Study of Cryptococcal Meningitis in HIV Seropositive Patients in a Tertiary Care Centre

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Abstract

Objectives: With the increase in the incidence of HIV infection, there is an increase in incidence of cryptococcal meningitis. The present study was taken-up to study the various manifestations of cryptococcal meningitis with respect to its clinical manifestations, diagnostic features, and response to therapy.

Methods: All patients who presented with features suggestive of meningitis and a low CD4 count were initially screened for cryptococcal meningitis. 100 HIV seropositive patients who were diagnosed to have cryptococcal meningitis based on CSF culture of Cryptococcus neoformans were included in the study.

Results: Most of the patients (77%) were in the age group of 26 - 40 years. Headache (95%), vomiting (76%), and fever (70%) were the most common presenting symptoms. Mean CD4 count was 60.27 ± 41.51 (range 4 - 192). Presenting symptoms in cryptococcal meningitis and mixed infection were similar. Raised CSF proteins, and CSF pleocytosis was significantly more in patients with mixed infection. Altered sensorium and CD4 count of ≤ 50 was associated with poor prognosis.

Conclusion: In half of the patients, cryptococcal meningitis was the AIDS-defining illness. Majority of the patients had an acute to subacute presentation and India ink negativity does not rule-out cryptococcal meningitis. Response to therapy with amphotericin B and fluconazole is well tolerated with a good recovery.

Key words: Opportunistic infection, AIDS, cryptococcus neoformans, amphotericin B.

Introduction

Cryptococcal meningitis is a common opportunistic infection and AIDS-defining illness in patients with late stage HIV infection, particularly in South-east Asia and Southern and East Africa1,2. With the increase in the incidence of HIV infection, there is an increase in incidence of cryptococcal meningitis3. Cryptococcus neoformans is the leading cause of meningitis in patients with AIDS4.

Cryptococcal meningitis also occurs in patients with other forms of immunosuppression and in apparently immunocompetent individuals. Cryptococcal meningitis has been reported as the most common opportunistic infection of the CNS of Indians patients with HIV5-7. It is the initial AIDS-defining illness in ~ 2% of patients and generally occurs in patients with CD4 counts < 100/µl8,9. Most of the patients have an acute to subacute presentation.

Mortality from HIV-associated cryptococcal meningitis remains high (10 - 30%), even in developed countries, because of the inadequacy of current antifungal drugs and combinations, and the complication of raised intracranial pressure10. However, the expansion of antiretroviral programmes now raises the prospect of transforming the long-term prognosis of these patients, provided that they survive the acute phase of the illness.

Bowring and Lady Curzon Hospital is a referral centre for HIV seropositive patients. After the establishment of antiretroviral therapy centre, the number of patients being referred with HIV/AIDS has increased considerably and more and more cases of cryptococcal meningitis are diagnosed.

Hence the present study was taken-up to study the various manifestations of cryptococcal meningitis with respect to its clinical manifestations, diagnostic features, and response to therapy.

Material and methods

Patients

100 patients of Cryptococcal meningitis who were HIV seropositive were studied prospectively at the Bowring and Lady Curzon Hospitals attached to Bangalore Medical...
College, Bengaluru. The study was done over a period of 30 months from October 2004 to March 2007.

All patients who presented with features suggestive of meningitis and a low CD4 count were initially screened for cryptococcal meningitis. All the HIV seropositive patients who were diagnosed to have cryptococcal meningitis based on CSF culture of Cryptococcus neoformans were included in the study.

Exclusion criteria included cryptococcal meningitis in patients who were not HIV seropositive, and children < 12 years of age.

**Laboratory methods**

CSF analysis was done for proteins, sugar, cell count, cell type, India ink smear, cryptococcal antigen, and cryptococcal culture. Cryptococcal antigen was demonstrated by latex agglutination test (latex Crypto Antigen Detection System, Immuno-Mycologics, Oklahoma, USA). Cryptococcal culture was done using Sabouraud’s dextrose agar and the cultures were incubated at 37°C. ELISA test for HIV, CT scan of brain, and renal function tests were done in all patients. CD4 count was determined by BD FACS count system.

**Statistical methods**

Chi-square and Fisher exact test were used to test the significance of study parameters. Odds ratio was used to find the strength of relationship between study parameters. Student t test (independent samples) was used to find the significance of investigations. The statistical software namely SPSS 11.0 and systat 8.0 were used for the analysis of the data.

