TOXOPLASMOSIS REVISITED

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Toxoplasmosis is a zoonotic infection in humans caused by the protozoal intracellular parasite Toxoplasma gondii, sporozoan protozoa in the genus of Toxoplasma. Cats are the primary hosts, while humans and other mammals serve as intermediate hosts. Infection with T gondii is common among humans, and it is estimated that one third of the world's population has been exposed. The seroprevalence varies widely in different regions and depends on socio-economic status, environmental factors and meat-cooking habits. Indian studies of prevalence of toxoplasmosis reveal a wide variation and one study reported prevalence, as high as 77% in women of reproductive age group. The average prevalence among Indian pregnant women is 7.7%. There is no published data on the disease prevalence in Kerala. A pilot study done in Kozhikode district revealed a sero-prevalence of 27.16%.

There is a close relationship between the incidence of toxoplasmosis and the seroprevalence of toxoplasma antibodies within a population. Infection with the parasite occurs among all age groups and as a consequence, serological evidence of the infection increases with increasing age. Most infections are however sub clinical and disease typically becomes apparent only as a congenitally acquired infection and in patients with significant immunodeficiency such as in acquired immunodeficiency syndrome (AIDS).
The protozoan was first discovered by Nicolle and Manceaux in 1908. He first isolated it from African rodents Ctenodactylus gundii. It was identified as an agent of infectious disease in 1932. In 1983 toxoplasmosis was more widely recorded as a cause of morbidity in immune deficient patients including AIDS and idiopathic CD4 cytopenia syndrome.

**Life cycle of Toxoplasma gondii**

Toxoplasma gondii occurs in 3 stages.

1. Tachyzoites, also called trophozoite is the rapidly multiplying form and can infect any cell in the body.

2. Bradyzoites and tissue cyst is a stage encysted in the tissue.

3. Oocyst is a cyst surrounded by a thick resistant wall. It is seen in definitive hosts formed by sexual reproduction. Trophozoites and tissue cysts represent stages in asexual reproduction.

Humans acquire infection via eating undercooked or raw meat infected with tissue cysts, via ingestion of food or water contaminated with infected cat feces carrying sporulated oocysts. Maternal to fetus transmission can also occur. Rare cases of individuals becoming infected through blood transfusions or organ transplantation have also been reported.

Sporozoites from oocysts and bradyzoites from tissue cysts invade intestinal mucosa and in epithelial cells multiply as tachyzoites. Tachyzoites spread to mesenteric lymph nodes and then via blood
stream and lymphatics reach organs such as brain, eye, liver, spleen, heart, skeletal muscle, lymph nodes and placenta of pregnant mother. Focal areas of necrosis develop in these organs.2

With the development of immunity tachyzoites are destroyed and acute infection resolves. Some of the tachyzoites may still persist and develop into tissue cysts containing bradyzoites, which remain viable for years. When there is suppression of immune system, infection is reactivated.

**Host immunity**

Development of both humoral and cellular immunity alter the course of toxoplasma infection and its clinical manifestations. Humoral immunity is characterized by the production of specific circulating antibodies, both IgM and IgG. Toxoplasma specific Ig M antibodies appear first, hence its detection is suggestive of an acute infection. IgG antibodies appear late and persist, and is suggestive of a chronic infection. Cell mediated immunity through activated macrophages and monocytes is suggested to play an important role in conferring resistance to re-infection as well as in the development of initial resistance in toxoplasmosis in co-operation with humoral antibodies. This stage is associated with the disappearance of tachyzoites from various tissues, especially from extra neural tissues and formation of tissue cysts. The tachyzoites may persist in the central nervous system and in the eye due to the absence of circulating antibodies in the tissues.

