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# Tuberculous and Cryptococcal Meningitis in a Setting with High TB and Low HIV Prevalence

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## ABSTRACT

**Objective:** To compare the differences in presentation and outcome of patients with tuberculous meningitis (TBM) and cryptococcal meningitis (CCM).

**Study Design:** Case series.

**Place and Duration of Study:** The Aga Khan University Hospital, Karachi, from December 1995 to December 2005.

**Methodology:** Patients with a confirmed diagnosis of TBM or CCM were included in this study. The signs and symptoms, laboratory findings and other variables of patients were entered and analyzed by Statistical Package for Social Sciences (SPSS) Software version 14.

**Results:** We compared 16 patients of TBM with 11 of CCM. None of the patients with TBM were Human Immunodeficiency Virus (HIV) positive while 4 patients with CCM had HIV. The common initial signs and symptoms in patients with TBM were fever, altered mental status and headache; and in patients with CCM were fever, headache and cough. The mean CSF glucose level decreased according to the Medical Research Council (MRC) stage in TBM. The mean CSF RBCs, WBCs, glucose and protein in TBM were 2010/mm<sup>3</sup>, 228/mm<sup>3</sup>, 52.32mg/dL and 289.48mg/dl respectively and in CCM were 178.54/mm<sup>3</sup>, 529.54/mm<sup>3</sup>, 32.63mg/dL and 432.18mg/dL respectively.

**Conclusion:** TBM and CCM should be suspected in all cases that present with symptoms of chronic meningitis. Patients with TBM are more likely to have altered mental status and higher CSF RBCs; those with CCM are more likely to have headache, cough and higher CSF WBCs.

**Key words:** Meningitis. Tuberculous. Cryptococcal.

## INTRODUCTION

The classification of meningitis can be based on its underlying cause or time course of the illness. It can be classified as acute or chronic based on the time course. The two most common types of chronic meningitis are tuberculous meningitis (TBM) and cryptococcal meningitis (CCM).<sup>1,2</sup> Tuberculous meningitis is a serious health problem due to high prevalence of pulmonary tuberculosis in most developing countries and the increasing prevalence of HIV infection worldwide.<sup>3,4</sup> In Africa, tuberculous meningitis is the main neurological complication among HIV-infected patients.<sup>5</sup> Also HIV infection is commonly complicated by infection with *Mycobacterium tuberculosis* in areas of high prevalence of tuberculosis. While in areas where the incidence rate is lower such as North America and Western Europe, extrapulmonary infection is seen primarily in adults with

reactivation disease and the dominant form of CNS infection is meningitis. TBM with HIV presents usually with both pulmonary and extra-pulmonary involvement.<sup>6,7</sup> *Mycobacterium tuberculosis* infects the central nervous system in three main forms: cerebral abscess and tuberculoma, meningitis and myelopathy.<sup>8-13</sup> The classic cerebrospinal fluid (CSF) profile in TBM is lymphocytosis, high protein and low glucose.

Cryptococcal meningitis occurs in 5 to 8 percent of patients with the acquired immunodeficiency syndrome (AIDS),<sup>14,15</sup> nevertheless, it is the most common life-threatening opportunistic fungal infection in patients infected with HIV type-1.<sup>14</sup> Cryptococcal meningitis can also be called meningoencephalitis because the brain parenchyma is almost always involved in this disease. The incidence of CCM has increased in recent years and apart from HIV infection, it is also seen in association with extensive antibiotic use and use of immunosuppressive agents.<sup>16</sup> CCM usually has the same clinical features and CSF findings as TBM.<sup>1,2</sup> Visual impairment, marked elevation of CSF pressure, papilledema and normal CSF protein usually occur in CCM, while marked elevation of CSF protein content (> 2 g/L) usually occurs in TBM.<sup>17</sup> However, CSF protein content may be variable and in one study of HIV-infected patients, 43% of patients with TBM had normal CSF protein concentrations.<sup>12</sup>

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Thus, the clinical presentation and CSF findings of TBM and CCM can be similar and it is usually difficult to decide one-way or the other until a confirmed laboratory result detecting the presence of the organism is received. Additionally, the incidence of both TBM and CCM is higher in immunocompromised patients.<sup>18</sup> Usually, these patients undergo complex diagnostic investigations including serological assays, multiple imaging and repeated lumbar punctures. To avoid unnecessary investigations, the type of laboratory testing should be based upon a good history and clinical findings in the patient and the subsequent probability that a specific disease is present.

The specific objective was to find the differences in predisposing factors, presentation, laboratory findings and outcome of patients with TBM and CCM to aid in early diagnosis.

