DOI: 10.14260/jemds/2015/2102

ORIGINAL ARTICLE

CLINICAL PROFILE OF CEREBRAL TOXOPLASMOSIS IN HIV INFECTED PATIENTS ADMITTED TO THE BOWRING AND VICTORIA HOSPITAL DURING THE PERIOD SEPTEMBER 2007 TO SEPTEMBER 2009

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HOW TO CITE THIS ARTICLE:
Hareesh R, Shiva Kumar B. R, Rekha G, Mohammed Zia Ur Rahaman. "Clinical Profile of Cerebral Toxoplasmosis in HIV Infected Patients Admitted to the Bowring and Victoria Hospital During the Period September 2007 To September 2009". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 85, October 22; Page: 14764-14776, DOI: 10.14260/jemds/2015/2102

ABSTRACT: BACKGROUND: TE was the frequent CNS opportunistic infection in AIDS in the pre-HAART era. It occurred in 10% of the patients or more depending on the geographic origin, in areas where HAART is not used widely and where AIDS patients are not on appropriate anti-parasitic prophylaxis. Cerebral toxoplasmosis in AIDS almost always occurs from recrudescence of previously acquired infection. It usually occurs in patients with CD4 counts less than 100/µL. Most recently the incidence of cerebral toxoplasmosis has further decreased in the HAART era. The clinical profile of Cerebral toxoplasmosis is as similar to other neuro infection, but differs radiologically and treatment response. **OBJECTIVES:** The present study is taken up with respect to its clinical manifestations, diagnostic features, response to therapy and outcome. **METHODS**: We carried out a prospective observational study in 30 patients of cerebral toxoplasmosis who were HIV Seropositive, at Bowring & Victoria Hospitals attached to Bangalore Medical College and Research Institute, Bangalore from September 2007 to September 2009. **RESULTS**: Out of 30 patients studied, the mean age was35.7±9.3 years. Prevalence of TE was more in males (Ratio was 2.01). Headache and altered sensorium were more common presentation 73.3% each. Mean CD4 count was 59.57±5.32 (4:14 cells/µL). 22(73.3%) were positive for serum antitoxoplasma IgG antibodies. Majority of the TE patients 76.7% showed bilateral multiple ring enhancing hypodense lesion, 20% of the patients showed solitary lesions. Among the 30 patients, clinical outcome was good with 18(60%) improved to combination therapy of pyrimethamine plus sulfadiazine for a period of 14±2 days with minimum toxicity and 6 (20%)patients died during the therapy and 6(20%) patients lost follow up. **CONCLUSION**: TE was the AIDS defining illness in 50% of our patients. In patients with AIDS, TE is usually a presumptive diagnosis. CT scan brain, was found to be the most useful approach to the diagnosis. There was a significant relationship between CD4 counts of less than 100 cells/µL and development of TE in HIV seropositive patients. Seronegativitiy for anti-toxoplasma antibodies, does not rule out TE. Combination of oral pyrimethamine plus sulfadiazine therapy for a period of 14±2 days was effective in TE.

KEYWORDS: HIV, AIDS, TE, CT, CD4+, HAART, Pyrimethamine, Sulfadiazine, Antitoxoplasma antibodies, CNS.

INTRODUCTION: T. Gondii is a obligate intracellular protozoal, ubiquitous and the likely natural survivors include cats, birds and domestic animals.[1] Its seroprevalence depends on the locale and the age of the population.[2] In the United States, depending on geographic locale and population group, 3 to 67% of adults have serologic evidence.[3] In other parts of the world, including tropical countries and some areas of Western Europe, up to 75% of adults are seropositive. TE in patients with acquired immunodeficiency syndrome (AIDS) and in bone marrow transplant recipients is almost always caused by reactivation of latent infection.

