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Infectious Diseases

Clinical Spectrum and Outcomes for Toxoplasma Encephalitis among AIDS Patients before and during the Era of Anti-retroviral Therapy in Mangalore, India

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ABSTRACT

Background: Toxoplasmosis (TS) which is associated with HIV infection is typically caused by the reactivation of a chronic infection and it manifests primarily as toxoplasmic encephalitis. This disease is an important cause of focal brain lesions in HIV-infected patients. This study was done to determine the clinical presentations and outcomes of CNS toxoplasmosis and to find out their association with the CD4 counts at the time of diagnosis and at the initiation of anti-retroviral therapy.

Materials and Methods This was a retrospective study which was done over 6 months at Kasturba Medical College Hospital (KMCH), Attavar, Mangalore, by reviewing the medical records of HIV-positive patients who were diagnosed with toxoplasmosis, who were admitted there from Jan 2001 to Dec 2010. The diagnosis was based on the clinical features, the demonstration of elevated IgG by ELISA and associated CT findings. The data which was obtained was then correlated with the CD4 counts and with the fact as to whether the patient was on ART or not. The analysis was done by using SPSS version 11.5.

Results: 2826 HIV positive patients attended the Infections Disease Cell clinic of our hospital from the year 2001 –2010, of which 33 (1.12%) had CNS toxoplasmosis. Among the 33 cases, 29 were males (88%) and 4 were females (12%). The mean age was 37.33 yrs, with an S.D of 6 yrs. 73% were married, 24% were single and 3% were widows. 10 out of the 33 cases (30.3%) had CNS toxoplasmosis as the initial manifestation of HIV. The most common clinical presentations were fever (58%) and headache (52%). 64% of the cases were already on ART when they were diagnosed with toxoplasmosis and 6% were started on ART after the diagnosis of toxoplasmosis. The mean CD4 count at the time of diagnosis of toxoplasmosis was 160.6, with an S.D. of 112. The mean level of IgG was 255.69, with an S.D of 99.62. The CT / MRI finding of the ringenhancing lesion or cerebritis was seen in 79 % of the cases, with 18% of the lesions being seen in both the basal ganglia and the parietal lobes. Cerebritis was the most common lesion which was found in the CT/MRI, which was seen in 16 (61.5%) cases, while ring enhancing lesions were seen in 10 (38.5%) cases. 82% of the cases improved with the treatment and 18% expired. Recurrence was seen in 6% cases, with seizures as the most common presentation. 6 (18.18%) toxoplasmosis cases in our study had IRIS. The mean CD4 count in them was 363, while the mean CD4 count in the absence of IRIS was 125, with a p value of 0.001.

Conclusions: The possibility of cerebral toxoplasmosis should be considered in every HIV-positive patient with neurological symptoms. In our study, we saw toxoplasmosis occurring at CD4 levels which were >150, which could warrant a prophylaxis for toxoplasmosis at a higher CD4 count. Parietal lobe lesions were common in our study, which was contrary to the other existing data, which have referred to the toxoplasma lesions usually as midline lesions. Cerebritis, which was more common than the ring enhancing lesions in our study, could have occurred due to the weakened immune response.

Key Words: Toxoplasma Encephalitis; Clinical Features, Outcomes, HIV/AIDS, CD4 count, India

BACKGROUND

Toxoplasma encephalitis (TE) is a common opportunistic infection (OI) in HIV-infected adults with the acquired immunodeficiency syndrome (AIDS) [1-4]. Despite the availability of highly active anti-retroviral therapy (ART), TE can lead to serious morbidity and mortality, especially in resource-limited countries [5-7].TE often results from the reactivation of endogenous infections in patients who are infected with HIV [1].

Patients with AIDS and a CD4 count of <100cells/μL, who are toxoplasma seropositive, have an approximately 30 percent probability of developing reactivated toxoplasmosis if they are not receiving effective prophylaxis [3]. The risk of TE varies with the seroprevalence of the toxoplasma infection. Natural history studies of HIV disease in India have reported the frequency of various OIs, both before and after the introduction of generic ART. In a retrospective autopsy study which was conducted between 1998 and 1996, TE was found to be the most frequent OI which caused CNS disease, which was noted in 13% of patients with AIDS, followed by tuberculosis (14%), cryptococcal meningitis (8%) and cytomegalovirus infection (Langewar et al AIDS 1998). However, the data is very limited on the clinical spectrum, the imaging characteristics and the outcomes of TE from India [10,11]. The objective of this study was to evaluate the clinical presentation, the imaging characteristics, the clinical course, and the outcomes of TE in HIV positive patients in India before and during the antiretorivral therapy (ART) era.

