/kg/day (~ 300 mg/day), pyrazinamide 25 mg/kg/day (~ 1500 mg/day), and ethambutol 15 mg/kg/day (~ 800 mg/day). This regimen was continued for 6 months. Thereafter, rifampicin and isoniazid were continued for another 1 year. Prednisolone 0.5 mg/kg (~ 40 mg/day) was prescribed for 1 month and tapered in next month. Aspirin 150 mg/day was also given (Kalita et al. 2016). The patients with raised intracranial pressure with hydrocephalous were subjected to the ventriculoperitoneal shunt. The patients with respiratory failure having arterial blood gas abnormally were mechanically ventilated. Outcomes at 3 and 6 months were evaluated using the modified Rankin Scale (mRS) and categorized as good (mRS ≤ 2) or poor (mRS > 2). Death and its causes were noted.

Statistical Analysis The normalcy of the data was checked by the Shapiro-Wilk test. Glutathione, MDA, and TAC levels in the patients and the controls were compared by Mann-Whitney *U* test. The correlation of demographic, clinical, and MRI findings were done using Karl-Pearson or Spearman correlation test. The statistical analysis was done by SPSS 16 version software and graphs were prepared by GraphPad Prism 5. The variables were considered significant if the two-tailed *p* value was < 0.05.

Results

There were 56 patients with TBM and their median age was 33 (9–70) years; 25 of whom were females. Eighteen patients had definite TBM, 36 highly probable, and two possible. The median duration of illness was 60 (15–120) days. All patients had a fever, 51 had headache, 14 seizures, 42 vomiting, and 32 had a focal weakness. Forty patients had altered sensorium, and GCS score was ≤ 8 in nine patients. Thirteen patients were in stage III meningitis, 38 in stage II, and five in stage I.

Laboratory Findings Sixteen patients had leukocytosis (> 11,000/mm^3), 28 had anemia (< 12 g/dL), and 13 had hypoalbuminemia (< 3.5 g/dl). Cerebrospinal fluid examination revealed pleocytosis in all and glucose was low (< 60% of corresponding blood sugar) in 26 patients. Cranial MRI revealed meningeal enhancement in 23, hydrocephalous in 26, infarctions in 27 and tuberculoma in 28 patients.

Oxidative Stress In the patients with TBM, plasma GSH (1.49 ± 0.49 vs 2.57 ± 0.39 mg/dl, $p < 0.001$) and TAC (0.25 ± 0.17 vs 2.20 ± 0.31 mmol Trolox Eq/L, $p < 0.001$) levels were lower, and MDA (6.61 ± 1.72 vs 3.09 ± 0.38 nmol/mL, $p < 0.001$) level was higher compared to the controls (Fig. 1). In nine patients, these markers were also measured at 3 months and the values were not significantly different compared to baseline and remained abnormal compared to the controls (Table 1).

Clinico-Radiological Correlation The patients with cranial nerve palsy had lower TAC level compared to those without (0.19 ± 0.08 vs 0.30 ± 0.22 mmol Trolox Eq/L, $p < 0.05$). Glutathione level was insignificantly lower in the patients with tuberculoma compared to those without (1.38 ± 0.43 vs 1.61 ± 0.53 mg/dL, $p = 0.08$). Total antioxidant capacity level correlated with CSF pleocytosis ($r = -0.27$, $p < 0.05$), and MDA level correlated with serum protein ($r = 0.28$, $p < 0.05$) and albumin ($r = 0.43$, $p < 0.01$). The stage of meningitis did not correlate with GSH ($r = -0.19$, $p = 0.15$), TAC ($r = -0.07$, $p = 0.58$), or MDA level ($r = -0.11$, $p = 0.40$). The remaining clinical, laboratory, and MRI findings did not correlate with oxidative stress markers. The relationship of GSH, TAC, and MDA levels with relevant clinical, laboratory, and MRI findings are shown in Tables 2 and 3.