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It is estimated that TE ultimately develops in 20 to 47% of HIV-infected, T. gondii-seropositive patients if they are not receiving appropriate antiparasitic prophylaxis or Highly active antiretroviral therapy (HAART).[3] Cerebral toxoplasmosis is typically observed in the later stages of HIV infection.[4,5,6] CNS disease occurs when, CD4 counts are <200 cells/μL. The greatest risk is in patients with CD4 counts <50 cells/μL.[7,8,9] TE was most frequent CNS opportunistic infection in AIDS in pre-HAART era; it occurs in 10% of the patients or more depending on the geographic origin. The incidence initially declined where TMP/SMX had been used as prophylaxis for PCP, because this regimen is also effective in reducing the development of TE.[10] Toxoplasmosis is a principle opportunistic infection of the CNS in persons with AIDS. Individuals with AIDS who are seropositive for T.gondii are at very high risk for TE.[2]

The clinical manifestation associated with toxoplasmosis in AIDS patients are most frequently associated with involvement of CNS, lungs, and eyes.[1] CNS findings at presentation range from non-focal to focal dysfunction. CNS findings include encephalopathy, meningoencephalitis, and mass lesions.[2] Patients may present with altered mental status (75%), fever (10-72%), seizures (33%), headaches(56%), focal neurologic findings (60%) including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual field loss and aphasia.[2,11] The characteristic presentation is usually one of the sub-acute onset with focal neurological abnormalities in 58 – 89% of the patients.

The most common focal neurological manifestations are hemiparesis and abnormalities of speech.[12,13,14] As many as two thirds of the patients with TE may exhibit generalized cerebral dysfunction including disorientation, decrease in mentation, lethargy and coma.[15] Diffuse TE is associated with generalized cerebral dysfunction without focal signs or symptoms. The clinical course is rapidly progressive and results in death within the several days.[16] Ocular pain and loss of visual acuity are common presenting complaints and fundoscopic examinations typically reveals findings consistent with necrotizing retinochoroiditis.[17,18] Ocular toxoplasmosis is the second most common retinal infection in AIDS; the most common is due to CMV retinitis.[19]

Different classes of specific toxoplasma antibodies may be detected by a variety of methods including the Sabin-Feldman dye test (IgG), indirect fluorescent antibody (IFA) test (IgG, IgM), agglutination test (IgG), enzyme-linked immunosorbent assay (ELISA) (IgG, IgM,etc).IgG toxoplasma antibody titers are significantly higher in AIDS patients with TE than those without TE.[20] IgM antibodies appear early, demonstrable within 1 to 2 weeks after infection.[21] In AIDS patients with TE, the median CD4 + T cell count has been observed to be approximately 50/mm^3. Of patients with TE, 90% have CD4+T cell counts below 200/mm^3, 80 to 84% below 100/mm^3, and 49% below 50/mm^3.[22,23] Findings in the CSF of patients with TE and AIDS are nonspecific. Mild mononuclear pleocytosis and mild to moderate elevations of CSF protein may be present.[24]

CT findings demonstrate multiple bilateral lesions in the cerebral hemispheres in 70 to 80% of the patients with TE, and single lesions may be present. Characteristic lesions are hypodense, exhibit contrast ring enhancement, tend to occur at the corticomedullary junction, and frequently involve the basal ganglia.[25] Findings on CT scan have revealed improvement in approximately 80 to 90% of patients after 2 to 3 weeks of treatment. Early signs of improvement include reduction in areas of contrast enhancement, reduced edema, and reduction of the mass effect. Reduction in the size of the lesion is the most reliable indicator of a favorable response. Complete resolution takes from 6 weeks to 6 months.[26]

Pyrimethamine dosage is 1 to 1.25mg/kg/day. The most common side effects of pyrimethamine are dose-related bone marrow suppression and skin rash. To ameliorate the bone marrow suppressive effect, 10 to 20mg/day of oral folinic acid (leucovorin), is recommended for AIDS patients.[27,28]

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Presently, the pyrimethamine+sulfadiazine combination is considered the therapeutic regimen of choice. For acute therapy, the recommended dose of sulfadiazine is the combination of 4 to 6 g/day (100 to 150mg/kg/day) by the oral route.

The combination of sulfadiazine at 2g/day and pyrimethamine at 25mg/day has also been used to some success for maintenance therapy. The most common side effects associated with sulfadiazine in AIDS patients include skin rashes that may be life threatening, crystal induced nephrotoxicity, and hematological toxicitiy.[29,30] Clindamycin(600mg every 6 hourly) in combination with pyrimethamine has been evaluated in prospective studies and shown to be comparable in efficacy and toxicity to pyrimethamine/sulfadiazine.[31,32] Monotherapy for treatment of TE in AIDS patients is usually associated with initial clinical improvement followed by relapse even while the drug is being continued.

