Toxoplasmosis in HIV infection: An overview

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INTRODUCTION

Toxoplasma gondii is a protozoan parasite present world-wide and causes major opportunistic infections in HIV infected people. Cell-mediated immunity (CMI) will be developed after acute infection with T. gondii and infection is controlled but not eradicated. In this chronic or latent phase of infection, the organisms persist in the tissues of infected individuals such as brain, skeletal muscle, and heart. In HIV infection, symptomatic disease most often occurs as a result of reactivation of latent infection. Toxoplasmosis has been reported as the most common opportunistic infection in HIV/AIDS in developed countries and most common cause of focal brain lesions, coma and death. It commonly causes encephalitis in HIV-infected patients.

KEY WORDS
CD4 counts, HIV infection, toxoplasmosis

ABSTRACT

Toxoplasma gondii is an obligate intracellular protozoan parasite presenting as a zoonotic infection distributed worldwide. In HIV-positive individuals, it causes severe opportunistic infections, which is of major public health concern as it results in physical and psychological disabilities. In healthy immunocompetent individuals, it causes asymptomatic chronic persistent infections, but in immunosuppressed patients, there is reactivation of the parasite if the CD4 counts fall below 200 cells/µl. The seroprevalence rates are variable in different geographic areas. The tissue cyst or oocyst is the infective form which enters by ingestion of contaminated meat and transform into tachyzoites and disseminate into blood stream. In immunocompetent persons due to cell-mediated immunity the parasite is transformed into tissue cyst resulting in life long chronic infection. In HIV-infected people opportunistic infection by T. gondii occurs due to depletion of CD4 cells, decreased production of cytokines and interferon gamma and impaired cytoxic T-lymphocyte activity resulting in reactivation of latent infection. The diagnosis can be done by clinical, serological, radiological, histological or molecular methods, or by the combination of these. There is various treatment regimen including acute treatment, maintenance therapy should be given as the current anti T. gondii therapy cannot eradicate tissue cysts. In HIV patients, CD4 counts <100; cotrimoxazole, alternately dapsone + pyrimethamine can be given for 6 months. Hence, early diagnosis of T. gondii antibodies is important in all HIV-positive individuals to prevent complications of cerebral toxoplasmosis.

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Toxoplasma gondii is an obligate intracellular protozoan parasite presenting as a zoonotic infection distributed worldwide. In HIV-positive individuals, it causes severe opportunistic infections, which is of major public health concern as it results in physical and psychological disabilities. In healthy immunocompetent individuals, it causes asymptomatic chronic persistent infections, but in immunosuppressed patients, there is reactivation of the parasite if the CD4 counts fall below 200 cells/µl. The seroprevalence rates are variable in different geographic areas. The tissue cyst or oocyst is the infective form which enters by ingestion of contaminated meat and transform into tachyzoites and disseminate into blood stream. In immunocompetent persons due to cell-mediated immunity the parasite is transformed into tissue cyst resulting in life long chronic infection. In HIV-infected people opportunistic infection by T. gondii occurs due to depletion of CD4 cells, decreased production of cytokines and interferon gamma and impaired cytoxic T-lymphocyte activity resulting in reactivation of latent infection. The diagnosis can be done by clinical, serological, radiological, histological or molecular methods, or by the combination of these. There is various treatment regimen including acute treatment, maintenance therapy should be given as the current anti T. gondii therapy cannot eradicate tissue cysts. In HIV patients, CD4 counts <100; cotrimoxazole, alternately dapsone + pyrimethamine can be given for 6 months. Hence, early diagnosis of T. gondii antibodies is important in all HIV-positive individuals to prevent complications of cerebral toxoplasmosis.
Infection occurs by ingestion of contaminated water, food from oocysts excreted by cats, or infected meat which is improperly cooked.\[^{[14-16]}\] Toxoplasma pneumonia occurs by respiratory route, transplacental route responsible for abortion and neonatal pathology, nosocomial through blood-transfusion, organ transplants, and laboratory accidents.\[^{[7-9]}\]

**MORPHOLOGY**

*T. gondii* has three morphological forms - oocyst, tachyzoites, and tissue cysts containing bradyzoites. Cats act as the definitive hosts and bring oocyst which are infective forms. Following ingestion by humans, the sporozoites present in the oocyst develop into tachyzoites, and enter into the nucleated cells of the host. These tachyzoites are invasive forms, multiply rapidly, lead to cell rupture and invade nearby cells and transported to other parts of the body via blood and lymphatic circulation. As a result of inflammatory response, tachyzoites are transformed into tissue cysts, which are dormant form containing numerous bradyzoites. The sites of cyst formation are brain, skeletal muscle, and cardiac muscle. In immuno-compromised persons, bradyzoites can be released from the cysts and transformed into tachyzoites.

