

Prevalence and outcome of headache in tuberculous meningitis

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ABSTRACT

الأهداف : لتقييم شدة الصداع ، وعلاقته مع الخصائص الاكلينيكية ، السائل النخاعي ، ومعامل التصوير العصبي لالتهاب السحايا السلي (الحفار) في المرضى ، وتأثيرها على النتائج .

الطريقة : أجريت هذه الدراسة الاستطلاعية في الجامعة الملك جورج الطبية لكانا ، الهند بين أكتوبر 2012م ومايو 2014م . شُخص حديثا 95 من مرضى السل تشخيصا اكلينيكيًا شاملاً ، والمختبرات ، وتقييم التصوير العصبي . وقد تم استخدام مقياس تصنيف رقمي لتقييم شدة الصداع ، وقسم المرضى إلى مجموعات صداع خفيف ، معتدل ، حاد ، وصداع لا يحتمل . قيمت نتائج المرضى خلال 6 أشهر من المتابعة .

النتائج : الصداع من نوع Holocranial stabbing $p=0.002$ ، تعديل مؤشر بارثل ≥ 12 ($p<0.001$) ، ازدواج الرؤية ($p=0.055$) ، ونوبات ($p<0.001$) ، ضعف البصر ($p=0.024$) ، شلل العصب القحفي ($p=0.002$) ، علامات السحايا ($p=0.016$) ، وحالات التهاب السحايا السلي ($p=0.001$) . المرحلة الثالثة $p<0.001$ ، والبروتين (أكثر من 2.5 غرام/لتر ($p<0.001$) كان مرتبط إلى حد كبير مع شدة الصداع . ترتبط خصائص العصب الشعاعي بشكل كبير مع شدة الصداع بالتعزيز السحائي ($p=0.015$) ، الإفرازات القاعدية ($p<0.001$) ، واستسقاء دماغي ($p=0.003$) . أحد عشر من أصل 15 من المرضى اللذين توفوا كان لديهم صداع لا يحتمل . من العلامات المنبئة للنتائج المحبطة في مجموعات الصداع الشديد والغير محتمل هو بروتين أكثر من 2.5 غرام/لتر ، شلل العصب القحفي ، خزل سفلي ، والاحتشاء . توقف صداع مرضى مجموعة الصداع الخفيف والمعتدل بعد 6 أشهر من المتابعة بنتائج جيدة .

الخاتمة : كان شدة الصداع مرتبط مع عدة عوامل اكلينيكية ، البروتين CSF ، والعوامل الإشعاعية . بما أن الصداع الغير محتمل والشديد يؤثر بشكل سلبي على النتائج ، يمكننا معرفة مرضى TBM بناءً على شدة الصداع .

Objective: To evaluate headache severity, and its correlation with clinical, cerebrospinal fluid, and neuroimaging parameters of tuberculous meningitis (TBM) patients, and its impact on outcome.

Methods: This prospective observational study was conducted at King George's Medical University,

Lucknow, India between October 2012 and March 2014. Ninety-five newly diagnosed TBM patients underwent detailed clinical, laboratory, and neuroimaging evaluation. A numeric rating scale was used to assess the headache severity, and patients were grouped into mild, moderate, severe, and intolerable groups. Patient outcome was evaluated at 6-months follow up.

Results: Holocranial stabbing type headache ($p=0.002$), modified Barthel index ≤ 12 ($p<0.001$), diplopia ($p=0.055$), seizures ($p<0.001$), visual impairment ($p=0.024$), cranial nerve palsy ($p=0.002$), meningeal signs ($p=0.016$), definite cases of TBM ($p=0.001$), British Medical Research Council stage III ($p<0.001$), and CSF protein >2.5 g/l ($p<0.001$) were significantly associated with severity of headache. Neuroradiological features significantly associated with severity of headache were meningeal enhancement ($p=0.015$), basal exudates ($p<0.001$), and hydrocephalus ($p=0.003$). Eleven out of 15 patients who died had intolerable headache at admission. Significant predictors of poor outcome in severe and intolerable headache groups were CSF protein >2.5 g/L, cranial nerve palsies, paraparesis, and infarcts. Patients of the mild and moderate headache group were headache free at 6 months follow up with good outcome.