### METHODOLOGY

A comparison of the case series of TBM and CCM was done by a review of patient records and data of patients with confirmed diagnosis of TBM and CCM during a period of 10 years (December 1995 through December 2005) at the Aga Khan University Hospital, Karachi. The selection criteria was a confirmed diagnosis of TBM or CCM. The diagnosis of TBM was confirmed by either a positive CSF culture of *M. tuberculosis* or by signs, symptoms along with suggestive results of investigations and good response to anti-tuberculosis medications. The investigations included biochemical and cytological profile of CSF compatible with TBM and/or suggestive findings on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). The diagnosis of CCM was confirmed by either a positive CSF smear, cryptococcal antigen test of CSF or CSF culture.

Those patients who left the hospital against medical advice after diagnosis and whose full workup was not completed were excluded from the study. Informed consent was also taken allowing the use of medical records for the purpose of research at the time of admission, while keeping the records completely confidential at the same time.

The signs and symptoms, laboratory findings, past medical history, significant concurrent illnesses, factors leading to compromised host status and BCG vaccination status were studied. Data on demographics and complications of illness was also collected as well as the outcome of initial treatment in TBM and CCM. Data was entered in Statistical Package for Social Sciences (SPSS) Software version 14. The mean standard deviations and percentages of relevant variables were calculated. Tests of significance were not performed due to the small sample size.

### RESULTS

The total number of TBM cases were 18. Of those, 2 patients left the hospital against medical advice after diagnosis and data could not be completed from their records, so these patients were excluded from the study. Therefore, a total of 16 cases of tuberculous meningitis were included in this study. Of those, only one patient had positive CSF cultures for *M. tuberculosis*. The CSF cultures were negative for any growth in the rest and the diagnosis was on clinical grounds along with suggestive CSF biochemical and cytological profile and findings compatible with TB on CT or MRI. Of the 16 cases, 12 (75%) were male and 4 (25%) female with a mean age of  $47.56 \pm 11.73$  years. Three had a previous history of pulmonary TB, one had a previous history of TB meningitis, and two had a previous history of hydrocephalus and a ventriculo-peritoneal shunt. None of the patients were HIV positive.

The main initial signs/symptoms of the patients at presentation were fever (81.3%), altered mental status (68.8%), headache (62.5%), vomiting (56.3%), neck stiffness (56.3%), seizures (25%) and weight loss (18.8%). Two patients had hemiparesis and 3 had back pain, 2 had photophobia and 3 had cranial nerve abnormalities. The cranial nerves involved were abducens, facial and hypoglossal, one in each of the cases (Table I).

The mean white cell count was of CSF  $228/\text{mm}^3 \pm 291.59/\text{mm}^3$ . Four cases showed a preponderance of neutrophils in CSF while the remaining 11 cases of TBM showed increase in lymphocytes. Mean CSF RBCs were  $2010.75/\text{mm}^3 \pm 4904.93/\text{mm}^3$ . The mean CSF glucose level was  $52.33 \pm 32.33$  mg/dL. In 9 cases, the CSF glucose level was less than 50mg/dL with mean of  $34.44 \pm 9.74$  mg/dL. In 7 cases, the CSF glucose level was greater than 50 mg/dL with a mean  $75.57 \pm 32.54$  mg/dL. The mean CSF protein was  $289.48 \pm 212.69$  mg/dL. Nine patients had a CSF protein of less than 250 mg/dL with a mean  $177.11 \pm 41.13$  mg/dL. Seven patients had a CSF protein of greater than 250 mg/dL with a mean  $433.95 \pm 259.89$  mg/dL. The mean hemoglobin level was  $13.41 \pm 1.64$  g/dL. Nine patients had hemoglobin levels less than 13.7 g/dL with a mean  $12.28 \pm 1.24$  g/dL. The mean blood WBC count was  $12.31 \pm 5.18 \times 10^9/\text{L}$ . Eleven patients had leukocytosis i.e a WBC count greater than the normal value of  $10 \times 10^9/\text{L}$  (mean =  $15.03 \pm 4.07 \times 10^9/\text{L}$ , Table II).

Of the 16 patients with TBM, 3 were determined to be in clinical stage 1 of the Medical Research Council (MRC) criteria (Table III), 11 in stage 2 and 2 in stage 3. The mean CSF glucose level decreased according to the stage. Mean CSF glucose was 65.66 mg/dL in stage 1, 51.45 mg/dL in stage 2 and 38.00 mg/dL in stage 3.