PATIENTS AND METHODS

Setting

This study was conducted at Kasturba Medical College (KMC) hospital, a major referral centre which is located in the coastal city of Mangalore, a high HIV prevalence area in the state of Karnataka The HIV program at KMC has been operational since and it is the only medical centre in Mangalore that has provided care and treatment to over 5000 patients. Approximately, 8-10 newly diagnosed HIV positive patients and 300 patients are being followed-up each month. All the patients receive treatment and prophylaxis according to the the WHO guidelines. The patients are started on nevirapine-based ART regimens when the CD4 count is <200 cells or when the CD4 count ranges between 200-350 with an AIDSdefining condition. Patients are seen in the clinic every 3-4 months or more frequently, as clinically indicated. CD4 count testing is done every 3-6 months.

Study population

We retrospectively reviewed the medical records of HIV-infected patients who were diagnosed with TE at KMC between January 2001 and December 2010. The clinical information was collected by using a standardized data collection sheet for demographic characteristics such as age, sex, marital status, occupation, clinical and laboratory data, treatment, and outcomes. The data which was obtained was then correlated with the CD4 count and with the fact as to whether the patient was receiving ART or not.

The inclusion criteria included all the HIV positive patients with TS, who were diagnosed by using the CDC criteria, who presented to the hospital from the year 2001 to 2010. The patients were excluded if the serological details for toxoplasma IgG and the neuroimaging findings were unavailable.

Definitions

The diagnosis of TS was made presumptively, based on the information which was provided by the physicians at KMC according to the criteria of the 1993 Centers for Disease Control and Prevention (CDC), which included the clinical signs and neuroimaging findings [CT scan or MRI scan of the head] which were compatible with TS, the demonstration of IgG antibodies by ELISA, and the response to therapy for toxoplasmosis [CDC. MMWR 1992;4:41(RR-17):1-19]. The serum IgG antibodies to *T. gondii* were measured by ELISA An IgG value of > 10 IU/ ml was considered to be diagnostic. None of the patients with a presumptive diagnosis of TS underwent a brain biopsy. Patients who clinically improved and survived during the follow-up period or died due to causes which were non-attributable to TS were defined as survivors. Patients who died due to TE were defined as non-survivors. Autopsies were not performed for the deceased patients.

The study protocol was approved by the Ethics Committee at KMC.

Statistical analysis

Data analysis was done by using the Statistical Package for the Social Sciences (SPSS version 11.5, Chicago, IL, USA). The qualitative variables were analyzed by using 'Chi Square' test. The quantitative variables were analyzed by using the T test and 'ANOVA'. May need to mention univariate analysis and multivariate analysis if the risk factors for mortality from TE can be analyzed. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Out of 2826 HIV positive cases which availed the treatment at our hospital, 33 (1.12%) had CNS toxoplasmosis. Tubercular meningitis/ Tuberculoma accounted for 56 (1.98%) cases. 7 cases (0.25%) had HIV encephalopathy. 12 cases (0.42%) had cryptococcal meningitis. Of the 33 cases in our study, 29 were males (88%) and 4 were females (12%). The male: female ratio was 7.25:1. The age of the cases ranged from 27-56 yrs, the mean age being 37.33 yrs, with a S.D of 6.1. 73% were married, 24% were single and 3% were widows.

The most common clinical presentations were fever (58%) and headache (52%), followed by generalized weakness and an altered sensorium (36%), vomiting (33%), focal neurological signs (21%), seizures (18%), decreased vision (15%) and involuntary movements like chorea(9%). Giddiness, tingling and numbness in the limbs were among the rare presentations.

Baseline Characteristics	Number (Percentage)
Age Groups	
15-30 yrs	4 (12.1)
30-44 yrs	25 (75.8)
≥ 45 yrs	4 (12.1)
Gender	
Male	29 (87.9)
Female	4 (12.1)
Marital Status	
Single	8 (24.2)
Married	25 (75.7)

[Table/Fig-1]: Baseline characteristics of HIV positive patients having CNS toxoplasmosis (n=33)

The mean CD4 count at the time of diagnosis of toxoplasmosis was 160.58, with an S.D of 112.2 and the mean level of IgG was 255.69 with an S.D of 99.62, The CT/MRI finding of the ring enhancing lesion or cerebritis was seen in 79% of the cases, with 18% of the lesions being seen in the basal ganglia and the parietal lobes each. Cerebritis was the most common lesion which was found in the CT/MRI, which was seen in 16 (61.5%) cases, while ring enhancing lesions were seen in 10 (38.5%) cases.

