Ocular Toxoplasmosis

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Toxoplasmosis is the most common cause of posterior uveitis in many parts of the world. Prevalence is more in tropical countries than cold areas. It is caused by *Toxoplasma gondii*, an obligate intracellular protozoan parasite which exists in three forms: oocyst, bradyzoite and tachyzoite. Tachyzoites are the invasive forms, bradyzoites are the encysted forms and sporozoites (oocysts) exist in the cat only. Cats are the definitive hosts where as humans and other animals act as intermediate hosts. Human infection by *T. gondii* can be acquired or congenital. The transmission occurs by ingestion of raw or undercooked meat infected with tissue cysts, ingestion of food and water contaminated with oocysts, ingestion of eggs and milk contaminated with tachyzoites, blood transfusion, organ transplantation and transplacental transmission. *T. gondii* can also rarely be transmitted via blood and infections of laboratory personnel through contact with contaminated needles.

**Congenital toxoplasmosis**

Congenital infection develops in 30% to 50% of infants born to mothers with acquired toxoplasmosis during pregnancy. The prevalence of acquired toxoplasmosis during pregnancy is 0.2% to 1%. The lowest incidence occurs in the first trimester (15% to 20%), and the highest incidence is in the third trimester (59%) possibly because of increased vascularity of the placenta at that time. Early maternal infection in the first trimester is severe and leads to spontaneous abortion. Transmission during second trimester may result in moderate disease that presents as fever, maculopapular rash, hepatosplenomegaly, seizures, jaundice, thrombocytopenia and lymphadenopathy. The classic triad of congenital toxoplasmosis is retinochoroiditis, hydrocephalus and cranial calcification. Maternal infection in the third trimester usually results in asymptomatic infants.

**Acquired toxoplasmosis**

Typically 70%-90% of immunocompetent patients who acquire toxoplasmosis are symptom free. Even a symptomatic disease is so mild and nonspecific that it goes unrecognized. The true incidence of ocular toxoplasmosis in the immunocompetent patients is estimated to be ranging from 2-20%. The time interval between systemic infection and the appearance of ocular lesions is variable, ranging from few days to years. Acquired toxoplasmosis initially starts as an acute flu like illness with malaise, myalgia, hay fever, maculopapular skin rash and lymphadenopathy. This picture is usually self-limiting and usually resolves in 2-4 weeks. Rarely the clinical manifestations may be severe leading to pneumonitis, polymyositis, myocarditis, encephalopathy, hepatitis and splenomegaly, resulting in significant morbidity and mortality. Toxoplasmosis can also affect immunocompromised patients with AIDS, Hodgkins disease, hematological malignancies, and organ transplant recipients. Ocular toxoplasmosis in AIDS patients occurs in 1-2% cases and 30 -50% of these patients have intracranial involvement. Hence, all AIDS patients with ocular toxoplasmosis must undergo a complete neurological evaluation including computed tomography (CT) or magnetic resonance imaging (MRI) with contrast and lumbar puncture.
Ocular toxoplasmosis

Ocular toxoplasmosis occurs when the parasite invades the intraocular tissue through the blood stream. The proliferating parasites cause retinal necrosis and hypersensitivity reaction to T. gondii antigens causes vasculitis, uveitis and papillitis. Recurrence of infection is due to multiplication of parasites from the retinal cysts located at the borders of retinochoroidal scars. Earlier reports suggested that ocular toxoplasmic scars were residua of congenital infection, however there are no laboratory methods to discern between congenital and acquired infection. Recent serological studies have shown that acquired infections play more role in ocular toxoplasmosis.

Clinical features

Symptoms: Children present with reduced visual acuity, strabismus, nystagmus and leucocoria. Adults complain of decreased vision, floaters, and metamorphopsia. Signs: The typical toxoplastic lesion is a focal necrotizing granulomatous retinochoroiditis at the edge of a pigmented scar accompanied by vitreous inflammation (Fig. 1). When vitritis is severe that the retinal lesion is just seen, it is described as “headlight in the fog”. Ophthalmoscopically, a yellowish-white exudate is seen with ill-defined borders due to surrounding retinal edema (Fig. 2). The lesion progressively decreases in size and cicatrisation occurs from the periphery towards the center, with variable pigmentary hyperplasia and choroid atrophy. Vitritis is usually seen in all cases. It may present as diffuse or localized exudates, pigments, hemorrhage or posterior vitreous detachment.

Vasculitis in ocular toxoplasmosis, either adjacent or distant from the active lesion, mainly involves the veins (Fig. 3). It may present as diffuse periphlebitis, frosted branch angiitis, (Fig. 4) or segmental vasculitis. It is produced by the antigen-antibody deposition in the vessel walls. Less commonly, kyrieleis arterialitis – presence of periarterial exudates or plaques, not associated with vascular leakage or obstruction may also be seen (Fig. 5 a, b). Complications such as retinal hemorrhages, vascular occlusions, shunts, and choroidal neovascular membrane (Fig. 6) are however uncommon. Anterior uveitis in ocular toxoplasmosis may either be granulomatous or non granulomatous. It is probably a hypersensitivity reaction to Toxoplasma antigen.
Table showing various antitoxoplasma drugs with dosage in adults and children

