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Research Article

CD4 count in patients with HIV and Tuberculous Meningitis co-infection. - A perfect surrogate marker of disease severity?

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Abstract

Introduction: Tubercular meningitis is frequently associated with HIV infection. There have been no markers identified till today which can indicate severity of Tubercular meningitis.

Aim: To test correlation between clinical severity grading and mortality of HIV patients suffering from tubercular meningitis with and to identify surrogate markers of severity of tubercular meningitis.

Material and Methods: We carried out retrospective analysis of the data from the clinical records of HIV infected patients with a diagnosis of TBM admitted between June 2010 to Dec 2012. The neurologic status of patients was classified according to the **BMRC** staging system. Correlation between clinical staging, laboratory parameters was analysed.

Results: Of the 44 cases included in the study 35(79%) were male, 11(21%) were female patients. Thirty two patients (72%) of 44 patients were using antiretroviral drugs at the time of admission. CD4 count was found to correlate with the mortality in the study group. But other factors like age or sex of the patient, patient's hemoglobin or total leucocyte count, and also CSF protein, sugar or cell count- were not found to correlate with the clinical severity grading or mortality.

Conclusion: Only CD4 cell counts correlate with clinical severity grading and mortality of patients with HIV infection suffering from tubercular meningitis.

Keywords: CD4 count, tubercular meningitis, BMRC staging

1. Introduction

Tuberculosis is the most common opportunistic infection in patients with Human immunodeficiency virus.[1] Neurological tuberculosis can sometimes be the initial presentation of HIV.[2] Tuberculous meningitis is the most severe clinical presentation of tuberculosis and cause high mortality and morbidity, particularly in HIV infected individuals in developing countries.[3] HIV infected patients are at increased risk for tuberculous meningitis, but HIV infection does not alter the clinical manifestations, CSF findings and response to therapy,[4,5] however CSF examination may frequently be normal in HIV seropositive subjects with TBM. In such patients radiological clues to the diagnoses of TBM include cisternal enhancement, multiloculated abscesses, communicating hydrocephalus and basal ganglia infarction, which are not the findings associated with CNS lymphoma or toxoplasma encephalitis. Despite recent advances, the early diagnosis of TBM continues to be difficult; lack of sensitivity of acid-fast bacilli staining and nucleic acid-based amplification and

delayed results of cultures make clinical and cerebrospinal fluid abnormalities ideal way to determine the initiation of empirical treatment.[3,6]

Clinical presentation is usually non-specific and particularly complicated in HIV-infected patients, where other diseases, such as cryptococcal meningitis, can show indistinguishable signs and symptoms.[7] TBM is characterized by a slowly progressing granulomatous inflammation of the basal meninges. This inflammatory reaction can lead to a number of complications, such as hydrocephalus, cerebral vascular infarction, cranial nerve palsy and death, if left untreated. Rapid diagnosis and initiation of treatment is therefore necessary to reduce the high mortality and severe sequelae associated with the disease. Diagnosing TBM can be difficult as the symptoms are nonspecific and mimic those of meningitis caused by other microbiological agents or other cerebrovascular events.[7]

2. Materials and Methods

We retrospectively analyzed the data from the clinical records of HIV infected patients with a diagnosis of TBM admitted between June 2010 to Dec 2012 at Karnataka Institute of Medical Sciences, Hubli. Our institute is a major tertiary care and teaching hospital in north Karnataka region, serving predominantly a population of low socioeconomic status. Clinical presentation is usually non-specific and particularly complicated in HIV-infected patients, where other diseases, such as cryptococcal meningitis, can show indistinguishable signs and symptoms.[8] Considering the limitations for rapid diagnosis of TBM (lack of sensitivity of acid-fast bacilli staining and nucleic acid-based amplification tests and delayed results of cultures) and the fact that CSF findings are critical to initiation of anti-tuberculosis agents, the diagnosis of TBM was based of CSF findings. CSF with the presence of pleocytosis (>5 cells/ml), high protein levels (>45 mg/dl), and low glucose levels (<45 mg/dl) was considered 'typical' of TBM. HIV infection was diagnosed by enzyme linked immunosorbent assay (ELISA).

The neurologic status of patients was classified according to the British Medical Research Council (BMRC) staging system, which grades TBM as follows: grade I, patient with non-specific symptoms and signs, no clouding of consciousness, and no neurologic deficits; grade II, patient with lethargy or behavioral changes, meningeal irritation, or minor neurologic deficits such as cranial nerve palsies; and grade III, patient with stupor or coma, abnormal movements, seizures or severe neurologic deficits such as paresis.