Conclusion: Severity of headache was associated with multiple clinical, CSF protein, and radiological factors. As intolerable and severe headache had an unfavorable impact on outcome, we could prognosticate the TBM patients on the basis of headache severity.

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Tuberculosis is a major public health concern worldwide, and India is in one of the high endemic zones. The incidence of CNS tuberculosis is dependent on the prevalence of tuberculosis in the general population.¹ Tuberculous meningitis (TBM) is the most common manifestation of CNS tuberculosis. It causes death, or serious disabilities in up to 51% of affected patients.² The various manifestations and complications of TBM such as convulsion, cranial nerve palsy, delayed treatment, stroke, low Glasgow coma scale score, vision loss, and hydrocephalus were associated with poor outcome.²⁻⁵ Headache is one of the common symptoms in TBM. Headache incidence was found in most of series as ranging from 50-100% in TBM patients.³⁻⁷ Headache in chronic meningitis like TBM can be acute, subacute, or chronic. Headaches in these patients are due to involvement of the meninges and other inflammatory changes that produces hydrocephalus and stroke. These inflammatory changes may be irreversible, such as communicating hydrocephalus.⁵ These changes are the source of headache during the disease process, and may occur even after resolution of infection (post meningitic headache). In many developing and poor countries, there is poor availability of advanced imaging techniques, such as MRI, which provide minute details of changes in brain parenchyma as well as the meninges. Headache is closely associated with these changes. Therefore, severity of headache can be used as an indirect measure of these changes in the brain. In this prospective observational study, we assessed the predictive factors of severity of headache at presentation and during the course of illness. We also evaluated the impact of severity of headache on the outcome of the disease.

Methods. We conducted this prospective observational study between October 2012 and March 2014 in the Department of Neurology, King George's Medical University, Lucknow, Uttar Pradesh, India. Our institution is situated in a high endemic zone of tuberculosis, which covers more than 100 million of the population of North India. The Institutional ethics committee approved the study protocol. We obtained written informed consent from all patients, or from their legal guardians, before enrolling in the study. We used the international classification of headache disorder II for the classification of headache. We conducted

the study according to the principles of the Helsinki Declaration.

Inclusion criteria. Ninety-five new cases of TBM were included in the study. The presence of headache was the prerequisite for enrolment. These patients presented with signs and symptoms (combination of headache, fever, vomiting, neck rigidity, convulsion, or focal neurological deficit) and cerebrospinal fluid abnormalities (mononuclear cell pleocytosis, low glucose level, raised protein level) suggestive of TBM. Neuroimaging abnormalities like meningeal enhancement, basal exudates, hydrocephalus, tuberculoma, and infarction alone or in combination helped in the diagnosis of TBM. The diagnosis of TBM was made according to the consensus criteria as given by Marais et al.⁸ The patients were divided into definite, probable, and possible TBM as per this criterion.⁸ Patients were classified according to the British Medical Research Council (BMRC) stage criteria.⁹ Patients with stage I disease had a Glasgow Coma Scale score of 15 with no focal neurological signs; patients with stage II had signs of meningeal irritation with slight or no clouding of sensorium and minor neurological deficit (like cranial nerve palsies) or no deficit (Glasgow coma scale score 11-14), and patients with stage III had severe clouding of sensorium, convulsions, focal neurological deficit, and involuntary movements (Glasgow coma scale score less than 10).⁹

Exclusion criteria. Patients with altered sensorium, HIV positive, or other causes for meningitis were excluded from the study.

