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A COMPARATIVE STUDY OF TB MENINGITIS IN HIV+ve AND HIV-ve PATIENTS

Medicine

Dr. Saiyed Rana	Consultant Cardiologist, NH - RN Tagore International Institute of Cardiac Science, Kolkata.
Dr. Manotosh Sutradhar	Assistant Professor, Department of Critical Care Medicine, IPGME&R, Kolkata.
Dr. Meghdeepa Sengupta	Junior Resident, Department of Medicine , Calcutta Medical College and Hospital , Kolkata.
Dr. Ritabrata Mitra*	Assistant Professor, Department of Pulmonary Medicine, IPGME&R, Kolkata. *Corresponding Author
Dr. Sisir Chakraborty	Assistant Professor, Department of General Medicine , College of Medicine and Sagore Dutta Hospital.
Dr. Indranil Thakur	Assistant Professor, Department of Medicine , Diamond Harbour Medical College and Hospital.
Dr. Debarshi Jana	Young Scientist, IPGME&R and SSKM Hospital, Kolkata.
Dr. Amitabha Sengupta	Professor and Head, Department of Pulmonary Medicine, IPGME&R, Kolkata.

ABSTRACT

Aim: To study the difference in clinical presentation, baseline laboratory parameters, radiological parameters, CSF picture, response to treatment, in-hospital outcome, final outcome in follow up & any parameters signifying poor outcome in advance in patients of TBM both in HIV+ve& HIV-ve group.

Material and methods: This comparative non-randomised prospective study was conducted from 16th June,2012 to 15th June,2013 in Medical College Hospital. Total 53 patients were referred where 23 patients had TB Meningitis with HIV and 30 patients had TB Meningitis without HIV.

Result: In our study we have found no statistically significant differences in age distribution, and distribution of symptoms at presentation. The classical symptoms like fever, headache, and vomiting, altered sensorium all are present in both groups and the differences are not statistically significant.

Conclusion:HIV+ve patients show relatively less intense reduction of CSF sugar level in relation to blood sugar level estimated simultaneously.Two factors with high mortality are advanced stage of TB meningitis at presentation, low CD4 count.

KEYWORDS

TB meningitis, Mortality, Baseline laboratory parameters.

INTRODUCTION

The increasing rate of human immunodeficiency virus(HIV) infection in many countries has had an impact ontuberculosis (TB) epidemiology. While TB prevalence hasremained stable, TB incidence continues to rise, especiallyin countries most severely affected by the HIV epidemic aswell as those facing political turmoil, migration, poverty andunemployment and where intravenous drug abuse is rampant.HIV is the most important known risk factor that promotesprogression to active TB in people with Mycobacterium tuberculosis infection (TB/HIV A Clinical Manual 2004)[1].The lifetime risk of tuberculosis in immunocompetentpersons is 5% to 10%, but in HIV positive individuals, thereis a 5% to 15% annual risk of developing active TB disease(Swaminathan et al 2000)[2]. WHO estimated 9.2 millionnew cases of TB globally in 2006 (139 per 100,000); ofwhom 7,09,000 (7.7%) were HIV positive (World HealthOrganization 2008)[3]. India, China, Indonesia, South Africaand Nigeria rank first to fifth in terms of incident TB cases.

In India, there were 2.5 million people living with HIVand AIDS (PLWHA) at the end of 2007 while the incidenceof TB was approximately 1.8 million cases per year (WHORelease 2007, RNTCP 2008). In a survey carried out amongnew tuberculosis patients by the Revised National TBcontrol Program (RNTCP) in 2007, HIV sero-prevalencevaried widely and ranged from 1% to 13.8% across the 15districts (Central TB Division, unpublished observations). Currently, it is not clear what role the HIV epidemic hasplayed in the TB situation in India. If HIV prevalence inthe community continues to increase, however, it couldaffect the TB control program, by decreasing cure rates andincreasing mortality and recurrent TB.

To study the difference in clinical presentation, baseline laboratory parameters, radiological parameters, CSF picture, response to treatment, in-hospital outcome, final outcome in follow up & any parameters signifying poor outcome in advance in patients of TBM both in HIV+ve& HIV-ve group. We would also like to study if there are any differences in parameters like age and sex distribution in between these two groups.