In HIV/AIDS patients, toxoplasma encephalitis is one of the most common opportunistic infections. Central nervous system (CNS) disease occurs when CD4 cell count is \(<200\) cells/µl. The greatest risk is in patients with CD4 count \(<50\) cells/µl. Patients with cerebral toxoplasmosis presented with higher titres of anti-*T. gondii* IgG antibodies than patients with other diseases.\[^{[13]}\]

**PATHOGENESIS**

Following ingestion of contaminated food, tachyzoites disseminate throughout the body, infect all nucleated cells, leading to production of necrotic focus surrounded by inflammation. As a result of CMI, tachyzoites are transformed into tissue cysts resulting in life-long infection. Cellular immunity mediated by T-cells, macrophages, and activity of Type-1 cytokines (interleukin-12 [IL-12] and interferon [INF] gamma) is necessary for maintaining the quiescence of chronic *T. gondii* infection.\[^{[14]}\] The production of IL-12 and INF gamma is stimulated by CD154 (also known as CD40 ligand) in human models of *T. gondii* infection. CD154 acts by triggering dendritic cells and macrophages to secrete IL-12, which in turn enhances the production of INF gamma by T-cells.\[^{[15]}\]

In HIV infection due to immunosuppression, opportunistic infection occurs with *T. gondii* due to depletion of CD4 T-cells, impaired production of IL-12 and INF gamma and impaired cytotoxic T-lymphocyte activity.\[^{[16]}\] There is decreased *in vitro* production of IL-12, INF gamma, and decreased expression of CD154 in response to *T. gondii*.\[^{[17-19]}\]

**CLINICAL MANIFESTATIONS**

Toxoplasmosis in HIV-infected patients manifests mainly as encephalitis, chorioretinitis, and pneumonitis or disseminated infection depending upon the immune status of the host. It is sub-acute in onset with focal neurological signs associated with fever, altered sensorium, and headache. Cerebellar, sub-cortical, or cortical lesions can be present in over 50% of infected cases resulting in hemiparesis, ambulatory gait, and speech abnormalities.\[^{[20]}\] Some people with encephalitis can also present with neuropsychiatric disorders including psychosis, dementia, anxiety, and personality disorders.\[^{[21]}\]

In HIV-infected patients, toxoplasmosis may present extracerebrally with or without encephalitis. The most common presentations can be ocular and pulmonary disease.\[^{[22]}\] Patients with chorioretinitis presents with blurred vision, scotoma, pain, or photophobia. Pulmonary manifestations are similar to pneumocystis jiroveci pneumonia. In HIV-infected patients, a disseminated toxoplasmosis may occur with fever, sepsis-like syndrome with hypotension, disseminated intravascular coagulation, elevated lactate dehydrogenase, and pulmonary dehydrogenase.\[^{[23-24]}\]

**EPIDEMIOLOGY**

The prevalence of toxoplasma infection varies depending on the geographical area and population groups and also with the age. In Europe and other tropical countries, the prevalence is over 50%.\[^{[25]}\] In Hong Kong, it was 9.8%.\[^{[21]}\] In US, about 1/3rd of HIV-infected patients have antibodies against *T. gondii* and seroprevalence data of HIV-infected patients come from small, predominantly male cohorts in which the range of prevalence is 3–22%.\[^{[26,27]}\]

The prevalence in Nigeria is 75.4%,\[^{[28]}\] 58.4% in Tunisia,\[^{[29]}\] 28.5% in HIV-infected women in Benin,\[^{[30]}\] 40.2% in Senegal.\[^{[31]}\] Spalding et al.\[^{[32]}\] reported 74.5% in South Brazil, Jeannel et al.\[^{[33]}\] reported 63.7% in Paris, Kodym et al.\[^{[34]}\] reported 30% in Chezech republic, Xiao et al.\[^{[35]}\] reported 12.5% of Toxoplasma seropositivity in HIV-positive patients in China.

In India, one study by Anuradha and Preethi, observed seroprevalence of 34.78% among HIV-positive patients.\[^{[36]}\] In one study by Sucilathangam et al. observed 15% of Toxoplasma seropositivity in HIV-positive people.\[^{[37]}\] In one study by Meisher et al.,\[^{[38]}\] seropositivity was 67.8% in HIV-infected people when compared to
immunocompetent adults (30.9%). The variation in prevalence rates could be due to differences within the geographical areas, infection is more common in tropical conditions and at lower altitudes than in cold and mountainous region. Another reason could be due to the recruited subjects, using different assay and the year of study.