Laboratory investigations. A detailed clinical evaluation was carried out in all patients. The laboratory tests, including complete blood count, erythrocytes sedimentation rate, blood glucose, blood urea nitrogen, serum creatinine, electrolytes, liver function test, chest x-ray, and enzyme-linked immunosorbent assay for (HIV) were performed. The CSF microscopy and biochemical analysis were also performed. The CSF sediments were stained and cultured (Lowenstein-Jensen media) by standard methods for detection of mycobacteria. The CSF specimens were also tested for mycobacterial tuberculosis DNA by polymerase chain reaction (PCR).

Headache severity assessment. A numeric rating scale (NRS) was used to assess the severity of headache. The NRS score range from zero to 10. Headache severity was categorized according to the number given by patients for their headache. Headache was categorized as no pain, mild, moderate, severe, and intolerable when scores were 0, 1-3, 4-6, 7-9, and 10.¹⁰ Headache was evaluated

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by administration of a headache questionnaire at the time of admission and during the follow up.

Radiological assessment. A brain MRI with gadolinium contrast was performed in all patients with a Signa Excite 1.5 Tesla instrument (General Electric Medical Systems, Milwaukee, WI, USA). Two experienced neuroradiologists, unaware of treatment and patient outcome reviewed the images. The abnormal neuroimaging features noted were meningeal enhancement, basal exudates, tuberculoma, hydrocephalus (communicating or non-communicating), and infarcts.

Treatment. All enrolled patients were treated according to the World Health Organization antituberculous regimen.¹¹ Patients received 2 months of daily oral rifampicin (10 mg/kilogram), isoniazid (5 mg/kilogram), pyrazinamide (25 mg/kilogram), and intramuscular streptomycin (20 mg/kilogram; maximum, 1 g/day), followed by 7 months of rifampicin and isoniazid at the same daily doses.¹¹ All patients received dexamethasone for 8 weeks. Patients were given 0.4 mg/kilogram body weight of intravenous dexamethasone per day, and then tapered off by 0.1 mg/kilogram every week. This was followed by oral treatment for 4 weeks, starting at a total of 4 mg/day and decreasing by one mg every week.¹² Oral pyridoxine 20-40 mg/day was given to all patients. In addition, 20% mannitol (1 gm/kg body weight/day in 4 to 6 divided doses; titrated to response) was given to patients with features of raised intracranial pressure. Antiepileptic drugs were used in patients who had seizures.

Follow up. Patients were followed for a period of 6 months after initiation of treatment. Headache severity was assessed at the first, third, and at the end of the

sixth month follow up using the NRS scale. Assessment of disability as per modified Barthel index (MBI) was carried out at baseline and at the end of the first, third, and sixth month of follow up. An MBI >12 at the end of 6 months was regarded as a good outcome, and ≤12 considered a poor outcome.

Statistical analysis. The Statistical Package for Social Sciences, version 16 for windows (SPSS, Chicago IL, USA) and Microsoft Excel were used for statistical analysis. Predictors for headache severity were identified using univariate and multivariate analysis. Univariate analysis was performed using Chi-square test for categorical data. Relative risks with 95% confidence interval were calculated. For multivariate analysis, binary logistic regression was performed to assess the impact of individual predictors of headache severity. Statistical significance was defined at $p < 0.05$, and the statistical analysis was two-tailed. The Kaplan-Meier survival curves for the length of time until occurrence of the poor outcome were calculated for the moderate and severe headache groups. The differences between the 2 groups were compared using the Log rank test.

Results. During the study period, 124 patients meeting the criteria of TBM were admitted to our department, out of which 95 eligible patients were enrolled in the study. Reasons for exclusion of the other 29 patients are as shown in Figure 1.