**Results and observations**

100 patients of cryptococcal meningitis who were HIV seropositive were included in the study. Out of the 100 patients, 70 patients had cryptococcal meningitis and 30 patients had a mixed neuroinfection, i.e., cryptococcal meningitis + tubercular meningitis. Hence comparison was done between the two groups.

The mean age was 35.40 ± 7.14 years (range 23 - 55 years). Most of the patients (85%) were < 40 years. 72% of the patients were males, whereas only 28% of the patients were females. Cryptococcal meningitis was the initial presenting illness of HIV seropositive cases in 53% of the patients (Fig. 1).

![Fig. 1: Duration of HIV positive status.](image)

Headache was the most common presenting symptom. It was present in 95% of patients (Fig.2). In all the patients who had headache, it was of severe intensity and was situated bifrontally. Vomiting was the second most common presenting symptom, and was seen in 76% of the patients. Fever was present in 70% of the patients and was of low grade. Other presenting symptoms included, altered sensorium (36%), seizures (10%), and motor deficits (4%). Most of the patients (77%) had neurological symptoms of < 30 days duration. 23% of patients presented with chronic meningitis. 14% of the patients were comatose. Frank meningeal signs were present in 38% of the patients. Cranial nerve involvement was seen in 15% of the patients. Sixth cranial nerve was most commonly involved. 12 (12%) patients had sixth cranial nerve involvement. 2 patients had seventh cranial nerve involvement, and 1 patient had third cranial nerve involvement.

![Fig. 2: Presenting symptoms.](image)
involvement. In 86% of the patients, fundus examination was normal. 4% of the patients had early features of raised intracranial pressure in the form of blurring of disc margin. 9% of the patients had papilloedema. Extracranial manifestations included eye involvement due to cryptococcal choroiditis in 1 patient, and 1 patient had skin involvement in the form of papular skin lesions.

CSF pressure was elevated in 60% of the patients. CSF India ink was positive in 90% of the patients. In all the 100 patients, CSF cryptococcal antigen and CSF cryptococcal culture was positive. Mean CSF glucose level was 36.32 ± 15.67 (range 10 - 82 mg/dl). In 66% of the patients CSF glucose was < 40 mg/dl. 34% of the patients had a CSF glucose of > 40 mg/dl. Mean CSF protein level was 94.24 ± 64.77 (range 12 - 330 mg/dl). 81% of the patients had a CSF protein of > 40 mg/dl. Mean CSF cell count was 44.00 ± 57.84 (range 0 - 290 cells). 64% of the patients had a raised CSF cell count (> 5 cells). Mean CSF lymphocyte count was 37.63 ± 52.31 (range 0 - 290). The predominant type of cell seen in CSF was the lymphocyte. Mean CSF polymorph count was 6.37 ± 11.85 (range 0 - 82). Mean CD4 count was 60.27 ± 41.51 (range 4 - 192). All the 100 patients had a CD4 count of < 200. 52% of the patients had a CD4 count of < 50 (Fig. 3). 85% of the patients had a CD4 count of < 100. 35% of the patients had a normal CT scan of brain. Diffuse cerebral atrophy was seen in 47% of the patients. Diffuse cerebral atrophy with ventricular dilatation was seen in 18% of the patients.

All the patients were followed-up for a period of 6 months. Mortality in HIV seropositive patients with cryptococcal meningitis was 32%. Recovery was good with treatment and was seen in 68% of the patients. Out of the 32 patients who died, 18 patients died within 1 week of initiation of treatment. 14 patients died in the 1 week 1 month period after initiation of treatment. All the 100 patients were put on amphotericin B (0.7 mg/kg body weight) for 2 weeks and oral fluconazole 200 mg twice daily for 8 weeks followed by 200 mg daily. 3 (3%) patients developed complications with amphotericin B. 2 patients developed severe allergic reaction in the form of rashes, itching, and bronchospasm; and amphotericin B had to be discontinued. These 2 patients were treated with oral fluconazole only. Out of these 2 patients, 1 patient recovered and 1 patient died. 1 patient had raised blood urea and serum creatinine after 14 days of amphotericin B therapy. Side-effects of amphotericin B were seen only in isolated cryptococcal meningitis cases.

