Profile of Tuberculous Meningitis with or without HIV Infection and the Predicators of Adverse Outcome

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ABSTRACT

Objectives: *To compare the clinical, radiological and cerebrospinal fluid (CSF) findings, at hospital admission, among adult patients with tuberculous meningitis (TBM) with or without HIV infection and to identify the factors that predict adverse outcome at six months.*

Methods: *A total of 82 adult patients with TBM were included (40 HIV-positive and 42 HIV-negative). Several clinical (duration of illness, Glasgow Coma Scale score, presence of high temperature, headache, cranial nerve or sphincter abnormality, seizures and endocrine dysfunction), radiological (presence of hydrocephalus, cerebral infarction and oedema, meningeal enhancement, granuloma) and cerebrospinal fluid parameters (glucose, protein, lactate, lymphocytes, neutrophils and adenosine deaminase values) were recorded along with CD4 count in the peripheral blood. Statistical analysis was performed using the chi-square test. Individual variables were evaluated as prognostic factors for adverse outcome in both groups by calculating the relative risk of association for each.*

Results: *Temperature more than 38.33°C was more common in the HIV-negative group while seizures, hydrocephalus, cerebral infarction and low CD_4 count occurred significantly more commonly in the HIV-positive group. Hydrocephalus had strong association with severe neurological deficit and seizure with death in both the groups.*

Conclusion: *Several clinical and laboratory features of TBM in patients who are HIV-positive are distinctly different from those without HIV infection; some of these have an association with the probability of adverse outcome.*

Perfil de la Meningitis Tuberculosa con o sin Infección por VIH y Predictores de la Evolución Clínica Adversa

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RESUMEN

Objetivos: *Comparar los hallazgos clínicos, radiológicos y del líquido cefalorraquídeo (LCR) entre pacientes adultos con meningitis tuberculosa (MTB) con o sin infección de VIH en su ingreso al hospital, e identificar los factores que predicen la evolución clínica adversa en seis meses.*

Métodos: *Un total de 82 pacientes adultos con MTB fueron incluidos (40 VIH positivos y 42 VIH negativos). Se registraron varios parámetros: clínicos (duración de la enfermedad, puntuación de la Escala de Coma de Glasgow, presencia de alta temperatura, dolor de cabeza, anormalidad del esfínter o nervio craneal, o anormalidad del esfínter, convulsiones y disfunción endocrina); radiológicos (la presencia de hidrocefalia, infarto cerebral, edema, realce meníngeo, granuloma); y del líquido (glucosa, proteína, lactato, linfocitos, neutrófilos, y valores de adenosina deaminasa), junto con un conteo de CD4 en la sangre periférica. Se realizó un análisis estadístico usando la prueba de chi-cuadrado. La variable individual se evaluó como factor pronóstico de la evolución clínica en ambos, calculando el riesgo relativo de asociación para cada uno.*

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Resultados: *Una temperatura de más de 38.33°C fue más común en el grupo VIH negativo, mientras que convulsiones, hidrocefalia, infarto cerebral, y bajo conteo de CD4 ocurrieron significativamente más normalmente en el grupo VIH positivo. La hidrocefalia estuvo fuertemente asociada con un déficit neurológico severo y la convulsión con la muerte en ambos grupos.*

Conclusión: *Varias características clínicas y de laboratorio del MTB en pacientes que son VIH positivos, difieren claramente de aquellos con infección por VIH. Algunas de estas características se hallan asociadas con la probabilidad de una evolución clínica adversa.*

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INTRODUCTION

Tuberculosis remains an endemic disease in developing countries. Diagnosing tuberculous meningitis (TBM) when the patient first presents is still fraught with difficulties and patients are often treated empirically on clinical suspicion before proof of tuberculosis is obtained. The incidence of severe cases, which include miliary tuberculosis, tuberculous meningitis and extrapulmonary tuberculosis are high among HIV-associated tuberculosis cases (1). Conversely, the association of tuberculosis with HIV is a poor prognostic factor in HIV infection (1). As the acquired Immune Deficiency Syndrome (AIDS) epidemic is expanding at an alarming rate, the combination of HIV and tuberculosis may be devastating (1).

AIM

The aim of the study is to compare the clinical, radiological and cerebrospinal fluid (CSF) findings of adult patients with TBM who were HIV-positive with those who were HIV-negative. An attempt was also made to identify the predictors of adverse outcome (death or severe neurologic deficit) at six months in these two groups of patients.

SUBJECTS AND METHODS

Over a period of three years (from January 2004 to December 2006), all the patients with proven or clinically probable TBM who were admitted in the Indoor Wards of our hospital were recruited into the study. A total of 82 patients were included of which 40 were HIV-positive.

When either CSF cultures for tuberculosis or polymerase chain reaction (PCR) for tuberculosis were positive or Ziehl-Neelsen (Z-N) staining showed acid fast bacilli (AFB), the case was classified as definite TB meningitis. All other patients who had tuberculosis at another site with characteristic clinical and CSF findings, or known previous tuberculosis who improved on antituberculous treatment coupled with characteristic clinical and CSF findings were classified as highly probable TBM.