Outcome At the time of discharge, six patients died and 50 survived. The patients who survived had higher GSH (1.56 ± 0.47 vs 0.89 ± 0.72 mg/dL, $p < 0.01$) and TAC (0.26 ± 0.18 vs 0.16 ± 0.06 mmol Trolox Eq/L, $p = 0.02$) compared to those who died. Malondialdehyde (6.53 ± 1.78 vs 7.25 ± 0.89, $p = 0.13$ nmol/mL) level was not significantly different between the two groups. Thirty-one patients at 3 months and 36 patients at 6 months had a good recovery, and their GSH level was higher compared to those who had poor recovery (Figs. 2 and 3).

Discussion

This study demonstrates evidence of oxidative stress in patients with TBM, and patients with lower levels of GSH and TAC had higher death and worse outcome. Tuberculoma negatively correlated with GSH and CSF pleocytosis with TAC level. This study highlights the role of GSH, TAC, and MDA levels in patients with

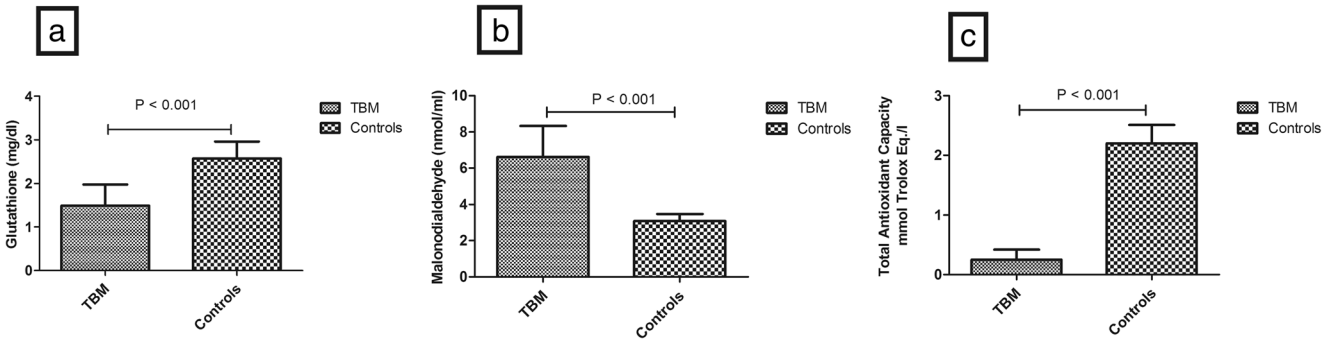

Fig. 1 Bar diagram shows plasma glutathione (GSH) (a), malondialdehyde (MDA) (b), and total antioxidant capacity (TAC) (c) in tuberculous meningitis (TBM) and controls. GSH and TAC levels were decreased and MDA level was elevated in TBM patients compared to the controls. Values are expressed in mean ± SD. Units for MDA are nmol/mL, GSH mg/dL, and TAC mmol Trolox Eq/L

TBM in determining clinical and radiological severity and outcome. There are few studies evaluating the role of oxidative stress in tuberculosis, and only two studies had measured these markers in the patients with TBM (Miric et al. 2013; Ray et al. 2000; Plit et al. 1998; Kumar et al. 1994; Madebo et al. 2003). A study on 27 TBM patients revealed higher levels of CSF and serum MDA and lower vitamin C. Malondialdehyde level continued to rise until 6 weeks of antitubercular treatment and then normalized to baseline. Vitamin C level did not improve following treatment (Miric et al. 2013). Oxidative stress markers in our patients also remained abnormal at 3 months. This may be due to ongoing infective or inflammatory process because of the chronicity of tubercular infection. In another study, both oxidants (reactive oxygen species and MDA) and antioxidant (super-oxide dismutase) were elevated in children with acute bacterial meningitis and TBM, which were more marked in acute bacterial meningitis (Ray et al. 2000). The abovementioned studies, however, have not correlated oxidative stress markers with clinical severity, MRI findings, and long-term functional outcome. The role of oxidative stress has also been reported in determining the severity and outcome of stroke (Allen and Bayraktutan 2009). In our study, the lack of correlation of GSH, TAC, and MDA levels with stroke may be due to small subcortical nature of infractions in TBM. Tuberculous meningitis characteristically produces lacunar stroke mostly in caudate, corpus stratum, anterior thalamus (tubercular zone), and subcortical white matter (Kalita et al. 2009; Hsieh et al. 1992). Majority of our patients were in stage II or stage III meningitis; therefore, oxidative stress markers might not have correlated with stage of meningitis.