Sequelae

2 patients had persistent motor deficit, and 3 patients had persistent cranial nerve palsy. Residual deficits were seen only in patients with mixed infection. Within 6 months of treatment 3 (3%) patients presented with relapse of cryptococcal infection. All the 3 patients were earlier treated with adequate dosage of amphotericin B for 2 weeks. All the 3 patients had discontinued fluconazole. 2 patients had a relapse after 2 months of discontinuing fluconazole, and 1 patient had a relapse after 3 months of discontinuing fluconazole. These 3 patients had also discontinued HAART. 4 (4%) patients presented with cryptococcal meningitis as a part of immune reconstitution syndrome. 2 patients developed immune reconstitution syndrome after 3 months, 1 patient after 4 months, and 1 patient after 5 months of starting HAART.

A multivariate logistic regression analysis for predicting risk factors of mortality showed that comatosed state was a significant predictor of bad prognosis (death). Comatosed state was 25.66 times more likely to predict death. Altered sensorium was 7.07 times more likely to predict death. A CD4 count of ≤ 50 was 4.73 times more likely to predict death.

Out of the 100 patients, 70 patients had cryptococcal meningitis (group A) and 30 patients had a mixed neuroinfection, cryptococcal meningitis + tubercular meningitis (group B). Hence, comparison was done.
between the two groups (Table I). No other mixed neuroinfection was seen.

Out of the 100 cases studied, cryptococcal meningitis was the initial presenting illness of HIV in 53% of the cases. 41% of the patients had isolated cryptococcal meningitis and 12% of the patients had mixed infection. Out of the 30 cases of tubercular meningitis studied, 12 patients had pulmonary tuberculosis. Most of the parameters were similar between the two groups. But there was a significant increase in CSF protein levels, CSF cell count, CSF lymphocytes, and CSF polymorphs in group B when compared to group A with P < 0.001.

The symptom of headache was the commonest presenting symptom in all the studies and in the present study also (Table II). Fever was the other important symptom in all the above studies, but the frequency is slightly variable with highest frequency seen in the study done by Darras-Joly et al. and by Kalra et al. India ink preparation is a simple procedure, and it is used as a screening procedure in cases of cryptococcal meningitis. The positivity in the present study with respect to India ink preparation was similar to studies done by Imwidthaya et al., Darras-Joly et al., and Khanna et al. (Table III).

Table I: Comparison of study characteristics between cryptococcal meningitis, and cryptococcal meningitis+ tubercular meningitis.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Cryptococcal meningitis (n = 70)</th>
<th>Cryptococcal meningitis + tubercular meningitis (n = 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years; mean ± SD</td>
<td>35.27 ± 7.22</td>
<td>35.70 ± 7.08</td>
<td>0.785</td>
</tr>
<tr>
<td>Male: female</td>
<td>51:19</td>
<td>21:9</td>
<td>0.771</td>
</tr>
<tr>
<td>Headache</td>
<td>65 (92.9%)</td>
<td>30 (100.0%)</td>
<td>0.318</td>
</tr>
<tr>
<td>Vomiting</td>
<td>53 (75.7%)</td>
<td>23 (76.7%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Fever</td>
<td>50 (71.4%)</td>
<td>20 (66.7%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>25 (35.7%)</td>
<td>11 (36.7%)</td>
<td>0.928</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>0</td>
<td>4 (5.7%)</td>
<td>0.313</td>
</tr>
<tr>
<td>Seizures</td>
<td>8 (11.4%)</td>
<td>2 (6.7%)</td>
<td>0.719</td>
</tr>
<tr>
<td>Terminal neck stiffness</td>
<td>60 (85.7%)</td>
<td>29 (96.7%)</td>
<td>0.166</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>9 (12.9%)</td>
<td>6 (20.0%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Abnormal fundus</td>
<td>7 (10.0%)</td>
<td>7 (23.3%)</td>
<td>0.114</td>
</tr>
<tr>
<td>CSF India ink +</td>
<td>65 (92.9%)</td>
<td>25 (83.3%)</td>
<td>0.161</td>
</tr>
<tr>
<td>CSF glucose; mean ± SD</td>
<td>37.01 ± 14.11</td>
<td>34.70 ± 18.99</td>
<td>0.203</td>
</tr>
<tr>
<td>CSF protein; mean ± SD</td>
<td>72.40 ± 44.47</td>
<td>145.20 ± 76.01</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>CSF cell count; Mean ± SD</td>
<td>21.11 ± 29.01</td>
<td>97.40 ± 72.13</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>CSF lymphocytes; mean ± SD</td>
<td>16.61 ± 22.68</td>
<td>86.67 ± 67.56</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>CSF polymorphs; mean ± SD</td>
<td>4.50 ± 11.39</td>
<td>10.73 ± 11.91</td>
<td>0.001**</td>
</tr>
<tr>
<td>Mortality</td>
<td>20(28.6%)</td>
<td>12 (40.0%)</td>
<td>0.262</td>
</tr>
</tbody>
</table>