2.1 Statistical analysis

The data were analyzed using the software SPSS. Mean and standard deviation for each continuous variable was calculated separately for males and females. The correlation between the age with anthropometric data and components of serum and sex of the patient, blood counts and results of CSF analysis with mortality was tested by Carl Pearson's correlation coefficient method. The impact of several independent predictors on mortality was tested by the logistic regression analysis. The influence of sex of the patient and Antiretroviral therapy on clinical severity staging was assessed by Chi square test.

3. Results

3.1 Clinical and laboratory characteristics

Of the 44 cases included in the study 35(79%) were male, 11(21%) were female patients. The median age of the patients was 37 years. Thirty two patients (72%) of 44 patients were using antiretroviral drugs at the time of admission to the hospital. Ten (22%) patients had extrameningeal tuberculosis in the form of concomitant pulmonary tuberculosis. The classic triad of fever, headache and meningeal irritation were seen in only twenty patients (45%) of the 44 patients studied. Fever and headache were present simultaneously in twenty nine (65%) patients.

The main clinical and laboratory features of the patients are showed in the table below.

Table 1. Baseline characteristics of the patients

Variable	Patients (N=44)
Age, median (years)	37(14-60)
Male, % (n)	79(35)
Symptoms at presentation % (n)	
Headache	65(29)
Altered mentation	77(34)
Focal deficit	09(03)
Seizures	29(10)
Signs at presentation, % (n)	
Fever	93(41)
Meningeal signs	29(13)
BMRC Severity Grade, % (n)	
Grade 1	09(03)
Grade 2	70(31)
Grade 3	21(10)
Extrameningeal tuberculosis, n (%)	21(10)
Prior tuberculosis, n (%)	14(06)
CT abnormalities, n (%)	27(12)
Prior HAART, n (%)	72(32)
CD4+ cell count/ micro lt	96(04-359)

BMRC: British Medical Research Council staging system. CT: Computed Tomography, HAART: Highly Active Anti Retroviral Therapy.

Only few patients among the study group had early grade of tubercular meningitis. Also, CD4 counts were low at presentation in the majority in the group of patients studied. CD4 count was found to correlate with the mortality in the study group. But other factors like age or sex of the patient, patient's hemoglobin or total leucocyte count, and also CSF protein, sugar or cell count- were not found to correlate with the clinical severity grading or mortality as shown below (table 2). The effect of each these independent predictors on mortality was further assessed by logistic regression, which again confirmed major influence of CD4 count on mortality (table 3).

Table 2: Correlation between mortality and other factors by Spearman's rank correlation

Variables	N	Spearman R	t-value	p-level
Age	43	0.2281	1.4998	0.1413
Sex	43	-0.1359	-0.8786	0.3848
On ART	43	-0.2468	-1.6304	0.1107
CD4 count	43	0.3138	2.1159	0.0405*
Protein	43	-0.0359	-0.2302	0.8191
Sugar	43	0.0777	0.499	0.6204
Cell Count	43	0.0868	0.5581	0.5798
HB%	43	0.0132	0.0843	0.9333
Total count	43	-0.1391	-0.8994	0.3737
Gradings	43	-0.1821	-1.1859	0.2425

Table 3: Logistic regression analysis of mortality rate by different factors

Variables	Estimates	Std. Err.	z-value	P-value	[95% Conf. Interval]	
Constant	0.217	3.703	0.06	0.953	-7.0407	7.4748
Age	0.0655	0.0501	1.31	0.191	-0.0327	0.1637
Sex	-0.883	1.0498	-0.84	0.4	-2.9405	1.1745
On ART	-0.471	0.8286	-0.57	0.57	-2.095	1.1531
CD4 count	0.0127	0.0067	1.9	0.058	-0.0004	0.0259
Protein	-0.0037	0.0032	-1.15	0.251	-0.0099	0.0026
Sugar	0.0004	0.0157	0.03	0.977	-0.0304	0.0313
Cell Count	0.0013	0.0019	0.71	0.476	-0.0023	0.005
HB%	-0.1874	0.1966	-0.95	0.34	-0.5728	0.1979
Total count	0	0.0001	0.12	0.902	-0.0003	0.0003
Gradings	-0.3485	0.7133	-0.49	0.625	-1.7466	1.0496