Glutathione, catalase, vitamin C, and MDA levels were compared in HIV patients with and without tuberculosis. Glutathione level was lower in HIV patients irrespective of tuberculosis compared to the controls. Malondialdehyde level was higher in the untreated group compared to antiretroviral-treated group (Awodele et al. 2012). The status of CNS involvement, however, was not mentioned in this study. None of our patients had HIV infection. There are few studies reporting on the role of oxidative stress in non-tubercular bacterial meningitis (Kastenbauer et al. 2002; Hamed et al. 2009). In a study on children with pyogenic bacterial meningitis, lower level of serum albumin, and elevated levels of NO, LPO, total

Table 1 Comparison of glutathione (GSH), total antioxidant capacity (TAC), and malondialdehyde (MDA) levels in tuberculous meningitis (baseline and 3 months) and controls

	TBM		Control ($n = 55$) C	p value		
	Baseline ($n = 56$) A	3 month follow up ($n = 9$) B		A vs B	A vs C	B vs C
MDA nmol/mL	6.61 ± 1.71	6.03 ± 1.68	3.08 ± 0.37	0.639	< 0.01	< 0.01
GSH mg/dL	1.49 ± 0.49	1.52 ± 0.54	2.57 ± 0.39	1.00	< 0.01	< 0.01
TAC mmol Trolox Eq/L	0.25 ± 0.17	0.25 ± 0.10	2.19 ± 0.31	1.00	< 0.01	< 0.01

Table 2 Comparison of demographic, clinical, and MRI findings with malondialdehyde (MDA), glutathione (GSH), and total antioxidant capacity (TAC) in the patients with tuberculous meningitis

	MDA nmol/mL	GSH mg/dL	TAC mmol Trolox Eq/L
Gender			
Male	6.33 ± 0.31	1.45 ± 0.08	0.23 ± 0.02
Female	6.96 ± 0.32	1.54 ± 0.10	0.26 ± 0.04
Focal weakness			
Present($n = 32$)	6.26 ± 1.69	1.49 ± 0.53	8025 ± 1.67
Absent ($n = 24$)	7.08 ± 1.68	1.49 ± 0.45	0.25 ± 0.19
Seizure			
Present ($n = 14$)	6.64 ± 1.72	1.4 ± 0.51	0.25 ± 0.18
Absent ($n = 42$)	6.61 ± 1.74	1.42 ± 0.33	0.29 ± 0.13
Cranial nerve palsy			
Present ($n = 27$)	6.99 ± 1.47	1.44 ± 0.44	0.19 ± 0.08*
Absent ($n = 29$)	6.26 ± 1.88	1.54 ± 0.54	0.30 ± 0.22
MRI findings			
Hydrocephalous			
Present ($n = 26$)	6.65 ± 1.54	1.57 ± 0.55	0.23 ± 0.12
Absent ($n = 30$)	6.58 ± 1.89	1.42 ± 0.43	0.27 ± 0.21
Infarcts			
Present ($n = 27$)	6.03 ± 1.20**	1.54 ± 0.51	0.27 ± 0.18
Absent ($n = 29$)	7.16 ± 1.97	1.48 ± 0.49	0.23 ± 0.17
Exudate			
Present ($n = 23$)	6.71 ± 1.68	1.57 ± 0.59	0.24 ± 0.16
Absent ($n = 33$)	5.54 ± 1.76	1.44 ± 0.41	0.26 ± 0.18
Tuberculoma			
Present ($n = 28$)	6.97 ± 1.56*	1.38 ± 0.43	0.20 ± 0.89
Absent ($n = 28$)	8.26 ± 1.82	1.61 ± 0.53	0.30 ± 0.22

*$p < 0.05$

thiol, SOD, and S100B have been reported. Cerebrospinal fluid LPO correlated with CSF protein, total thiol with LPO indices, S100 B with GCS score, and CSF LPO with S100B. Oxidative stress markers have also been studied to determine the severity of septic shock and outcome (Hamed et al. 2009; Cowley et al. 1996; Niki 2010). Mean plasma retinol and tocopherol levels were lower in the patients with septic shock compared to the healthy controls. Plasma carotene and lycopene were undetectable in patients (Goode et al. 1995). In another study on sepsis, plasma antioxidant was reduced in the patients with organ failure, and failure to attain normal antioxidant level was associated with unfavorable outcome (Cowley et al. 1996).