**Table I:** Presenting symptoms and signs in patients with TBM and CCM.

Sign and symptoms	TB Meningitis n=16	Cryptococcal Meningitis n=11
	Number of patients (%)	Number of patients (%)
Fever	13 (81.3)	10 (90.9)
Headache	10 (62.5)	8 (72.7)
Vomiting	9 (56.3)	2 (18.2)
Neck Stiffness	9 (56.3)	4 (36.4)
Cough	1 (6.3)	6 (54.5)
Backache	3 (18.8)	2 (18.2)
Weight loss	3 (18.8)	3 (27.3)
Seizures	4 (25)	1 (9.1)
Photophobia	2 (12.5)	0 (0)
Arthralgia	1 (6.3)	1 (9.1)
Hemiparesis	2 (12.5)	3 (27.3)
Altered mental status	11 (68.8)	4 (36.4)
Cranial nerve involvement	2 (12.5)	2 (18.2)

**Table II:** Lab findings in patients with TBM and CCM.

Lab findings	TB Meningitis		Cryptococcal Meningitis	
	Mean ± standard deviation	Range	Mean ± standard deviation	Range
Hemoglobin (g/dl)	13.41 ± 1.64	5.20	10.75 ± 2.60	8.30
Platelets (x10 <sup>9</sup> /L)	285.5 ± 145.06	486.00	233.27 ± 98.18	270.00
Blood WBCs (x10 <sup>9</sup> /L)	12.31 ± 5.18	20.50	8.7 ± 3.8	14.30
CSF WBCs (/mm <sup>3</sup> )	228 ± 291.59	1038.00	529.54 ± 756.61	2006.00
CSF RBCs (/mm <sup>3</sup> )	2010.75 ± 4904.93	17896.00	178.54 ± 300.92	981.00
CSF PMN (%)	35.20 ± 29.44	88.00	40 ± 39.15	90.00
CSF Lymphocytes (%)	62.13 ± 30.72	88.00	60 ± 39.15	90.00
CSF Glucose (mg/dl)	52.43 ± 30.3	126.00	32.63 ± 26.30	75.00
CSF Protein (mg/dl)	289.48 ± 212.69	1009.00	432.18 ± 761.05	2657.00

WBCs = White blood cells; RBCs = Red Blood Cells; CSF = Cerebrospinal Fluid.

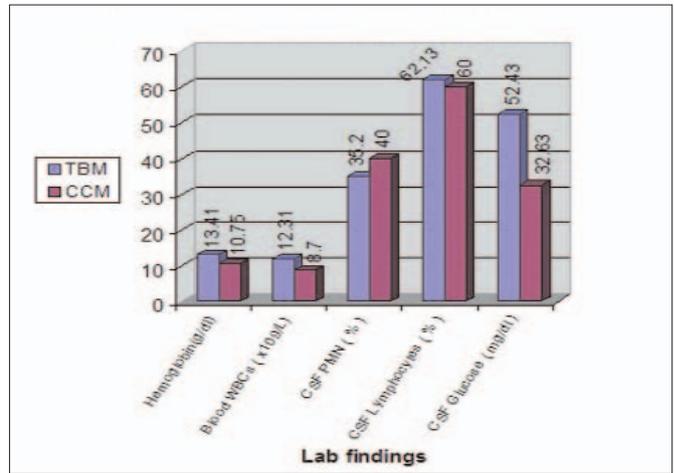
**Table III:** Medical Research Council (MRC) criteria for meningitis.<sup>22</sup>

Stage 1 (early)	Patients with no or minimum signs and symptoms of meningitis and diagnosis mainly based on CSF findings.
Stage 3 (advanced)	Patients who are in deep stupor or comatose or have paresis.
Stage 2 (medium)	Patients whose condition is in between the above two groups.

Apart from symptomatic treatment, Isoniazid, rifampin, pyrazinamide and ethambutol along with corticosteroids were prescribed in all 16 cases and mannitol in 3 cases of TBM. All patients showed marked improvement and were discharged on anti-tuberculosis regimen.

The total number of CCM cases were 12, one patient was excluded from the study because the patient left the hospital against medical advice after diagnosis for treatment elsewhere and complete data could not be obtained. Thus a total of 11 cases of cryptococcal meningitis were diagnosed. Nine patients were male and 2 female. The mean age was 50.63 ± 11.84 years. CSF culture was performed in 7 patients and was positive in all cases. India ink test was positive in 5 cases. Four out of 11 patients were HIV positive. Of those 4, 2 were identified as HIV positive for the first time after a diagnosis of cryptococcal meningitis was made. All HIV positive patients were male.

The main signs and symptoms at presentation were fever (90.9%), headache (72.7%), cough (54.5%) and neck stiffness (36.4%). Others included altered mental



**Figure 1:** Comparison of lab findings in patients with TBM and CCM.

status (36.4%), hemiparesis (27.3%). Cerebral infarction was identified in 3 patients on CT. Two patients had cranial nerve involvement; in one facial and vagus and in the other facial abducens. Three patients had presented at other hospitals initially where anti-tuberculosis therapy was started but were referred within 5 days, as there was no improvement.