Therefore, until there is clear evidence to the contrary, we recommended that acute and maintenance therapies should include at least two drugs. Other Drug combinations are pyrimethamine plus sulfadiazine are pyrimethamine-dapsone, pyrimethamine-azithromycin,clarithromycin-pyrimethamine, atovaquone-pyrimethamine.[33]

The empirical treatment of TE based on characteristic clinical and neuroradiological findings evolved when it became apparent that the definitive diagnosis could be made only by brain biopsy and that TE was the most common cause of focal brain lesions in patients on CT or MRI scans. In the presence of a compatible clinical syndrome, a positive toxoplasma IgG serological test and multiple ring-enhancing lesions on CT or MRI, the predictive value for TE is approximately 80%.[34]

The presence of multiple lesions on neuroimaging studies markedly increases the probability of TE versus other causes of CNS lesions in AIDS.[34] Acute therapy should be administered for at least 3 weeks. For more severely ill patients who have not achieved a complete clinical and/or neuroradiological response, 6 weeks or more are recommended. Most investigators agree that the combination of pyrimethamine/sulfadiazine is the therapy of choice for AIDS patients with toxoplasmosis.

The regimen of pyrimethamine/clindamycin appears comparable in efficacy to pyrimethamine/sulfadiazine. Pyrimethamine/clindamycin may be regarded as a suitable alternative in those patients who are unable to tolerate pyrimethamine/sulfadiazine.[12] Relapse of TE will occur in approximately 50 to 80% of patients within several months of discontinuing therapy for TE. After an initial 3 to 6 weeks of primary therapy, all patients must receive lifelong maintenance therapy to prevent relapse.[13]

A higher relapse rate with the use of pyrimethamine/clindamycin compared with pyrimethamine/sulfadiazine as secondary prophylaxis has been reported.[13,14] Toxoplasmic encephalitis is uniformly fatal if left untreated. The mortality rate for treated patients ranges from approximately 1 to 25%.[14,18,27,35] Prevention of TE in HIV patients involves two major strategies, the first is directed at instituting primary prophylaxis with TMP/SMX, pyrimethamine/dapsone, and Fansidar to patients who are toxoplasma seropositive. The second, is directed especially to those patients who are toxoplasma seronegative and hence uninfected, in these individuals education on how to avoid acquisition of primary infection is needed.[36]

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For the toxoplasma-seropositve HIV-infected individuals	
Suggested regimen	
TMP/SMX	One double-strength tablet daily
Alternative regimens	
Pyrimethamine - Dapsone	Pyrimethamine, 50mg once each week, plus dapsone, 50mg qd, plus folinic acid (leucovorin), 25mg qd
	Pyrimethamine, 75mg once each week, plus dapsone, 200 mg once each week, plus folinic acid (leucovorin), 25 mg qd
TMP/SMX	One single-strength tablet daily
For the Toxoplasma-seropositive HIV-infected pregnant women	
Spiramycin	1 g q8h

Table 1: Primary Prophylaxis For Toxoplasmosis In Aids Patients[37]

MATERIALS AND METHODS:

Source of Data: 30 patients of cerebral toxoplasmosis who were HIV seropositive were studied prospectively at Victoria & Bowring and Lady Curzon Hospital attached to Bangalore Medical College, Bangalore, over a period of 2 years.

Method of Collection of Data: 30 patients of cerebral toxoplasmosis who were HIV seropositive were included in the study. A detailed clinical evaluation and relevant laboratory/radiological investigation were enrolled.

Inclusion Criteria: 30 patients of HIV seropositive with radiological evidence of toxoplasmosis.
Patients presenting with recurrent toxoplasmic encephalitis.

Exclusion Criteria: Patients with cryptococcal meningitis, primary CNS lymphoma, tubercular meningitis and tuberculoma, primary multifocal lymphoma and cytomegalovirus encephalitis were excluded.