Table 3 Correlation of malondialdehyde (MDA), glutathione (GSH), and total antioxidant capacity (TAC) with various clinical and laboratory parameters in the patients with tuberculous meningitis

	MDA (r)	GSH (r)	TAC (r)
Age	− 0.004	− 0.17	− 0.94
Glasgow Coma Scale	0.21	0.06	0.08
CSF cell	0.09	− 0.16	− 0.27*
CSF protein	− 0.02	0.16	− 0.10
CSF sugar	− 0.02	− 0.08	− 0.08
Hemoglobin	0.14	0.07	− 0.15
White blood cell	− 0.06	0.01	− 0.23
Serum protein	0.28*	0.04	− 0.14
Serum albumin	0.43**	0.06	−0.01

CSF, cerebrospinal fluid, *$p < 0.05$, **$p < 0.01$

Glutathione is a potent water-soluble antioxidant and is widely expressed in most of the organs. Total antioxidant capacity measures the hydrophilic antioxidant capacity including uric acid (Cowley et al. 1996), and MDA is the end product of the lipid peroxidation and suggests the extent of ROS activity (Halliwell Band S Chirico 1993). Acute CNS insult

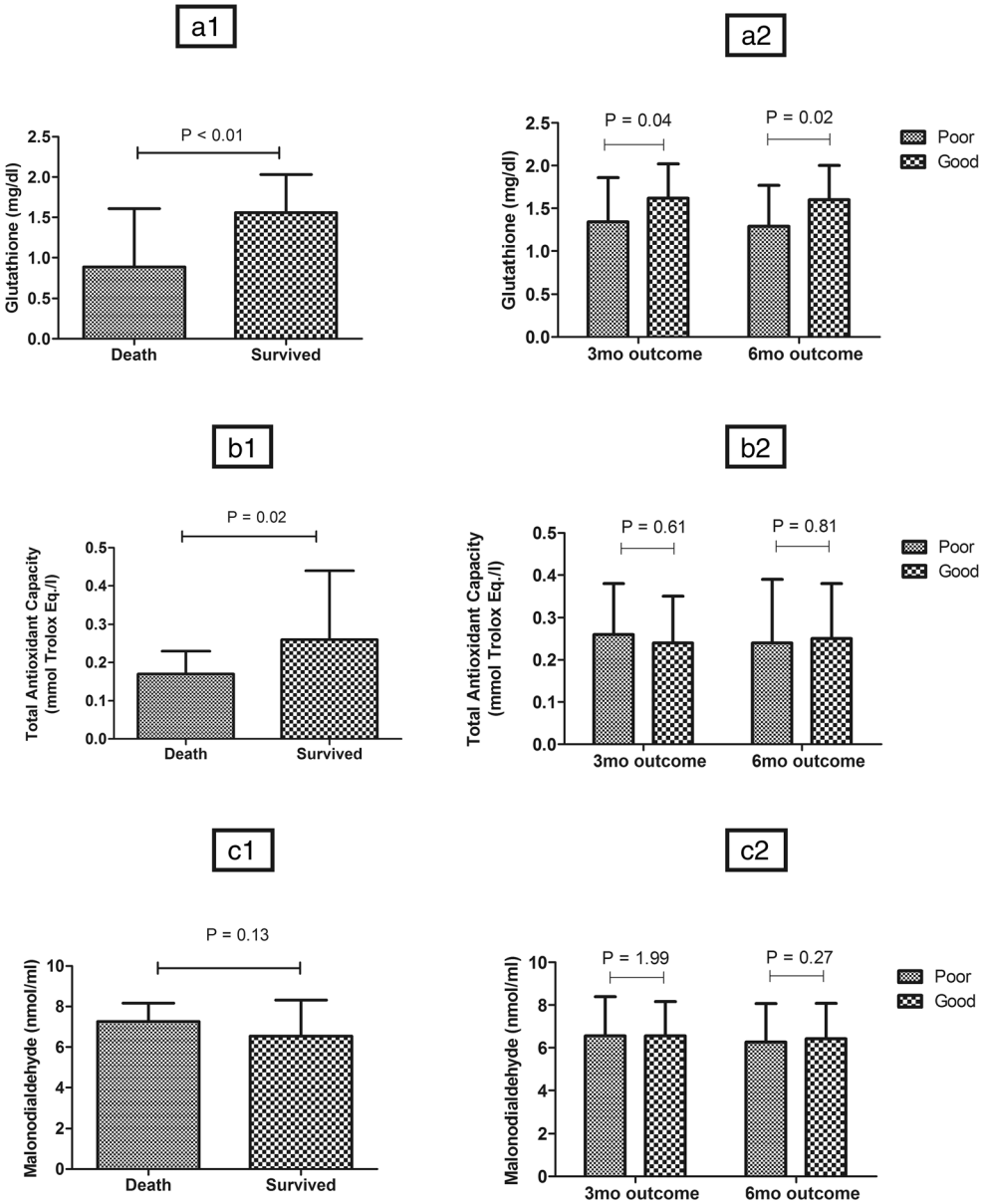

Fig. 2 Bar diagram shows the relationship of glutathione (GSH), total antioxidant capacity (TAC), and malondialdehyde (MDA) with death (a1, b1, and c1) and 3 and 6 months functional outcome (a2, b2, and c2). Values are expressed in mean + SD. Units for MDA are nmol/mL, GSH mg/dL, and TAC mmol Trolox Eq/L

has been considered as severe stress (Meisel et al. 2005). There is excess liberation of catecholamine resulting in increased metabolic demand, which in turn generates ROS. If ROS is not neutralized by antioxidants, there may be an imbalance between antioxidants