The patients were evaluated clinically and chest X-rays (CXR), contrast-enhanced computed tomography (CECT) scan of the brain, CSF profiles, HIV serology and routine blood tests were done at the time of hospital admission. The HIV status was determined by enzyme linked immunosorbent assay (ELISA) and confirmed by Western blotting where possible.

Clinical features analyzed were duration of illness, level of consciousness at admission (as per Glasgow Coma Scale [GCS]), presence of temperature > 38.33°C, headache, cranial nerve involvement, sphincter abnormality, occurrence of seizures within 24 hours of admission, endocrine dysfunction (syndrome of inappropriate antidiuretic hormone, central diabetes insipidus). Radiological criteria evaluated were presence of hydrocephalus/enlarged ventricles, cerebral infarction, meningeal enhancement, granuloma and cerebral oedema on CECT of brain. Cerebrospinal fluid criteria evaluated were glucose, total protein, lactate, lymphocytes, neutrophils and adenosine deaminase (ADA) values. The CD count was done in all irrespective of HIV serostatus.

Patients were followed-up even after discharge and all the clinical events were recorded for six months. According to outcome at six months, the patients were divided into two groups:

i) A '*good neurological outcome*' – in patients with no neurological deficit (NND) or only a minor neurological deficit (MND) *ie* if they did have evidence of neurological lesion but could return to former level of functioning, and
ii) An '*adverse outcome*' – in patients who either died or had a severe neurological deficit (SND) *ie* were bedridden/could not return to former level of functioning.

Statistical analysis was performed using the chi-square test to evaluate whether significant differences exist for specific tests between the two groups of patients. The relative risk of association for individual variables was calculated to determine the probability of having an adverse outcome in subgroups with that variable.

RESULTS

Comparison of clinical, biochemical and radiological parameters are shown in Table 1. Mean age of the patients was 32.8 years in patients who were HIV-positive and 36.1 years in those HIV-negative. Average duration of illness and mean GCS score was also comparable between the groups. Amongst the clinical symptoms, a temperature reaching > 38.33°C at admission was more common in patients who were HIV-negative and the occurrence of seizures was more common in HIV-seropositive individuals while the incidence of cranial nerve abnormality, sphincter abnormality, and

Table 1: Comparison of clinical and laboratory parameters

Parameter	HIV positive (40)	HIV negative (42)	*p*
Clinical			
Age	32.8 ± 6.8 years	36.1 ± 8.3 years	> 0.5
Average duration of illness	14 ± 2.3 days	12 ± 2.1 days	> 0.5
Average GCS score	12/15	11/15	> 0.5
Temp. > 101°F	5/40 (12.5%)	16/42 (38.1%)	> 0.05
Headache	36/40 (90%)	40/42 (95.23%)	> 0.5
Cranial nerve involvement	6/40 (15%)	8/42 (19.1%)	> 0.5
Sphincter abnormality	1/40 (2.5%)	1/42 (2.38%)	> 0.5
Seizures	12/40 (30%)	4/42 (9.52%)	> 0.05
Endocrine dysfunction	1/40 (2.5%)	1/42 (2.38%)	> 0.5
Radiological			
Hydrocephalus	12/40 (30%)	3/42 (7.14%)	> 0.05
Infarction	11/40 (27.5%)	2/42 (4.76%)	> 0.01
Meningeal enhancement	26/40 (65%)	28/42 (66.7%)	> 0.5
Granuloma	2/40 (5%)	2/42 (4.76%)	> 0.5
Cerebral edema	4/40 (10%)	5/42 (11.9%)	> 0.5
Abnormal CXR	6/40 (15%)	17/42 (40.47%)	> 0.05
Biochemical			
Low CSF glucose	35/40 (87.5%)	34/42 (80.95%)	> 0.5
High CSF protein	38/40 (95%)	39/42 (92.85%)	> 0.5
Elevated CSF lactate	3/40 (7.5%)	4/42 (9.5%)	> 0.5
CSF lymphocytosis	33/40 (82.5%)	36/42 (85.7%)	> 0.5
CSF neutrophilia	5/40 (12.5%)	5/42 (11.9%)	> 0.5
Elevated CSF ADA	36.6 IU	32.3 IU	> 0.5
Mean CD_4 count in blood (per cmm)	184 (Range 7 – 324)	658 (Range 121 – 1320)	> 0.05

endocrine dysfunction were not significantly different between the groups. On CECT of brain, hydrocephalus and cerebral infarction were more commonly associated with HIV infection. However, meningeal enhancement, granuloma and cerebral oedema were equally prevalent in both groups. Neither of the CSF criteria evaluated showed any significant difference between the two groups. In patients who were HIV-positive, the mean CD4 count was 184/cmm (with 60% having a value of < 200/mm^3) compared to 558/mm^3 in patients without HIV infection ($p < 0.01$).