Investigation done: Complete hemogram

- Renal function test.
- Blood Glucose.
- ELISA test for HIV.
- CD4 count was determined by BD FACS count system.
- Serum serological test for toxoplasma IgM and IgG antibodies was done by serum latex agglutination test.
- CSF analysis for: Protein and sugar, Cell count and cell type, India ink smear and Cryptococcal antigens.
- CT scan brain.
- Chest X-ray.
- Urine analysis.

Statistical Methods: Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% is

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associated with statistical significance. P±1.96*SE(P), Where SE(P) is the Standard error of proportion = P*Q/√n.

Statistical software: The Statistical software namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data.

RESULTS: A prospective clinical study of 30 patients of cerebral toxoplasmosis who were HIV seropositive is undertaken to study the clinical manifestations, diagnostic features, and response to therapy. The mean age was 35.67+9.30 years (range 20-55 years).

Age in years	Number of patients	%
20-30	10	33.3
31-40	12	40.0
41-50	6	20.0
51-60	2	6.7
Total	30	100.0

Table 2

Gender	Number of patients	%
Male	20	66.7
Female	10	33.3
Total	30	100.0

Table 3: Male: Female ratio was 2.01.

Headache and altered sensorium was the most common presenting symptoms and each symptom was present in 73.3% of patients. Motor deficits was the second most common presenting symptoms and was seen in 66.7% of the patients, most of the patients presented with hemiparesis.

Presenting Symptoms	Number of patients (n=30)	%
Headache	22	73.3
Altered sensorium	22	73.3
Motor deficits	20	66.7
Fever	14	46.7
Seizures	10	33.3
Vomiting	8	26.7

Table 4: 13.3% patients showed meningeal signs.

Meningeal Signs	Number of patients (n=30)	%
Absent	16	53.3
Terminal neck stiffness	10	33.3
Frank meningeal signs	4	13.3

Table 5

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Fundus	Number of patients (n=30)	%
Normal	22	73.3
Blurring of disc margin	3	10.0
Papilledema	3	10.0
Toxoplasmic necrotizing retinochoroiditis	2	6.7

Table 6: Only 2(6.7%) patients had Toxoplasmic Necrotizing Retinochoroiditis.

Serum Serological test for toxoplasma IgM Antibodies	Number of patients (n=30)	%
Positive	20	66.7
Negative	10	33.3

Table 7: 20(66.7%) were positive for serum Antitoxoplasma-IgM Antibodies.

Serum serological test for toxoplasma IgG Antibodies	Number of Patients (n=30)	%
Positive	22	73.3
Negative	8	26.7

Table 8: 22(73.3%) were positive for Serum Antitoxoplasma-IgG Antibodies.

CSF Glucose levels (mg/dl)	Number of patients (n=30)	%
0-10	1	3.3
11-20	5	16.7
21-40	14	46.7
41-60	8	26.7
>60	2	6.7

Table 9: CSF Analysis showed no abnormal changes.

CSF Protein Levels (mg/dl)	Number of patients (n=30)	%
0-40	18	60.0
41-100	10	33.3
101-200	1	3.3
>200	1	3.3

Table 10

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CSF Cell count (cells/µL)	Number of patients (n=30)	%
0-5	9	30.0
6-20	6	20.0
21-50	4	13.3
51-100	7	23.3
>100	4	13.3
Table 11		

CSF lymphocytes (cells/µL)	Number of patients (n=30)	%
0-5	11	36.7
6-20	5	16.7
21-50	6	20.0
51-100	5	16.7
>100	3	10.0
Table 12		

CSF polymorphs (cells/µL)	Number of patients (n=30)	%
0-5	16	53.3
6-20	8	26.7
21-50	4	13.3
51-100	2	6.7
Table 13		

Mean CD4 cell count was 59.57±5.32. Range (4-142 cell/µL). All the 30 patients had a CD4 count of <200 cells/µL. 53.3% of the patients had a CD4 count of less than 50 cell/µL. 83.3% of the patients had a CD4 count of less than 100 cell/µL.

CD4 count (cells/µL)	Number of patients (n=30)	%	95%CI
0-50	16	53.3	36.14-69.77
51-100	9	30.0	16.66-47.88
101-200	5	16.7	7.34-33.58
Table 14			

Only 36.7% of the patients were on HAART treatment before coming to the hospital and majority 63.3% of patients was not on HAART treatment.