1. To see if there is significant difference regarding Stage of disease (BMRC Classification TB Meningitis) at presentation.
2. To see if there are significant differences in clinical parameters like distribution of fever, neck rigidity, vomiting, altered sensorium, nerve palsy, lymphadenopathy in between these two groups.
3. To see if there is any significant differences in baseline laboratory parameters like Blood Count, Sugar, Urea, Creatinine, LFT, Serum Electrolytes , serum albumin, serum globulin level.
4. To see if there is any differences in special laboratory parameters like CT Scan Brain, CSF analysis at presentation and after 10 days of giving ATD & other therapy.
5. To see if there is any differences in demographic profile like age, sex distribution in between these two groups.
6. To see if there is significant difference in in-hospital outcome between these two groups
7. To see if there is any significant differences in final outcome in between these two groups on follow up.

MATERIAL AND METHODS

PLACE OF STUDY:

- Dept. of Medicine, Medical College Hospital
- Dept of Neurology, Medical College Hospital

- School of Tropical Medicine, Kolkata
- APEX CLINIC, Medical College Hospital

STUDY PERIOD: 1 year starting from 16th June,2012 to 15th June,2013

SAMPLE SIZE: Total 53
TB Meningitis with HIV-23
TB Meningitis without HIV-30

SAMPLE DESIGN:
INCLUSION CRITERIA:
A patient with fever, headace, vomiting, altered sensorium, neck rigidity were considered as a case of tubercular meningitis if followings are present

1. **PRESUMPTIVE DIAGNOSIS-** CSF picture presumptively suggestive of tubercular meningitis, which is confirmed by improvement followed by ATD therapy
2. **PROBABLE DIAGNOSIS-**CT brain or MRI brain suggestive of tubercular meningitis.
3. **DEFINITIVE DIAGNOSIS-** Presence of AFB in ZN smear from CSF.

EXCLUSION CRITERIA:
1. Age less than 12 years
2. Presence of other co morbid condition (advanced cardiovascular disease, advanced renal failure) which affects the outcome of treatment.
3. Simultaneous co infection with cryptococcal and toxoplasma meningitis.
4. Tubercular meningitis in immunocompromised condition other than AIDS(like aplastic anemia, leukemia, patient on immunosuppressive drugs).
5. Cases of TB meningitis with previously existing neurodeficit.

STUDY DESIGN:
This is a comparative non-randomised prospective study.

STATISTICALANALYSIS-
Collected data are put on master chart. Continuous and discrete both variables in both groups werecompared with the help of appropriate statistical test like student t test, paired t test, chi square test, fisher's exacttest, ANOVA test etc. statistical software used are SPSS, IBM version 17 and EPi-info. Before analysis was startedthe data were coded suitably as per consultation with statistician of Dept. Preventive & Social Medicine. This wasdone to facilitate analysis. The results were then rechecked and represented appropriately with the help ofdiagrams like pie chart, bar diagram etc for better understanding. A P value <0.05 is considered to be significantin this study.

RESULTAND DISCUSSION
During analysis of result it is found that there is male sex predilection in HIV+ve group. There are 19 male patients out of 23 in this group whereas the sex distribution is almost equal in HIV-ve group. This difference is found to be statistically significant with a p value of 0.04. So the findings are statistically significant. The difference in our study might be due to a confounding factor due to the fact that not all female HIV patients can reach to tertiary care centre like STM, KOLKATA due some social factor. During our OPD follow up we have seen that female patients with HIV were always blamed and socially isolated more than male counterparts. The matter complicates much more when the same female patients develop tuberculosis in any form. It is the time when the family member loses interest in her. We have seen in our study that many male patients who were HIV positive and were working abroad secretly marrying HIV negative girl, completely concealing their disease status deliberately. But this cannot be the only factor behind this sex predilection for male patients. There are several studies worldwide where it was found that HIV with TB meningitis is much more common in male patients than female patient with HIV. [4,5]

In our study we have found no statistically significant differences in age distribution, and distribution of symptoms at presentation. The classical symptoms like fever, headache, and vomiting, altered sensorium all are present in both groups and the differences are not statistically significant. However the mean duration(in days) of those symptoms are less in HIV positive group may be due to the fact that these groups are more in contact with health care systems. But it is a well known fact that in HIV positive patients the GCS deteriorate rapidly once they develop TB meningitis. [6] Among HIV positive group 11 patients were diagnosed for first time, the rest were previously diagnosed as HIV positive. The CD4 count status was on better side among those patient who were on observation and yet to start ART. CD4 count was on poorer side among those who were first diagnosed during this illness.