Baseline characteristics. The male:female ratio was 0.8. The mean age was 32 ± 13.9 years, and the mean duration of symptoms was 78 ± 54.8 days. Most of the patients had holocranial and throbbing type headaches. Other baseline details are summarized in Table 1. Headache was mild in 22 (23.2%), moderate in 22

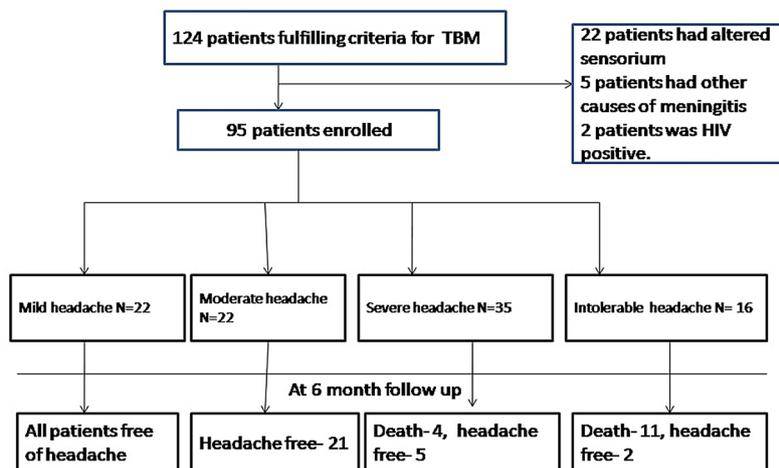


Figure 1 - Flow diagram of study participants among tuberculous meningitis patients assessed for headache severity.

Table 1 - Baseline characteristics among 95 tuberculous meningitis patients assessed for headache severity.

Characteristics	n	(%)
Age (mean±SD)	32.54±13.9	
Male	44	(46.3)
Duration of illness (days) (mean±SD)	78.80±54.8	
History of tuberculosis	24	(25.3)
BMRC staging		
I	21	(22.1)
II	41	(43.2)
III	33	(34.7)
Fever	92	(96.8)
Headache severity		
Mild	22	(23.2)
Moderate	22	(23.2)
Severe	35	(36.8)
Intolerable	16	(16.8)
Vomiting	76	(80.0)
Seizures	44	(46.3)
Diplopia	38	(40.0)
Cranial nerve involvement	52	(54.7)
Hemiparesis	7	(7.4)
Papilledema	55	(57.9)
Optic atrophy	16	(16.8)
Ataxia	7	(7.4)
Paraparesis	5	(5.3)
Vision		
Normal	84	(88.4)
Low vision	7	(7.4)
Blindness	4	(4.2)
Neck rigidity	73	(76.8)
Kerning sign	74	(77.9)
AFB stain positive	23	(24.2)
Culture positive	14	(14.7)
PCR positive	51	(52.7)
Diagnostic category		
Definite	53	(55.8)
Probable	22	(23.2)
Possible	20	(21.0)
MRI findings		
Exudates	38	(40.0)
Meningeal enhancement	42	(44.2)
Hydrocephalus	42	(44.2)
Tuberculoma	35	(36.8)
Infarct	13	(13.7)
Normal	14	(14.7)
Follow up at 6 months		
Death	15	(15.8)
Good outcome (MBI >12)	72	(75.8)
Poor outcome (MBI ≤12)	8	(8.4)

BMRC - British Medical Research Council, MBI - Modified Barthel index, AFB - acid-fast bacillus, PCR - polymerase chain reaction

(23.2%), severe in 35 (36.8%), and intolerable in 16 (16.8%). Most patients had a throbbing (46, 48.4%) headache, followed by sharp (20, 21.05%), stabbing (18, 18.95%), and tight band like (11, 11.6%). The most frequent location of headache was holocranial (57, 60%), followed by frontotemporal (16, 16.8%), frontal (13, 13.6%), fronto-parieto-temporal (5, 5.3%) and occipital (4, 4.2%) (Table 2).

Headache after 6 months. All patients with mild headaches became headache free at 6-month follow

up. Out of 22 patients with moderate headache, only one still had headache, which was mild at the end of follow up. In the severe headache group, 5 (14.85%) became headache free, 4 (11.4%) died, and 26 (74.3%) had mild headache at the end of 6-months follow up. Out of 16 patients with intolerable type headaches, 11 (68.75%) died, 3 (18.75%) had mild headache, and 2 (12.5%) became headache free at end of follow up.