The two largest toxoplasma seroprevalence studies of HIV-infected US women included 169 and 139 women and reported seroprevalence is 22% and 20%, respectively. In one study by Falusi et al. observed 15.3% seropositivity in HIV-infected women and 14.3% positivity in uninfected women. In one study, conducted by Anuradha and Preethi showed the seropositivity in HIV patients was 34.78% with 28.95% in males and 38.89% in females and the most common age group affected was 31–40 years. In one study by Meisheri et al. showed that highest prevalence at third and fourth decade of life. The increase in prevalence rate with increase in age may be due to the increase risk of exposure with infection with increase in age.

ASSOCIATION WITH CD4 COUNTS

There is an association between CD4 count and prevalence of toxoplasmosis. In a study conducted by Anuradha and Preethi in patients with CD4 count 51–100 cells/mm³ without any neurological symptoms, toxoplasma IgG antibodies are present in 75% of cases. In one study by Osunkalu et al. reported that 79.4% of HIV-positive patients without neurological symptoms has CD4 count <100 cells/mm³. In one study by Eliaszewicz M et al., in France, showed that 79% of patients with neurological symptoms had CD4 counts <150 cells/mm³. In one study by Suciithangam et al., CD4 counts were <100 cells/mcl in toxoplasma seropositive patients. These findings are also correlating with other studies.

DIFFERENTIAL DIAGNOSIS OF TOXOPLASMOSIS IN HIV PATIENTS

Differential diagnosis of toxoplasma encephalitis may be lymphoma of CNS, progressive multifocal encephalopathy, tuberculosis including tuberculoma, focal CNS lesions caused by fungi such as Cryptococcus neoformans, Aspergillus spp., Nocardia spp., cytomegalovirus and herpes simplex encephalitis, and bacterial brain abscess.

DIAGNOSIS

Cerebral toxoplasmosis is common in HIV/AIDS positive patients and causes more serious manifestations. Hence, definitive diagnosis for cerebral toxoplasmosis is important. Presumptive diagnosis can be made by clinical presentation, radiological findings, molecular studies, serological tests, and also response to therapy. The clinical diagnosis can be made in HIV positive patients with CD4 count <100 cells/µL presenting with compatible focal neurological lesions. In case of cerebral toxoplasmosis, there is an improvement of clinical and radiological features after 2-3 weeks of empirical therapy and outcome will be good.

SEROLOGICAL DIAGNOSIS

Anti T. gondii IgG antibodies start increasing after 1–2 weeks of infection and reaches peak in 6–8 weeks. They decline gradually over next 1–2 years but they can persist for life time in some cases. Demonstration of high titers of anti-T. gondii IgG antibodies with high IgG avidity gives serological evidence of infection and also indicates the secondary reactivation of latent or chronic toxoplasma infection. Hence, it is important to detect toxoplasma seropositivity status in all HIV-infected patients to estimate the risk for cerebral toxoplasmosis.

RADIOLOGICAL DIAGNOSIS

Computed tomography (CT) or MRI gives presumptive diagnosis of cerebral toxoplasmosis. The findings are observed as hypodense lesions with ring enhancing and peri-lesional edema, which are seen in majority of patients. In 20% of patients, the findings will be hypodense lesions without contrast enhancing and without focal lesions. An unusual and highly suggestive imaging of cerebral toxoplasmosis is the eccentric target sign in which small asymmetric nodule along the wall of enhancing ring is seen. A computerized axial tomography scan is sensitive diagnostic method for focal neurological deficits but it may not diagnose the minimal inflammatory response seen in early stages. Magnetic resonance imaging is more sensitive than computed tomography scan in diagnosing toxoplasmosis from brain lesions. However, newer imaging techniques such as signal photon emission CT or positron emission tomography can enhance the specificity to rule out other CNS lesions such as lymphoma.

BRAIN BIOPSY

For the demonstration of tachyzoites and tissue cysts, it gives definitive diagnosis but it is not considered because the empirical therapy of suspected toxoplasmosis can usually confirm the diagnosis.

MOLECULAR DIAGNOSIS

Direct detection of T. gondii DNA in biological samples by polymerase chain reaction has provided a breakthrough for the diagnosis of toxoplasmosis. For cerebrospinal fluid and blood samples, it gives poor results and variable sensitivity.
PREVENTION OF TOXOPLASMOsis IN HIV/AIDS

All HIV-infected individuals should be tested for baseline IgG antibodies to toxoplasma to detect latent infection. All HIV-infected individuals should be counseled regarding the exposure to toxoplasma infections.[54] Eating of raw or undercooked meat must be avoided. Proper hand washing should be done after contact with raw meat, gardening or contact with soil. Fruits and vegetables should be washed well before eating them raw. Handling cat’s litter is to be avoided. Pet animals such as cats should be fed with canned or dried commercial food or well cooked food but not raw, undercooked meat.