Among signs, neck rigidity was found to be more prevalent in HIV negative group and this difference is extremely significant with a p value <0.001. This may due to the increased level of inflammation of meninges in this group due to intact cell mediated immunity. This finding is consistent with several previous studies that neck rigidity is less common in HIV infected group with TB Meningitis. [7]

No statistically significant differences in grading of TB meningitis (BMRC Criteria) at presentation was foundthough grade 3 is more common in HIV+ve group and grade 2 is more common in HIV-ve group.May be a study with large sample can prove this observation to be statistically significant. According to previousstudies HIV positive patients with TB meningitis tends to present with poor GCS than HIV negative group. [7]

No difference was found regarding CT scan brain abnormality if considered overall. Most commonly the lateral and third ventricles were dilated and it is present in both group. No significant difference was noted regarding presence of CT brain abnormality other than ventricular dilatation like presence of basal adhesion, tuberculoma, and infarction. Though a tendency was noted that tuberculoma was present more in HIV+ve patients and basal adhesion, infarction was noted more in HIV-ve group (Bar diagram-3). A larger study with large sample size is needed to prove any significance. There is one study favouring this fact that vasculitis like phenomenon like infarction, thrombosis, basal adhesion are less common in HIV infected patients and CNS tuberculoma is much more common in these patients. [8]HIV+ve patients are found to be more anaemic than HIV-ve counterpart and this difference is found to be extremely significant with a p value <0.0001. This is consistent with findings of previous study.

Hyponatremia was almost auniversal laboratory finding in both group but no statistically significant difference was noted regarding distribution. Comparation for hyponatremia is done at the level of serum Na<120meq/dl. The cause of this hyponatremia is SIADH and cerebral salt wasting syndrome. statistically extremely significant (p<0.0001) difference was noted regarding cellular response in CSF with more robust cell count in HIV-ve group.

Same kind of difference was also found regarding level of raised CSF protein level with p value 0.01. For comparation of CSF protein level, a value >400mg/dl of CSF is considered as the very high level with chance of shunt blockage is high at this level. The CSF sugar value was much more reduced compared to plasma value in HIV-vegroup(p <0.0003). Normally CSF sugar is said to be low if the ratio of CSF sugar/blood sugar is <1/3. But no significant difference is noted when compared at this level. When compared at the level of <1/6 (extreme low CSF sugar compared to blood) there is statistically significant differences. This finding is extremely significant and is due the fact that more is the cellular response, less is the CSF sugar level. ZN smear was more frequently positive in HIV+ve group but this difference is not statistically significant may be due small sample size of this study. One study revealed that smear positivity is more common in HIV positive group. [9]

A comparation was done regarding CSF ADA level in this study and statistically significant difference was found at value level of 10 IU/ml. The p value is 0.008. So there must be a rethinking on cut-off value of CSF ADA level in HIV+ve patients just like cut off value of mantoux test. Recent studies revealed that a CSF ADA level of 10 IU/ml has 90% sensitivity for diagnosing TB meningitis but this is not applicable for certain situations like CNS lymphoma or HIV positive with TB meningitis. [10]

Serum albumin level of >3.5 gm/dl is considered to be normal in this study and it is found that many patients in HIV+ve group has in fact serum albumin level lower than that. This finding is statistically significant with p value <0.0001. In same kind of comparation for serum globulin level (normal is <3.5gm/dl) the p value is found to be <0.0001 which is also extremely significant. It is an expected findings since HIV+ve patients tends to have high serum globulin due to aberrant antibody production and albumin reduction is part of acute inflammation as a negative marker.

Though in-hospital outcome is not statistically significant between these groups, a significant difference was found in final outcome during follow-up with a p value of 0.0001. In hospital and follow-up mortality, both are much higher in HIV+ve patients with TB meningitis as revealed by numerous studies done previously.