and oxidants resulting in lipid peroxidation. The increased oxidative stress plays an important role in the pathogenesis of brain damage, as the brain is highly active metabolically. Elevated oxidative stress may result in the breakdown of the blood-brain barrier and DNA (Levonen et al. 2014). Tuberculous meningitis not only produces meningeal inflammation, but also associated with hydrocephalus, infraction, and tuberculoma (Thwaites and Hie 2005; Levonen et al. 2014; Ray et al. 2000; Misra et al. 2018). These pathological changes may result in raised intracranial pressure leading to herniation and stress.

The present study is limited by lack of oxidative stress markers in CSF. The cerebrospinal fluid analysis in TBM, although is a routine procedure, was not considered ethical to do lumbar puncture in healthy individuals.

This study highlights elevated oxidative stress in TBM. The lower level of antioxidants is associated with death and poor outcome. Role of antioxidant may be explored in the outcome of TBM patients.

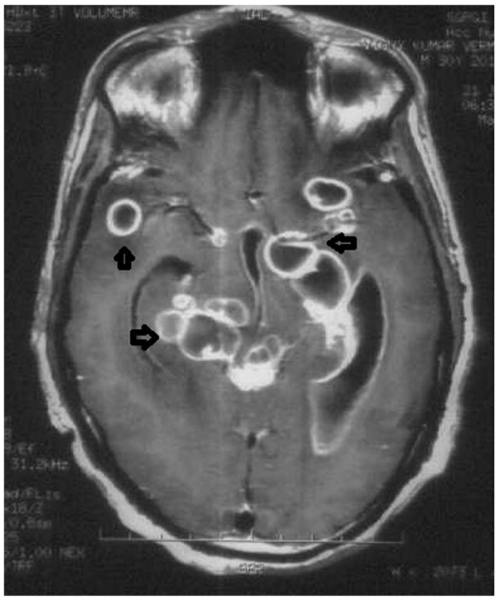

Fig. 3 Contrast MRI on axial section shows multiple enhancing granuloma (black arrow) and meningeal enhancement in a patient with tuberculous meningitis. His glutathione and total antioxidant capacity levels were low and had a poor outcome at 6 months

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was approved by the Institute Ethics Committee, SGPGIMS Lucknow, India.

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