64% of the cases were on ART when they were diagnosed with toxoplasmosis, 30% were not on ART and 6% were started on ART after the diagnosis of toxoplasmosis. 82% of the toxoplasmosis cases improved with the treatment and 18% expired. Recurrence was seen in 6%, with seizures as the most common presentation. Among the 27 toxoplasmosis cases that improved with the treatment, irrespective of the final outcome, the mean CD4 was 163 and 20 (74%) were on ART. Among the 6 cases who didn't improve, the CD4 was 151 and 5 (83%) were on ART.

DISCUSSION

The most common clinical presentations of toxoplasmosis in the HIV patients in our study were fever and headache, which was similar to that in a previously reported study in Malaysia [10]. Most of the cases were males in the fourth decade of life. Most of them were married.

A majority of the cases were already on ART, with a mean CD4 of above 150. Cerebritis was the most common lesion which was found in CT/MRI, with predominance in the parietal lobe and in the basal ganglia. Parietal lobe lesions were common in our study, which was contrary to the findings of other existing data, which mentioned that the toxoplasma lesions had a predilection for the corticomedullary junction and the basal ganglia [11].

Clinical Characteristics	Number (Percentage)
Clinical Presentations *	
Fever	19(57.6)
Headache	17(51.5)
Generalized weakness	12(36.4)
Altered sensorium	12(36.4)
Vomiting	11(33.3)
Focal neurological signs	7(21.2)
Seizures	6(18.2)
Decreased vision	5(15.2)
Involuntary movements like chorea	3 (9.1)
Others **	6(18.2)
CD4 Count At Diagnosis Of Toxoplasmosis	
< 100	12(36.1)
100–200	13(39.1)
> 200	8 (24)
MEAN CD4 COUNT AT DIAGNOSIS OF TOXOPLASMOSIS (± S.D)	160.58 ± 112.2
MEDIAN CD4 COUNT	126
Serum Toxoplasma IgG Level(Iu/Ml)	
100-200	6(18.2)
200-300	24(72.7)
>300	3 (9.1)
MEAN SERUM TOXOPLASMA IgG LEVEL (IU/ml) (± S.D)	255.69 ± 99.62
CT/MRI Findings	
Yes	26(78.8)
No	1 (3)
Not known	6 (18.2)
Area Of Involvement	
Basal Ganglia	6(19.35)
Parietal	6(19.35)
Frontal	5(16.12)
Thalamus	4(12.90)
Temporal	3 (9.68)
Cerebellum	3 (9.68)
Occipital	2 (6.45)
Others ***	2 (6.45)
Antiretroviral Therapy	
No	8 (24.2)
Yes : before Toxoplasmosis	21(12.2)
: at / after Toxoplasmosis	4 (63.6)
Outcome	
Improved / Survived	27(81.8)
Expired	6 (18.2)
Recurrence In Those Who Survived	
Yes	2 (7.4)
No	25(92.6)

[Table/Fig-2]: Clinical manifestations, investigations and treatment outcomes of the CNS toxoplasmosis cases.

* More than one abnormality could be found in one patient.
** Giddiness, tingling and numbness, gait disturbance, urinary incontinence, emotional lability
*** Midbrain, Brain stem.

The geometric mean serum T. gondii antibody titer was 382.7 for the AIDS patients with CNS toxoplasmosis and it was 64.4 for the seropositive AIDS patients without CNS toxoplasmosis, according to a study in New York [12]. The mean IgG against toxoplasma in our study was 256. The high toxoplasma IgG levels in our study could be explained by the high rate of infections in India, which was also a reason for us to suspect opportunistic infections at a higher CD4 count. HIV-infected patients with toxoplasma encephalitis (TE) are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies [13-15,16]. The absence of the IgG antibody makes the diagnosis of toxoplasmosis unlikely, but not impossible. The anti-toxoplasma immunoglobulin M (IgM) antibodies are usually absent and the quantitative antibody titers are not diagnostically useful.

Toxoplasmosis rarely occurs as an opportunistic infection among patients with CD4 counts which are >200 cells/μL. The greatest risk occurs among patients with a $CD4^+$ count of <50 cells/μL [13-15,17]. Toxoplasma -seropositive patients who have a CD4 count of <100 cells/μL should be administered prophylaxis against TE [18]. In a previous study which involved 57 TE cases, the overall range of the CD4 cell count was from 0–1312, with a median of 229 cells/cumm, while the range of the CD4 cell count was 0–239 with a median of 25 cells/cumm at the time of diagnosis in patients with TE [19]. However, in our study, the range of the CD4 cell count during toxoplasmosis was 48–435, with the median CD4 count being 126 cells /cumm. The mean CD4 count was 160.58, with an S.D. OF 112.2. In our study, the finding that, toxoplasmosis occurred at a higher CD count of > 150 should warrant the prophylaxis for toxoplasmosis at a higher CD4 count. HIV-infected persons should be tested for the IgG antibody to toxoplasma soon after the diagnosis of the HIV infection to detect a latent infection with *T. gondii*.