Death or disability at 6 months. Fifteen (15.8%) patients died by 6 months follow up. In the severe headache group, 4 patients (11.4%) died. Out of 16 patients with intolerable type headaches, 11 (68.75%) died. Out of 80 patients who survived, 72 patients had good outcome (MBI >12), and only 8 patients had poor outcome (MBI ≤12).

Predictors of severity of headache. On univariate analysis, holocranial throbbing type headache ($p=0.002$), modified Barthel index <12 ($p<0.001$), diplopia ($p=0.055$), seizures ($p<0.001$), visual impairment ($p=0.024$), cranial nerve palsy ($p=0.002$), meningeal signs ($p=0.016$), definite cases of TBM ($p<0.001$), advanced stage of TBM ($p<0.001$), and CSF protein >2.5 g/l ($p<0.001$) were associated with severity of headache. Neuroradiological features significantly associated with severity of headache were meningeal enhancement ($p=0.015$), basal exudates ($p<0.001$), and hydrocephalus ($p=0.003$) (Table 3). On binary logistic regression analysis, seizure ($p=0.029$), CSF protein >2.5g/L ($p=0.027$) and basal exudates ($p=0.017$) were significant predictors of headache severity. These predictors had high sensitivity (98%), specificity (93.2%), and positive predictive values (94.3%), for prediction of severe headache.

Outcome of tubercular meningitis after 6-months. On univariate analysis, factors associated with poor outcome were stabbing headache ($p=0.006$), cranial nerve involvement ($p=0.009$), hemiparesis ($p<0.001$), paraparesis ($p<0.001$), CSF protein >250 mg/dl ($p=0.005$), advanced stage (stage III) ($p<0.001$), and MBI <12 ($p<0.001$). On neuroimaging, infarct ($p<0.001$) was associated with poor outcome. On binary logistic regression analysis, cranial nerve involvement ($p=0.003$), paraparesis ($p=0.006$), CSF protein >250mg/ dl ($p=0.025$), and infarct ($p=0.001$) were associated with poor outcome.

The Kaplan-Meier survival curves for the length of time until occurrence of the poor outcome were calculated for the moderate and severe headache groups. The difference between the 2 groups was compared using the Log rank test. Results indicated a significant difference between the time to reach poor outcome between the 2 groups (log rank test $p=0.004$) (Figure 2).

Table 2 - Character, location, and lateralization of headache in patients with tuberculous meningitis.

At baseline	Headache n (%)					Death n (%) (N=15)
	Total	Mild	Moderate	Severe	Intolerable	
<i>Character of headache</i>						
Throbbing	46	6 (13.0)	13 (28.3)	21 (45.65)	6 (13.0)	3 (20.0)
Sharp	20	8 (40.0)	4 (20.0)	8 (35.0)	1 (5.0)	1 (6.7)
Stabbing	18	4 (22.2)	3 (16.7)	2 (11.1)	9 (50.0)	10 (66.7)
Tight band like	11	4 (36.4)	2 (18.2)	5 (45.45)	0 0	1 (6.7)
<i>Location of headache</i>						
Holocranial	57	1 (1.75)	10 (17.5)	30 (52.6)	16 (28.1)	15 (100)
Frontal	13	8 (61.5)	4 (30.8)	1 (7.7)	0 (0)	0 (0)
Frontotemporal	16	9 (56.25)	5 (1.25)	2 (12.5)	0 (0)	0 (0)
Occipital	4	2 (50.0)	0 (0)	2 (50.0)	0 (0)	0 (0)
Fronto-parieto-temporal	5	2 (40.0)	3 (60.0)	0 (0)	0 (0)	0 (0)
<i>Lateralization of headache</i>						
Bilateral	69	10 (14.5)	12 (17.4)	31 (44.9)	16 (23.2)	15 (100)
Unilateral	26	12 (46.15)	10 (38.5)	4 (15.4)	0 (0)	0 (0)

Table 3 - Significant predictors of headache severity on univariate analysis in tuberculous meningitis (TBM) patients.