The mean CSF white cell count was 529.54 ± 756.61/mm<sup>3</sup>. Seven cases showed an increase in lymphocytes in CSF while 4 showed a preponderance of neutrophils (Figure 1). Mean CSF RBCs was 178.54 ± 300.92/mm<sup>3</sup>. Two patients had normal CSF glucose levels; the rest had decreased CSF glucose. The mean CSF glucose level was 32.63 ± 26.30 mg/dL. Only one patient had normal CSF protein level. The mean CSF protein level was 432.18 ± 761.05 mg/dL. Eight patients had CSF protein levels less than 250 mg/dL with a mean of 151.75 ± 65.53 mg/dL. The mean hemoglobin level was 10.75 ± 2.60 g/dL. Ten patients had hemoglobin levels less than 13.7 g/dL. The mean blood white cell count was 8.7 ± 3.88 x 10<sup>9</sup>/L (Table II).

Of the 11 patients with CCM, 4 were in clinical stage 1, 4 in stage 2 and 3 in stage 3. The mean CSF glucose levels in stage 1, 2 and 3 were 36.75 mg/dL, 11.25 mg/dL and 55.66 mg/dL respectively. The mean CSF protein levels in stage 1, 2 and 3 were 747.25 mg/dL, 296.5 mg/dL and 193 mg/dL respectively.

All patients were treated with a combination of amphotericin B and fluconazole. Except 3 patients who were initially started on anti-fungal treatment, the rest were initially started on anti-tuberculosis therapy on presentation. After positive CSF reports and/or antigen testing, antifungal therapy of amphotericin B and fluconazole was started. All patients were given corticosteroids and 2 patients were also given mannitol. Of the 11 patients, 2 expired during hospital stay, while 9 were discharged.

## DISCUSSION

None of the patients with TBM were infected with HIV. A study in Chile found 30% of patients with TBM infected with HIV out of 53 cases.<sup>19</sup> Four out of 11 patients with cryptococcal meningitis were HIV positive. The remaining 7 patients had no apparent cause for immunosuppression. They had no past medical history of transplant, Hodgkin's disease, sarcoidosis or any condition leading to immunity compromise except in one case in which the patient was diabetic.

There were several differences of signs and symptoms between the two groups (Table I). Nine patients (56.3%) with TBM had vomiting as opposed to 2 (18.2%) patients with CCM. Only 1 patient (6.3%) with TBM had cough, while 6 patients (54.5%) with CCM complained of cough. Altered mental status was more common in patients with TBM. Eleven patients (68.8%) with TBM had altered mental status as opposed to 4 patients (36.4%) with CCM. In the study by Enburg *et al.* 66% of patients with TBM had altered mental status.<sup>19</sup> It is important to note that neck stiffness was not reported in 44% patients with TBM and in 64% patients with CCM. Four patients (25%) with TBM experienced seizures while only 1 (9.1%) with CCM had seizures. It is essential that clinicians are aware that the classic signs and symptoms of meningitis are not present in many patients with the disease. Thus, the index of suspicion must be very high for this disease and CSF analysis done early. Apart from the presenting signs and symptoms, the latest rapid diagnostic tests can be used wherever available, like the *ex vivo* Mycobacterium tuberculosis-specific enzyme-linked immunospot assay (ELISPOT).<sup>20</sup> This assay is able to detect an immune response to *M. tuberculosis* in the CSF of patients and can reliably confirm a diagnosis of tuberculous meningitis. Similarly, enzyme immunoassay can be used for a rapid diagnosis of CCM.<sup>21</sup>

Except one HIV positive case of CCM, in whom the CSF WBC count was within normal range, there was an increase in CSF WBCs in all cases of CCM and TBM. The mean CSF protein in TBM was 52.43 mg/dL as opposed to 32.63 mg/dL in CCM. The mean CSF RBCs in TBM was 2010/mm<sup>3</sup>, while in CCM, it was 178.54/mm<sup>3</sup>. The mean CSF glucose in TBM was 52.43 mg/dL while in CCM, it was 32.63 mg/dL. Thus, the mean concentration of proteins, RBCs, and glucose in the CSF of patients with TBM was higher than those with CCM. It should be noted that a number of patients with TBM have normal CSF glucose levels. Two patients with CCM expired during hospital stay. One of them was HIV positive and the other was diabetic. The rest responded well to initial therapy, completed the course of amphotericin B and were alive till their last follow-up in the clinic.

## CONCLUSION

TBM and CCM should be suspected in all cases that present with symptoms of chronic meningitis. A high index of suspicion is valuable in this setting, which has a high prevalence of tuberculosis. Also, the low prevalence of HIV in Pakistan should not exclude the differential diagnosis of CCM as most of the cases in this study with CCM were not HIV positive. Patients with TBM are more likely to have altered mental status and higher CSF RBCs; those with CCM are more likely to have headache, cough and higher CSF WBCs. The possibility of CCM should be kept in mind and an India ink staining of CSF done wherever available.

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