According to the CDC guidelines, the initial therapy of choice for TE consists of the combination of pyrimethamine, sulfadiazine and leucovorin [20-23]. TMP-SMX was reported in a small (77 patients) randomized trial, to be effective and better tolerated than pyrimethamine-sulfadiazine [24]. The double-strength tablet, daily dose of TMP-SMX, which was recommended as the preferred regimen for the PCP prophylaxis also is effective against TE and is therefore recommended [18]. TMP-SMX, one double-strength tablet, three times weekly, is an alternative treatment.

The standard treatment regimen which was followed for toxoplasmosis in our hospital was cotrimoxazole once daily and a combination of sulphadiazine and pyremethamine thrice daily for 21 days, followed by secondary prophylaxis with cotrimoxazole till the CD4 count of > 100 was maintained for 6 months. In the setting of the absence of response or the emergence of adverse effects during the treatment, clindamycin 600mg IV thrice daily for 21 days was prescribed. A cure was based on the clinical improvement.

Toxoplasma-seronegative persons who had not taken a PCP prophylactic regimen which was known to be active against TE (e.g., aerosolized pentamidine), had to be retested for the IgG antibody to toxoplasma when their CD4 counts declined to <100 cells/μL, to determine as to whether they had seroconverted and were therefore at a risk for TE. Patients who had seroconverted had to be administered the prophylaxis for TE as has been described previously.

Toxoplasmosis as an initial manifestation of HIV was seen in 10 out of the 33 cases (30.3%). The lack of effectiveness of VCTC could have been the reason for this late presentation.

6 (18.18%) cases in our study developed toxoplasmosis, which was accompanied by an increase in the CD4 count after the initiation of ART. Several cases of neurological diseases have been attributed to immune reconstitution and toxoplasmosis, but more data are needed to verify that such cases were IRIS, which was related to *T. gondii* [25]. This pattern of disease after the start of an effective ART is called “Immune Reconstitution Inflammatory Syndrome” (IRIS) because it is believed to be the result of the recovering immune system belated (and often overly robust) response to an opportunistic infection (OI). According to a study in Houston, the most significant risk factor for developing IRIS was a dramatic drop in the viral load [26]. However, serial viral load studies were not available in our study due to financial constraints. In the developed world, patients with less advanced HIV disease usually get started on ART before developing extensive OIs , and thus would be less

likely to develop IRIS. However, in resource-limited settings, the clinicians need to be alerted to the dangers of IRIS in already ill patients who were starting with their first anti-retroviral regimen. In our study, among those who had IRIS, the mean CD4 was 363, while the mean CD4 in the absence of IRIS was 125, with a p value of 0.001.

HIV-infected persons, including those who lacked the IgG antibody to toxoplasma, should be counseled regarding the sources of the toxoplasma infection. To minimize the risk for acquiring toxoplasmosis, HIV-infected persons should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison. Specifically, lamb, beef, venison, and pork should be cooked to an internal temperature of 165°F–170ºF [27]. If the patient owns a cat, the litter box should be changed daily, preferably by an HIV-negative, non-pregnant person; alternatively, patients should wash their hands thoroughly after changing the litter box.

Patients who had completed the initial therapy for TE had to be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) [20-21] unless immune reconstitution occurred as a consequence of the ART, in which case the discontinuation of the treatment was indicated.

Adult and adolescent patients who receive the secondary prophylaxis (i.e., chronic maintenance therapy) for TE are at a low risk for the recurrence of TE. When they have successfully completed the initial therapy for TE, they remain asymptomatic with regards to the signs and symptoms of TE, and have a sustained increase in their $CD4^+$ counts of >200 cells/μL after the ART (e.g., >6 months) [28,29,30,31] A secondary prophylaxis (chronic maintenance therapy) for TE should be reintroduced if the $CD4^+$ count decreases to <200 cells/μL

LIMITATIONS

The seroprevalence rates of toxoplasmosis couldn't be evaluated as it was a hospital based retrospective study.

A definitive diagnosis couldn't be made due to lack of brain biopsies.

CT/MRI couldn't be repeated after implementing the treatment for toxoplasmosis for all the patients, and serial viral load studies were not available to document IRIS better, as a result of financial constraints.

RECOMMENDATIONS

The possibility of cerebral toxoplasmosis should be considered in every HIV-positive patient with neurological symptoms and empirical therapy should be instituted on wide indications.

In our study, we saw toxoplasmosis occurring at CD4 levels which were >150, which should warrant the prophylaxis for toxoplasmosis at a higher CD4 count.

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