**Infection in the immune-competent host**

In humans, asymptomatic or benign toxoplasmosis is the rule in immunocompetent patients. Eighty to ninety percent of T gondii
infections in immunocompetent hosts are asymptomatic. Generally, when acute infection is symptomatic, manifestations include symmetric fever, nonspecific rash and lymphadenopathy. The most common presentation of symptomatic postnatally acquired toxoplasmosis in immunocompetent patients is painless cervical adenopathy. When fever and lymph node enlargement persist, more often it ends in biopsy studies and the common histologic picture is necrosis with granulomas. In majority of cases the clinical course is benign and symptoms and signs resolve within a few weeks. However, severe manifestations of infection, including chorioretinitis, can occur in some immunocompetent hosts.3

Chorioretinitis or ocular toxoplasmosis is a relatively common manifestation of T. gondii infection. Ocular toxoplasmosis occurs when cysts deposited in or near the retina become active, producing tachyzoites. Focal necrotizing retinitis is the characteristic lesion, but retinal scars from prior reactivation are typically present. Clinical presentation usually is with eye pain and decreased visual acuity. Adults who had acquired disease in infancy usually present with bilateral eye involvement. Adults with acute infection generally present with unilateral ocular involvement.4

Figure 1. White focal lesions with inflammation of vitreous humor (the classic ‘headlight in the fog’ appearance) seen on ophthalmoscopic examination in a patient with ocular toxoplasmosis.

Depending on the location and severity of toxoplasmic chorioretinitis, infection can result in permanent retinal scarring and loss of visual acuity. Recurrent episodes are common, resulting in multiple areas of retinal scarring and functional loss.
Studies have shown that in high endemic areas there is an association between a typical genotype and severe toxoplasmosis acquired by immune competent adults. It has also been recently reported that an unusual abundance of atypical strains in the environment is associated with human ocular toxoplasmosis and with severe forms of congenital toxoplasmosis.

**Congenital infection**

Approximately 10-20% of pregnant women infected with *T. gondii* have clinical symptoms of the disease. The most common signs of infection are lymphadenopathy and fever. If the mother was infected prior to pregnancy, there is virtually no risk of fetal infection, as long as she remains immunocompetent. If the infection is acquired during the pregnancy, there is risk of infection to the fetus. The rate of transplacental infection has been estimated to be 50% for untreated mothers and 25% for treated mothers.

The rate of fetal infection varies with trimester with 10-25% of infections occurring in the first trimester, 30% in the second trimester, and 50% in the third trimester. Infection during the first or second trimesters appears to be most severe. The clinical features of congenitally acquired *T. gondii* infection include chorioretinitis, blindness, seizures, microcephaly, anemia, and encephalitis. Infections acquired during the third trimester are usually subclinical; however, clinical disease may still occur later in life. 75% of infants congenitally infected with *T. gondii* manifest no symptoms, 14% had evidence of chorioretinitis and 9% demonstrate signs of CNS involvement.
Infection in immunocompromised patients

Most cases of toxoplasmosis in immunocompromised patients are a consequence of latent infection and reactivation. In patients with AIDS, *T. gondii* tissue cysts can reactivate with CD4 counts less than 200 cells/μL. When CD4 counts are less than 100 cells/μL, clinical disease is more likely. Patients with CD4 counts less than 100 cells/μL and *T. gondii* IgG positivity have a 30% risk of eventually developing reactivation disease, if adequate prophylaxis is not given or immune function is not restored.

Although toxoplasmosis in immunocompromised patients may manifest as chorioretinitis, reactivation disease in these individuals is typically in the central nervous system with brain involvement being common.

Toxoplasmic encephalitis and brain abscess presents most commonly as headache, focal neurologic deficits and seizures. Lumbar puncture studies performed when there is no evidence of raised ICT reveals a picture mimicking tuberculous meningitis. With significant disease, patients may also have the signs and symptoms of elevated intracranial pressure. Cerebral toxoplasmosis is generally identified on CECT scan as multiple ring-enhancing lesions; solitary lesions may also be seen. Absence of lesions in CT or MRI scans does not rule out the diagnosis of central nervous system toxoplasmosis. When plain CT scan of a patient reveals an infarct like picture, contrast study must be done, as many cases are misdiagnosed as vascular events. In a patient who is immunosuppressed and has focal neurologic deficits, if CT scan is normal, MRI scan is advisable.

Aside from central nervous system toxoplasmosis, toxoplasmic pneumonitis, myocarditis, as well as disseminated toxoplasmosis are also
commonly identified in immunocompromised patients. Toxoplasmic pneumonitis typically presents with symptoms, which are typical for an infectious pulmonary process. Symptoms include fever, dyspnea, and cough. Chest radiography is often nonspecific, but findings may be similar to that of Pneumocystis jiroveci pneumonia. Diagnosis is established via broncho-alveolar lavage (BAL). Most patients with extra-central nervous system manifestations of toxoplasmosis will also be noted to have central nervous system lesions when appropriate radiographic studies have been performed.