Diagnostic management, treatment and prophylaxis of toxoplasmosis are shown in Figure 1 and Tables 1-3.[52,55]

NEWER APPROACHES

Further studies can be done for the prevention not only by giving chemoprophylaxis but also by immunization. In one study by Meng et al.[56] worked on animal models and compared the protective efficacy of different immunization strategies in BALB/c mice. They suggested that vaccination regimens can trigger significantly high levels of CMI and humoral immune response than the control groups injected with phosphate buffer saline or pEGFP (eukaryotic expression vector). DNA vaccines followed by peptide boosting significantly increased the levels of IgG, IgG2a, and INF-gamma. Cytokines play an important role in the host resistance against T. gondii and gives protection in the early infection and controls the replication of the protozoa.[57] They also estimated the levels of cytokine production in mouse. INF-gamma is important in restricting the growth of T. gondii in acute infections and preventing the reactivation of parasites from dormant cysts.[58] In their study high levels of TNF-gamma production was induced in experimental animals and compared to controls.

A study by Maggi et al. suggested that INF-gamma correlates with the differentiation of TH1 cells and INF4 cells.[59] Hence, INF-gamma is also an important marker for the protective immunity against T. gondii.

Further studies can be done and systemic evaluation of immune response can be generated by different experimental parameters.

Table 1: Treatment of crebral toxoplasmosis

| Treatment regimens | Drugs and dosage |
|--------------------|------------------|
| First choice       | Sulphadiazine oral 1000 (260 kg) to 1500 mg (260 kg) 6h + pyrimethamine oral 200 mg loading dose, then 50 (<60 kg) to 75 (≥60 kg) mg PO qd + folinic acid (leucovorin) oral, IV, or IM, 10-20 mg qd (≤50 mg qd) |
|                    | Clindamycin oral or IV 600 mg 6h (IV≤1200 mg 6h) + pyrimethamine oral 200 mg loading dose, then 50 (<60 kg) to 75 (≥60 kg) PO qd + folinic acid (leucovorin) oral, IV, IM, 10-20 mg qd (≤50 mg qd) |
| Alternative        | Pyrimethamine + folinic acid+one of the following |
|                    | Atovaquone oral 100 mg q12h |
|                    | Clarithromycin oral 500 mg q12h |
|                    | Azithromycin oral 900-1200 mg qd |
|                    | Dapsone oral 100 mg qd |
|                    | Co-trimoxazole oral or IV 5 mg/kg (trimethoprim component) q12h |

Table 2: Maintenance treatment for toxoplasmosis

| Maintenance regimen | Drugs and dosage |
|---------------------|------------------|
| First choice        | Same as treatment regime but half doses, discontinue if >200 CD4 cells/μl for >6 months (asymptomatic with normal MRI or without contrast enhancement in MRI) |
| Possibly            | Co-trimoxazole 2 tablet or 960 mg qd |

MRI: Magnetic resonance imaging

Table 3: Primary prophylaxis regimen for toxoplasmosis

| Primary prophylaxis regimen | Drugs and dosage |
|-----------------------------|------------------|
| Standard                    | Co-trimoxazole 1-2 tablet or 480-960 mg qd |
| Alternative                 | Dapsone 50 mg qd |
|                             | Dapsone 50 mg qd + pyrimethamine 50 mg/week + folinic 25 mg/week |

CNS s/s, e.g. headache

Brain imaging

Mass lesions

Yes

Additional investigation e.g. LP, rerepeat

Empiric treatment for Toxoplasticencephalitis

Ant-toxoplasma serology

+ve

Definitive diagnosis and Treat accordingly

Yes

Clinical or radiological Improvement in 2 weeks

Presumptive diagnosis of TE and continue treatment followed By maintenance therapy

Figure 1: Management of toxoplasmosis in HIV patients
CONCLUSIONS

*T. gondii*, coccidian protozoan intracellular parasite, is one of the most causative agents of opportunistic infections in HIV/AIDS patients. Their epidemiological and clinical aspect in association with HIV-infected patients was reported worldwide. In HIV infection due to immunosuppression, there is reactivation of chronic latent infection resulting in Toxoplasma encephalitis. The prevalence rates of toxoplasma infection in HIV-positive patients are variable across different geographical areas. The prevalence rates are increasing with age. The risk of infection is more when the CD4 counts are <100 cells/µL. Diagnosis can be made by clinical, serological, radiological, histological, and molecular methods. Due to the high rate of reactivation in HIV-positive patients and complications of cerebral toxoplasmosis, all HIV-positive patients must be tested for the presence of *T. gondii* antibodies. Those who tested positive for anti *T. gondii* antibodies should be considered for chemoprophylaxis. Proper treatment and prophylaxis with maintenance therapy will control the infection. However, proper preventive measures and counseling regarding the exposure to toxoplasma infection can also help in prophylaxis. Further research can be done on the immunization methods, which will enhance the CMI.

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Conflicts of interest
There are no conflicts of interest.

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