Pt. on HAART	Number of patients (n=30)	%	95%CI
Yes	11	36.7	21.87-64.48
No	19	63.3	45.51-78.13
Table 15			

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Only 36.7% of the patients were on TMP/SMX prophylaxis before coming to hospital on majority 63.3% of the patients was not on prophylaxis.

Pt. on TMP/SMX prophylaxis	Number of Patients (n=30)	%	95%CI
Yes	11	36.7	21.87-64.48
No	19	63.3	45.51-78.13

Table 16

CT Brain Findings	Number of patients (n=30)	%	95%CI
1.Multiple bilateral ring enhancing hypodense lesions	23	76.7	59.07-88.21
2.Solitary ring enhancing hypodense lesions	6	20.0	9.51-37.31
3.Diffuse cerebral atrophy with ventricular dilatation	1	3.3	0.6-16.67

Table 17: Majority of the patients 23 (76.7%) showed bilateral Multiple ringenhancing Hypodense lesions.

CT Showing site of involved region	Number of patients (n=30)	%
1.Cerebral cortex+ Basal ganglia	8	26.7
2.Cerebral cortex+ Cerebellum	7	23.3
3.Cerebellum	6	20.0
4.Cerebral cortex+ Basal ganglia+ Cerebellum	5	16.7
5.Cerebral cortex+ Basal ganglia+ Brain stem	3	10.0
6.Diffuse cerebral atrophy	1	3.3

Table 18: Main locations were Cerebral Cortex (76.66%), Basal Ganglia (53.33%), Cerebellum (60.0%).

Majority of the patients 18 (60.0%) out of 30 patients in HIV seropositive with TE recovered with combination of therapy of pyrimethamine plus sulfadiazine. 6 (20%) out of 30 patients died and 6 (20%) out of 30 patients lost to follow up.

Outcome	Number of patients (n=30)	%	95%CI
Improved	18	60.0	42.32-75.41
Dead	6	20.0	9.51-37.31
Lost to follow up	6	20.0	9.51-37.31

Table 19

TREATMENT: All 30 patients enrolled in the study were started on combination therapy pyrimethamine (1 to 1.25mg/kg/day i.e.75mg/day) plus sulfadiazine (100 to 150 mg/kg/day i,e., 4 to 6gm/day) along with folinic acid (10 to 25 mg/day) for 2-6 weeks. Out of 30 patients, 18 (60.0%) patients improved clinically and got discharged from the hospital with advise to continue combination therapy for about 6 weeks and repeat CT scan-brain showed resolved ring enhancing lesion with

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disappearance of cerebral edema. About 6(20%) attended OPD, were started on combination therapy to home, and were lost for follow up, and 6(20%) died during therapy.

Out of 15 patients, 7(23%) are comatose. Majority of the death, 6(85.7%) seen in comatose patients. There was statistically significant association of death with comatose patients.

Level of consciousness	Total number of patients	Outcome		
		Improved	Death	Lost-to-follow up
Conscious	8	8(100%)	0(0%)	0(0%)
Drowsy	15	9(60.0%)	0(0%)	6(40.0%)
Comatose	7	1(14.3%)	6(85.7%)	0(0%)
Total	**30**	**18(60%)**	**6(20%)**	**6(20%)**
Inference	Comatose is positively significantly associated with death with P<0.001**			

Table 20

Out of 30 patients, 16 patients had CD4 count below 50 cell/μL. 10 (62.5%) patients improved out of 16 patients CD4 count below 50 cells/μL. There is a significant improvement showed in a group of patients were CD4 count above 50 cells/μL. There was no statistically significant correlation between CD4 count and outcome.

DISCUSSION: Our study is undertaken to describe cerebral toxoplasmosis in HIV infected patients with respect to clinical course, laboratory findings, response to therapy and outcome. The mean age of patients was 35.67+9.30 years, the range being 20-55 years. 40% patients were in age group between 31-40 years, in accordance with the study done by Benjamin et al. Male: Female ratio is 2.01. In the study done by Benjamin J. Luft et al[38]. 88% of the patients were males.

In our study half of the patients (50%) were detected to be HIV seropositive at the time of admission. In other words TE was the initial presenting illness of HIV seropositive status in 50% of the patients in our study. A study done by Veeranoot et al[39], showed TE is a secondary brain disease and the third most common opportunistic infection of the CNS among AIDS patients.