On independent risk factor analysis in patients with HIV infection, a GCS score of less than 9/15, occurrence of seizures and a CD_4 count of less than 200/mm^3 were strongly associated with mortality while the presence of hydrocephalus and cerebral infarction in CECT and cranial nerve involvement on clinical examination were associated with SND (Table 2). In individuals who were HIV negative, the relative risk of death was more in those with seizures and CSF glucose less than 30 mg/dL. Presence of hydrocephalus on cranial CT showed a strong association with SND in this group (Table 2). However most patients with (70%) or without (~90%) TBM did not present with seizure. Only three patients had seizure with temperature > 38.33°C in the HIV-seropositive group; their mean CD_4 count was 213/mm^3.

Table 2: Significant risk factors for death or severe neurological deficit in patients who are HIV-positive and HIV-negative

Parameter	Incidence	Relative risk	Association
Patients who are HIV-positive			
Death (25%)			
GCS score < 9/15	80%	2.01	positive
Seizures	40%	1.4	positive
CD4 count < 200/cmm	90%	3.3	positive
Severe neurological deficit (27.5%)			
Hydrocephalus	36.36%	1.6	positive
Cerebral infarction	36.36%	1.8	positive
Cranial nerve involvement	18.18%	1.29	positive
Patients who are HIV-negative			
Death (19.1%)			
Seizures	25%	1.5	positive
CSF glucose < 30 mg/dl	75%	1.3	positive
Severe neurological deficit (33.33%)			
Hydrocephalus	7.69%	1.04	positive

DISCUSSION

In this study, the aim was to analyse clinical, radiological and CSF findings in TBM cases to evaluate whether HIV infection significantly influences the characteristic findings. The results showed that most of the patients who were HIV-positive were in the AIDS portion of the HIV spectrum (CD_4 count < 200/cmm). They failed to mount a significant rise in temperature owing to underlying immunosuppression and had seizures more commonly due to the presence of a gamut of subclinical CNS diseases (opportunistic infections as well as noninfectious causes). Also hydrocephalus and cerebral infarction were more common in them. Co-existing HIV encephalopathy, opportunistic infections and extensive vasculopathy probably contributed to such radiological findings. Notwithstanding previous reports (2), HIV infection in the patients did not significantly altered the presenting CSF findings.

Berenguer *et al* reported that infection with HIV does not appear to change the clinical manifestations or the outcome of TBM (3). Similar results were found by Bossi *et al* (4). In a study from South Africa, clinical and CSF findings were similar in HIV-infected and uninfected TBM patients but ventricular dilatation and infarcts were more frequent in patients who were HIV-positive and GCS was a better indicator of prognosis than CD_4 count (5). Similar to our observations, one group from India found that many of the clinical, radiological and pathological features of TBM in patients who were HIV-positive was distinctly different from those without HIV infection (6).

The presence of hydrocephalus is an established risk factor for poor outcome in TBM patients while a low GCS score is a predictor of 6-month outcome in HIV-infected patients (2, 7). In addition, disease severity at admission,

presence of focal weakness, prolonged somatosensory evoked potential and absence of corticosteroid use had been shown to be associated with death or poor prognosis in various analyses (7, 8).

REFERENCES

1. Aaron L, Saadoun D, Calatroni I, Launay O, Mémain N, Vincent V et al. Tuberculosis in HIV- infected patients: a comprehensive review. Clin Microbiol Infect 2004; **10:** 388–98.
2. Lu CH, Chang WN, Chang HW. The prognostic factors of adult tuberculous meningitis. Infection 2001; **29:** 299–304.
3. Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A et al. Tuberculous meningitis in patients infected with human immunodeficiency virus. N Engl J Med 1992; **326:** 668–72.
4. Bossi P, Reverdy O, Caumes E, Mortier E, Meynard JL, Meyohas MC et al. Tuberculous meningitis: clinical, biological and x-ray computed tomographic comparison between patients with or without HIV infection. Presse Med 1997; **26:** 844–7.
5. Schutte CM. Clinical, cerebrospinal fluid and pathological findings and outcomes in HIV-positive and HIV-negative patients with tuberculous meningitis. Infection 2001; **29:** 213–7.
6. Katrak SM, Shembalkar PK, Bijwe SR, Bhandarkar LD. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. J Neurol Sci 2000; **181:** 118–26.
7. Misra UK, Kalita J, Roy AK, Mandal SK, Srivastava M. Role of clinical, radiological, and neurophysiological changes in predicting the outcome of tuberculous meningitis: a multivariable analysis. J Neurol Neurosurg Psychiatry 2000; **68:** 300–3.
8. Yechoor VK, Shandera WX, Rodriguez P, Cate TR. Tuberculous meningitis among adults with and without HIV infection. Experience in an urban public hospital. Arch Intern Med 1996; **156:** 1710–6.