Characteristic	Headache n (%)					Significance	
	Total	Mild	Moderate	Severe	Intolerable	χ^2	P-value
CSF protein >250mg/dl	37	1 (2.7)	2 (5.4)	20 (54.05)	14 (37.84)	39.93	0.000
Cranial nerve involvement	52	7 (13.5)	15 (28.85)	16 (30.8)	14 (26.92)	14.35	0.002
Vision involvement	30	3 (10.0)	4 (13.3)	16 (53.3)	7 (23.33)	9.43	0.024
Seizure	44	3 (6.8)	3 (6.8)	28 (63.6)	10 (22.73)	36.55	0.000
Neck rigidity	73	12 (16.4)	17 (23.3)	32 (43.8)	12 (16.44)	10.36	0.016
BMRC stage III	33	0 (0)	7 (21.2)	11 (33.3)	15 (45.45)	41.75	0.000
Headache character - throbbing	46	6 (13.0)	13 (28.3)	21 (45.65)	6 (13.04)	26.47	0.002
Headache location - holocranial	57	1 (1.75)	10 (17.5)	30 (52.6)	16 (28.07)	56.50	0.001
Meningeal enhancement	42	6 (14.3)	6 (14.3)	19 (45.2)	11 (16.84)	10.46	0.015
Basal exudates	38	3 (7.9)	1 (2.6)	22 (57.9)	12 (31.58)	33.67	0.000
Hydrocephalus	42	5 (11.9)	7 (16.7)	24 (57.1)	6 (14.29)	14.19	0.003
MBI <12	56	6 (10.7)	8 (14.3)	27 (48.2)	15 (26.79)	26.55	0.000
TBM diagnosis definite	53	5 (9.4)	10 (18.9)	24 (45.3)	14 (26.42)	23.53	0.001

BMRC - British Medical Research Council, MBI - Modified Barthel index

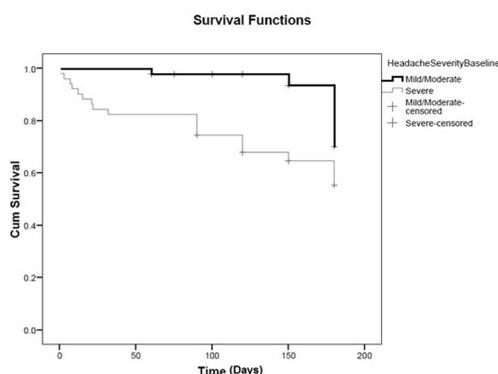


Figure 2 - Kaplan Meier survival curves in tuberculous meningitis patients with headache observed at the time of inclusion in the study.

Discussion. In our study, all patients fulfilled the criteria for headache applied to lymphocytic meningitis.¹³ Headache severity was assessed according to the numeric rating scale.

Headache from infectious diseases originate mainly from meningeal inflammatory reactions, as the meninges are richly innervated by trigeminal nerves. The pathophysiology of the origin of headache in infectious disease is not well understood. Intracranial hypertension syndrome, chemical meningeal irritation, and direct activation of pain-producing structures through stimulation of the trigeminovascular system are all considered in the pathogenic mechanism of headache.¹⁴

After rupture of Rich foci in the subarachnoid space, tubercular bacilli spread into all potential spaces including the interpeduncular fossa, suprasellar, and prepontine cistern, leading to formation of exudates. These exudates spread along the meningeal covering of cranial nerves and blood vessels in subarachnoid spaces, which creates obstruction in the flow of CSF at the tentorial opening, causing hydrocephalus and increased intracranial pressure. The increased intracranial pressure causes stretching of the meninges (richly innervated by trigeminal nerves), and thus produces headache. Cytokines play a central role in the neuropathogenesis^{15,16} of tubercular granuloma¹⁷ formation, altered blood-brain barrier permeability, and CSF leukocytosis.^{18,19} Microglia and astrocytes in the brain produce different cytokines in response to bacterial infections. Tumor necrosis factor (TNF)- α , interleukin (IL) -6, IL- β , CCL2, CCL5, and CXCL10²⁰ are important cytokines associated with generation of pain,²¹ and inflammation.