Most of the patients (70%) had neurological symptoms of <30 days duration. 30% of the patients presented with chronic meningitis. In the present study headache (73.3%) and altered sensorium (73.3%) was the predominant symptoms. In a study done by Veeranoot et al[39]. Fletcher et al, headache and altered sensorium were the most common presenting symptoms. The frequency of fever in the present study correlated with the study done by Veeranoot et al[39], and Fletcher et al[40]. Motor defects (66.7%) is similar to study done by Ya-Ch-Ho et al[41].

53.3% of the patients had no meningeal signs and frank meningeal signs were seen in only 13.3% of the patients which was similar to study done by Renald et al[42]. and Cohn et al. In the present study out of 30 patients, 6 (20%) patients had cranial nerve involvement. Sixth cranial nerve was most commonly involved, which was similar to study done by Renald et al[42], were 17%.

In 73.3% of the patients fundus was normal, and 10.0% of the patients had papilledema.

30 patients TE, 20 (66.7%) were positive for serum toxoplasma IgM antibodies and 22 (73.3%) patients were positive for serum toxoplasma IgG antibodies.

Mean CD4 cell count was 59. This is in accordance with the observation that TE presents in the late stage of HIV infection and when CD4 count less than 100cells/μL.

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From our data, the CT scan findings of the majority of the patients with TE showed a typical appearance of multiple bilateral ring enhancing hypodense (76.7%) lesions, solitary ring enhancing hypodense (20%) lesions of the patients, and 3.3% of the patients showed diffuse cerebral atrophy with ventricular dilatation.

In our study most of the TE patients showed lesions in cerebral cortex (76.66%), basal ganglia (53.33%), cerebellum (60.0%), Brain stem (10%) and diffuse cerebral atrophy (3.33%).

Mortality was 20%, compared to study done by Ya-Chi-Ho et al[41], mortality was 16.6%. 18 (60%) patients out of 30 showed improvement with combination therapy after 14+2 days.

In the present study the poor prognostic factors were altered sensorium, coma, age >40 years, and presence of meningeal signs. Altered sensorium was a significant predictor of bad prognosis.

CONCLUSION: TE was the AIDS defining illness in 50% of our patients. TE has an acute to sub-acute presentation in majority of the patients. In our study the peak incidence of TE was seen in patients less than 40 years and was highest among those between 31-40 years.

In patients with AIDS, TE is usually a presumptive diagnosis based on the clinical manifestation, a positive antitoxoplasma antibodies titer, and characteristic neuroradiological abnormalities, and response to therapy. Clinical findings at the time of presentation range from non-focal to focal dysfunction. Headache, altered sensorium, motor deficits, fever and seizures were the most common presenting symptoms. CT scan brain findings of majority of the patients with TE showed a typical appearance of multiple bilateral, hypodense ring enhancing lesions in the cerebral hemisphere. CT scan brain was found to be the most useful approach to make a diagnosis.CD4 count is considered to be a prognostic or risk factor to monitor the progression of HIV.

There was significant relationship between CD4 count of less than 100 cells/μL and development of TE in HIV seropositive patients. Regarding serodiagnosis, 20 patients of TE were shown to be positive for IgM antibodies and 22 TE patients were shown to be positive for antitoxoplasma IgG antibodies, which indicates the importance of screening for this organism particularly where there is high risk of suspicion. Seronegativity for antitoxoplasma antibodies does not rule out TE. Histological confirmation with brain biopsy was not feasible because of the high mortality. Combination of oral pyrimethamine plus sulfadiazine was effective for treatment of TE. Response to combination therapy with pyrimethamine plus sulfadiazine was seen in 60% of the patients with minimal toxicity in a period of 14+2 days. Altered sensorium was associated with poor prognosis. All patients were subsequently started on HAART treatment and TMP/SMX prophylaxis.

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DOI: 10.14260/jemds/2015/2102

ORIGINAL ARTICLE

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FINANCIAL OR OTHER COMPETING INTERESTS: None

Date of Submission: 11/10/2015.
Date of Peer Review: 12/10/2015.
Date of Acceptance: 14/10/2015.
Date of Publishing: 20/10/2015.