Figure 2. Contrast Enhanced Computed Tomographic scan (CECT) of brain. Multiple ring enhancing lesions can be seen.

Toxoplasmic encephalitis and brain abscess can result in permanent neurologic sequelae depending on the location of the lesion and the extent of local damage and inflammation.8

Diagnosis

Diagnosis is confirmed by isolation of toxoplasma from blood or body fluids, demonstration of parasite in tissues, detection of specific nucleic acid sequence with DNA probes, or detection of toxoplasma specific immunoglobulin. Polymerase chain reaction (PCR) amplification is used to detect the DNA in body fluids and tissues. Amniotic fluid, brain tissue, BAL fluid, cerebrospinal fluid, vitreous and aqueous fluid, urine and peripheral blood can be used for PCR. IgM levels are estimated to demonstrate acute infection. IgG levels are assayed for diagnosing past infection. Many tests for avidity of Toxoplasma IgG antibodies have been
introduced to differentiate between recently acquired and distant infection. 9

**Treatment**

Immuno-competent, non-pregnant patients do not require treatment. If there is eye involvement or central nervous system involvement, treatment should be started. Treatment includes six-week regimen of pyrimethamine (100 mg loading dose per orally followed by 25-50 mg/d) plus sulfadiazine (2-4 g/d divided four times a day) or pyrimethamine (100 mg loading dose per orally followed by 25-50 mg/d) plus clindamycin (300 mg per orally four times a day) and folic acid (leucovorin) (10-25 mg/d) to prevent hematologic toxicity of pyrimethamine. Trimethoprim (10 mg/kg daily) and sulfamethoxasole (50 mg/kg/daily) can also be used. In patients with history of allergy to the former drugs azithromycin 500 mg daily or atovaquone 750 mg twice a day can be considered. Atovaquone is a promising alternative for the treatment of ocular toxoplasmosis in immune competent patients. Atovaquone tablets (750 mg four times a day) for 3 months along with prednisolone (40 mg) tablets on tapering dose added on day 3 onwards is as effective as conventional therapy. Consider administration of steroids in patients with radiologic midline shift, clinical deterioration after 48 hours, or elevated intracranial pressure.

**Pregnant patients**

Spiramycin and pyrimethamine-sulfonamide are both used. Spiramycin appears to be somewhat more easily tolerated than pyrimethamine-sulfonamide combination. The dose of spiramycin is 1g per orally every
8h. Pyrimethamine (25 mg/daily per orally) and sulfadiazine (4 g/ daily per orally) divided twice or thrice daily until delivery (this drug may be associated with marrow suppression and pancytopenia) and leucovorin 10-25 mg/ daily per orally to prevent bone marrow suppression. Pyrimethamine can be excreted through breast milk, hence affected women should not nurse infants.10

Patients with AIDS

Patients with acquired immune deficiency syndrome (AIDS) are treated with pyrimethamine 200 mg per orally initially, followed by 50-75 mg/daily per orally plus folinic acid 10 mg/ daily per orally plus sulfadiazine 4-8 g/ daily per orally for as long as 6 weeks, followed until immune reconstitution or as lifelong suppressive therapy.

Suppressive therapy for patients with AIDS (CD4 < 100) is pyrimethamine 50 mg/daily per orally plus sulfadiazine 1-1.5 g/daily per orally plus folinic acid 10 mg/daily per orally for life or until immune reconstitution.

Patients with AIDS, central nervous system toxoplasmosis and evidence of midline shift or increased intracranial pressure may benefit from adjuvant steroid therapy.11

Summary

Toxoplasma remains a highly prevalent infection particularly in immunosuppressed people. Infection with Toxoplasma in immune-competent people is generally without symptoms and consequently it is considered of low impact from a public health perspective. Infection can
be severe in immunocompromised individuals with AIDS in whom infection can lead to cerebral toxoplasmosis. Seroconversion in pregnant women could result in the transmission of the parasite to the fetus with severe sequelae or with a delayed damage, developing to chorioretinitis at the adult stage. T. Gondii is considered a re-emerging parasite and is a significant cause of morbidity and mortality in humans.

References