Discussion

Cryptococcal meningitis was the first manifestation of AIDS in 53% of the patients. This finding is similar to the study done by Chuck SL et al., wherein cryptococcal meningitis was the AIDS-defining illness in 45.28% of the patients.

In the present study mean CD4 count was 60.27. In the study done by Imwidthaya et al., mean CD4 count was 45. In another study done by Darras-Joly et al., mean CD4 count was 46. This is in accordance with the observation that cryptococcal meningitis presents in late stage of HIV infection; and lower the CD4 count, higher
the occurrence of cryptococcal meningitis. In the present study, mortality was 32%. In the study done by Khanna et al., mortality was 32.18%. In the present study, the poor prognostic factors included altered sensorium, and CD4 count of ≤ 50. This is in concordance with various other studies which have shown that altered sensorium is associated with poor prognosis. But the study done by Satishchandra et al. included HIV seronegative patients also. Response to therapy with amphotericin B and fluconazole was good and recovery was seen in 68% of the patients.

Conclusions

In half of the patients, cryptococcal meningitis was the AIDS defining illness. Majority of the patients had an acute to subacute presentation and India ink negativity does not rule-out cryptococcal meningitis. Lower the CD4 count, higher is the occurrence of cryptococcal meningitis in HIV seropositive patients. Response to therapy with amphotericin B and fluconazole is well tolerated with a good recovery.

Acknowledgement

I extend my gratitude to the Medical Superintendent of Bowring and Lady Curzon Hospital for his co-operation and encouragement to carry-out this study.

Table II: Comparison of presenting symptoms with other studies.

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Chuck et al.11(n = 106)</th>
<th>Martinez-Fernandez et al.11(n = 25)</th>
<th>Darras-Joly et al.13(n = 65)</th>
<th>Kalra et al.14(n = 15)</th>
<th>Present study(n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>73%</td>
<td>88%</td>
<td>67%</td>
<td>80%</td>
<td>95%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>42%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>76%</td>
</tr>
<tr>
<td>Fever</td>
<td>45%</td>
<td>68%</td>
<td>86%</td>
<td>86.6%</td>
<td>70%</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>28%</td>
<td>–</td>
<td>29%</td>
<td>26.6%</td>
<td>36%</td>
</tr>
<tr>
<td>Seizures</td>
<td>–</td>
<td>20%</td>
<td>–</td>
<td>–</td>
<td>10%</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>–</td>
<td>28%</td>
<td>–</td>
<td>–</td>
<td>4%</td>
</tr>
</tbody>
</table>

Table III: Comparison of CSF India ink, cryptococcal antigen, and cryptococcal culture positivity with other studies.

<table>
<thead>
<tr>
<th></th>
<th>Imwidthaya et al.15(n = 87)</th>
<th>Darras-Joly et al.13(n = 65)</th>
<th>Khanna et al.16(n = 87)</th>
<th>Present study(n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF India ink positivity</td>
<td>91%</td>
<td>87%</td>
<td>87.36%</td>
<td>90%</td>
</tr>
<tr>
<td>CSF Cryptococcal antigen positivity</td>
<td>100%</td>
<td>92%</td>
<td>98.81%</td>
<td>100%</td>
</tr>
<tr>
<td>CSF Cryptococcal culture positivity</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Legends

- AIDS – Acquired immunodeficiency syndrome
- CNS – Central nervous system
- CSF – Cerebrospinal fluid
- CT – Computed tomography
- ELISA – Enzyme linked immunoassay
- HAART – Highly active antiretroviral therapy
- HIV – Human immunodeficiency virus

References

6. Satishchandra P, Nalini A, Gourie-Devi M et al. Profile of


Flavedon MR