Table 4: Correlation between Gradings and other factors by Spearman's rank correlation

Variables	N	Spearman R	t-value	p-level
Age	43	0.0317	0.2033	0.8399
Sex	43	0.2233	1.4667	0.1501
On ART	43	0.1946	1.2705	0.2111
CD4 count	43	-0.3493	-2.3868	0.0217*
Protein	43	-0.048	-0.3078	0.7598
Sugar	43	-0.045	-0.2882	0.7747
Cell Count	43	-0.0477	-0.3056	0.7614
HB%	43	-0.2495	-1.6499	0.1066
Total count	43	0.1109	0.7145	0.479

*p<0.05

Tubercular meningitis clinical grading correlated with CD4 counts, (table 4), but, there was no association between tubercular meningitis clinical severity grading and sex of the patient (table 5) or anti retroviral therapy (table 6).

Table 5: Association between sex and gradings

Gradings	Male	%	Female	%2	Total
1	3	75	1	25	4
2	23	88.46	3	11.54	26
3	8	61.54	5	38.46	13
Total	34	79.07	9	20.93	43

Chi-square= 3.8404 df=2 p=0.14662

Table 6: Association between on ART and gradings

Gradings	No	%	Yes	%2	Total
1	3	75	1	25	4
2	23	88.46	3	11.54	26
3	8	61.54	5	38.46	13
Total	34	79.07	9	20.93	43

Chi-square= 1.6816; df=2; p=0.43158

4. Discussion

Human Immunodeficiency Virus (H.I.V.) infection has become widely spread all over the world for last three to four decades. Tuberculosis is very closely associated with H.I.V. infection. Tubercular meningitis, a severe form of tuberculosis is observed frequently in individuals with Acquired Immune Deficiency Syndrome (A.I.D.S.) and has been identified as one of the AIDS defining illnesses. CD4 count has been well accepted as a marker of severity of HIV infection. However, till now, it is not clearly known whether CD4 count correlates with mortality in patients with tubercular meningitis also. We conducted this study to identify the laboratory parameters which could be used as surrogates of clinical severity grading of tubercular meningitis. We graded patients according to clinical severity and tested correlation of various laboratory parameters including CD4 cell count, CSF cytology and biochemical findings with clinical severity. We have found only CD4 counts to be correlating with the clinical severity of TBM. None of the other factors including age& sex of the patient, hemoglobin, total leukocyte count, CSF cytology or biochemical findings were found to correlate with TBM clinical severity staging.

Tuberculosis occurs in patients with any stage of HIV disease. In developing countries, 25 to 65% of patients suffering from HIV-infection have been reported to have co-infection with tuberculosis of one the organs.[9] Tubercular co-infection is common in HIV infected and more so with falling CD4 cell level.[10] The diagnosis of tubercular meningitis is often very difficult because of the varied cerebrospinal fluid (CSF) changes, which may vary from acellular with normal glucose to lymphocytosis or neutrophilia.[11,12] Preliminary reports suggest that that the ELISPOT assay may be useful tool to rule-in tuberculosis.[13-16] But, ELISPOT cannot be used to rule-out TBM. We attempted to identify laboratory parameters which can be used as surrogates of clinical severity of tubercular meningitis. We found only CD4 counts to be correlating with clinical severity grading as well as mortality. None of the other laboratory parameters correlated with clinical severity or mortality.

Several others studies have studies prognostic factors in patients witn tuberculous meningitis. Hristea *et al*.,[17] have concluded that HIV infection is associated with increased mortality in patients with TBM and that the mortality is more in patients with lower baseline CD4 counts. Predictors of adverse outcome in tuberculous meningitis was also studied by Bandyopadhyay *et al*,[18] who found hydrocephalus to be associated strongly with adverse outcomes. Age, stage of the disease, focal weakness, cranial nerve palsy and hydrocephalus have been found to correlate with adverse outcomes in a study on patients with tubercular meningitis.[19] Thus, though clinical staging is a useful guide indicating prognosis in patients with tuberculous meningitis with HIV co-infection, there are no definite laboratory parameters to rely upon as a guide for assessing prognosis in this condition.

5. Conclusion

Only CD4 cell counts correlate with clinical severity grading and mortality of patients with HIV infection suffering from tubercular meningitis and hence is a very good surrogate marker of disease severity. Other laboratory parameters like hemoglobin, leucocyte count, CSF biochemical and cytology findings cannot be used as surrogates of clinical severity grading.

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