In our study, we found a significant correlation between neuroimaging features and severity of headache. Forty-two (44.2%) patients had hydrocephalus, out of which 30 (71.4%) patients had severe (57.1%), and intolerable (14.3%) headache. Meningeal enhancement and basal exudates, which are markers of inflammation, are also associated with severity of headache. Out of 42 patients who had meningeal enhancement, 30 patients belong to the severe and intolerable category. Basal exudates were present in 38 patients, in which 34 (89.5%) had severe and intolerable headache.

In TBM, the basal exudates are usually most pronounced around the circle of Willis, and they produce a vasculitis like syndrome. Inflammatory changes in the vessel wall may be seen, and the lumen of these vessels may be narrowed or occluded by thrombus formation. The vessels most severely involved are those located at the base of the brain, which include the internal carotid artery, proximal middle cerebral artery, and perforating vessels. The most common site of infarction is around the Sylvian fissure and basal ganglia.

Infarction in tuberculous meningitis is because of vasculitic changes in the small arteries of the vertebrobasilar system and middle cerebral artery. Encircling of these vessels by exudates contributes to vasculitic changes and results in infarct.²² The basal ganglion, and the areas around the Sylvian fissure are the most common sites of infarction.¹⁶ Vasculitic changes in the brain are associated with headache. In our study, out of 13 patients who had infarct, 4 patients had severe, and 4 had intolerable headache.

Increased total leukocyte count (TLC), and protein

in CSF is associated with a disrupted blood-brain barrier and is a marker of the inflammatory reaction. In our study, increased CSF protein, and TLC were significantly associated with severer headache.

Headache is a common symptom of tuberculous meningitis and is a component of the meningitis triad (fever, headache, and meningeal sign). Headache severity is influenced by many factors in tubercular meningitis like fever, seizure, meningeal sign, increased intracranial pressure, hydrocephalus, basal exudates, meningeal enhancement, and vasculitic changes. Some of these inflammatory changes in the brain parenchyma, as well as in the meninges, result in permanent fibrotic changes and these changes could be the generator of headache during the disease process as well as even after resolution of infection (post meningitic headache). In our study, meningeal enhancement, basal exudates, and hydrocephalus were significantly associated with severity of headache. Out of 51 patients with intolerable and severe headache, only 7 (19.4%) became headache free at the end of 6 months. These findings indicate a severe inflammatory reaction and permanent changes in the brain that produces episodic headache in the intolerable and severe headache group. Therefore, in patients of suspected tubercular meningitis, severity of headache can be used as marker of severe inflammatory changes in the brain if advanced neuroimaging techniques are not available. The mild and moderate headache group was associated with good outcome and most of the patients became headache free during 6-month follow up. One important limitation of our study was patients with TBM who presented to us with altered sensorium were excluded as they could not provide a proper account of their headache. This led to the exclusion of 22 patients.

In conclusion, headache severity in patients with TBM is an important clinical tool for assessment of inflammatory changes in the brain in the absence of neuroimaging facilities, especially in poor countries, and these changes are associated with poor outcome. Patients with TBM with intolerable and severe headache are at increased risk of poor outcome; therefore, they should be monitored more carefully to avoid adverse clinical outcome. In our study, 30 patients had mild intensity headache at the end of 6-month follow up. Therefore, these patients should be followed for at least 3-months after completion of treatment for signs of post meningitic headache.

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