In our study the HIV+ve patients were further subdivided as per CD4 count and it is noted that mortality is higher if CD4 count is low. Also markers of cellular inflammation like basal adhesion in CT brain, neck rigidity, cranial nerve palsy, were also higher if CD4 count is on the higher side. Patients with low CD4 count tend to present with severe grade of TBM. Also these patients has low CSF cell count, low CSF protein level. The 4 patients whose CSF was positive in ZN stain in this group and another 4 in this group who shows tuberculoma in CT brain, all of them had CD4 count less than 100. Also in our study we found 3 patients in HIV-ve group who shows persistent headache and vomiting despite improvement of other symptoms on therapy. Repeat CSF study showed normal cell count, normal CSF sugar level with very high CSF protein level in range of more than 3000mg/dl. On CT brain imaging communicating hydrocephalus was present in all of them with dilated lateral, third, aqueduct, and fourth ventricles. Two of these patient required VP shunt placement for relieve of symptoms. One patient improved subsequently on acetazolamide. Among two patients with shunt placement one patient died within one year, the cause is unknown to us since we lost follow up. Other patient is doing well till date with completion of ATD. Prevalence of drug induced hepatitis is found in both group with 3 in HIV-ve group & 2 in HIV+ve group. 2 patients in HIV+ve group were discharged in vegetative condition who died subsequently in home. So the neuromorbidity is also higher in case of TB meningitis co infected with HIV. [11]

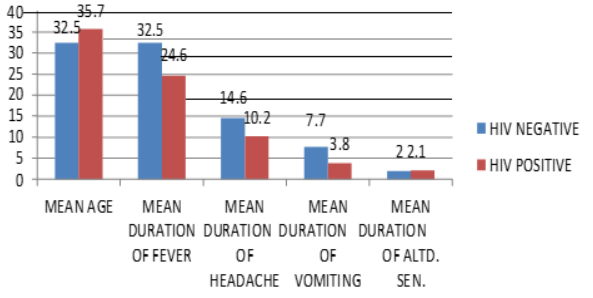

Diagram 1. The classical symptoms like fever, headache, and vomiting, altered sensorium all are present inboth groups

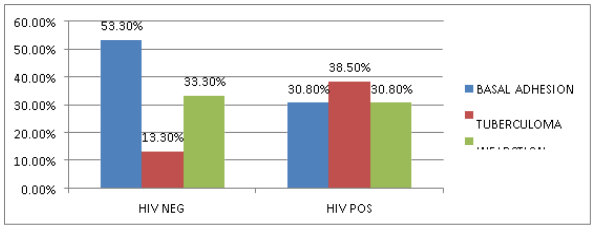

Diagram 2

CONCLUSION

1. TB meningitis is more common in male patients in HIV positive group.
2. There is no difference in age distribution in between these two groups.
3. Mortality is high in case of TB meningitis associated with HIV infection.
4. There is no significant difference in distribution of presenting symptoms in between these two groups.
5. Neck rigidity is more common in HIV-ve group.
6. Anaemia is significantly higher in TB meningitis associated with HIV.
7. No significant differences in overall abnormality in brain imaging (CT Scan Brain).
8. HIV+ve patients show less cellular response in CSF.
9. HIV+ve patients show less rise of CSF protein level.
10. HIV+ve patients show relatively less intense reduction of CSF sugar level in relation to blood sugar level estimated simultaneously.
11. Hyponatremia is present in both group and no difference is present regarding severity of hyponatremia and distribution of hyponatremia.
12. HIV+ve group has hypoalbuminemia and hypergammag lobulinemia significantly more than HIV-ve group.
13. Two factors with high mortality are advanced stage of TB meningitis at presentation, low CD4 count.

Apart from those findings which are statistically significant there are few more obvious findings which are not statistically significant, may be due to less sample size. These are worth to be mentioned. May be another study with large sample size may prove their significance.

1. Though there is no difference in overall abnormality of CT scan brain, the pattern of abnormality is something differs. Tuberculoma is more common in HIV+ve patients with low CD4 count but basal adhesion and vasculitis like phenomenon is more common in HIVve patients.
2. Though there is no difference regarding stage of TBM at presentation but stage 3 is more common in HIV+ve patients and stage 2 is more common in HIV-ve patients.
3. Communicating hydrocephalus is the most common type of hydrocephalus in both groups.
4. Morbidity is also higher in case of HIV+ve group.
5. Requirement of shunt placement is higher in HIV-ve patients.

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