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
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<tbody>
<tr>
<td>Pyrimethamine</td>
<td>Loading dose: 100mg</td>
<td>Infants: 1mg/kg once daily for 1 year</td>
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<tr>
<td></td>
<td>Treatment dose : 25mg/day</td>
<td>Children:Loading dose 2mg/kg/day (max. 100mg/day)</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>7.5 - 15 mg in alternate days</td>
<td>5mg every 3 days</td>
</tr>
<tr>
<td>Sulphadiazine</td>
<td>4g daily divided every 6 hours</td>
<td>Newborns: 100mg/kg/day divided every 6 hours</td>
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<tr>
<td></td>
<td></td>
<td>Children : Loading dose :75mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment dose :120-150 mg/kg/day ; divided every 4-6 hours (max.dose : 6g/day)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>150-450 mg/dose every 6-8 hrs (max. dose: 1.8g/day)</td>
<td>8-25 mg/kg/day in 3-4 divided doses</td>
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<td></td>
<td>Commonly used 300mg 4 times a day.</td>
<td>6-12 mg TMP/kg/day in divided doses every 12 hours</td>
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<tr>
<td>Trimethoprine –</td>
<td>1 tablet twice daily for 4-6 weeks</td>
<td>Loading dose: 10mg/kg/day (max dose: 500mg/day)</td>
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<tr>
<td>sulphamethoxazol</td>
<td></td>
<td>Treatment dose 5mg/kg/day (max. dose: 250mg/day)</td>
</tr>
<tr>
<td>DS tablet (160mg/800mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Loaded dose: 1g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment dose :500 mg once daily for three weeks</td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>750mg every 6 hours</td>
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</tbody>
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It presents as mutton fat keratic precipitates, fibrin, anterior chamber cells and flare, Koeppe and Busacca nodules and posterior synechiae. In case of delayed treatment, complications like pupillary block, rubeosis iridis, cataract and glaucoma may develop.

Atypical presentations of ocular toxoplasmosis may be:
1. Punctate outer retinal toxoplasmosis
2. Neuroretinitis
3. Papillitis
4. Multiple pseudoretinitis
5. Fuchs’ heterochromic iridocyclitis

Fig. 4. Frosted Branch Angiitis with retinochoroiditis

Fig. 5. a - Active retinitochoroiditis with overlying vitritis and Kyrieleis arterialitis. b - Healed lesion after 2 months of antitoxoplasma therapy

Fig. 6. Healed toxoplasmic retinochoroiditis scar with choroidal neovascular membrane
Fuchs’ heterochromic iridocyclitis

The incidence of chorioretinal scars in Fuchs’ patients varies from 8% to 65%. It has been proposed that primary retinochoroidal inflammation results in production of antibodies which cross react with anterior chamber antigens causing anterior uveitis, iris atrophy and heterochromia.

Multifocal or diffuse retinochoroiditis is usually seen in immunocompromised or elderly patients (Fig. 8). Toxoplasmic scleritis is associated with severe retinitis producing overlying choroidal and scleral inflammation.

Complications of ocular toxoplasmosis include cataract, secondary glaucoma, band keratopathy, retinal detachment, cystoid macular edema, optic atrophy and choroidal neovascular membrane.

Ocular toxoplasmosis in AIDS

Lesions are multifocal, extensive, aggressive, and may be bilateral, with large areas of confluent retinal necrosis (Fig. 9). Moderate to severe vitritis may be seen, although vitritis may be minimal in some cases. Lesions do not occur adjacent to a retinochoroidal scar, instead the lesions develop in a peri-vascular distribution, which suggests newly acquired infection or dissemination of parasites from non-ocular sites in the body. Infection usually produces a full-thickness retinal necrosis, but early lesions may be confined to either the outer or inner layers.
Diagnosis

The definitive diagnosis of ocular toxoplasmosis can be made by either isolation of the organism from body fluids, or detection of *T. gondii* DNA using polymerase chain reaction (PCR) or detection of antibodies. Various serological tests for diagnosing toxoplasmosis include Sabin-Feldmann dye test, indirect fluorescent antibody test, immunosorbent agglutination assay and enzyme-linked immunosorbent assay (ELISA). ELISA test is the standard test used by most laboratories to detect IgG, IgM, IgA and IgE antibodies, however, false positive results can occur due to presence of rheumatoid factor (RF) and antinuclear antibodies (ANA). In cases of diagnostic dilemmas, ocular fluids (aqueous or vitreous) can be tested for polymerase chain reaction and antibodies. Antibodies titers are measured in aqueous humor and serum and Witmer-Goldman coefficient is calculated. Detection of *T. gondii* antibodies by ELISA and DNA by PCR test in aqueous humor helps in diagnosing ocular toxoplasmosis especially in immunocompromised patients.

Management

Ideal therapy of ocular toxoplasmosis should completely eradicate the parasite. But current treatment aims to stop the multiplication of the parasite and limit the intraocular inflammation. The standard treatment includes a course of antiparasitic drugs along with oral corticosteroids for a minimum of 4-8 weeks. Holland et al studied various treatment regimens for ocular toxoplasmosis given by uveitis specialists all over the world. They concluded that the most popular regimen known as ‘classic therapy’ consists of pyrimethamine, sulphadiazine and prednisolone. Quadruple therapy includes clindamycin along with the triple regimen. Other systemic antibiotics which are used especially when there is intolerance to the above drugs include trimethoprim – sulphamethoxazole, azithromycin, spiramycin, atovaquone and tetracyclines.

Indications for treatment in ocular toxoplasmosis are:

1. Lesions affecting the posterior pole close to macula or optic nerve
2. A lesion within the temporal arcade
3. Lesion threatening a large vessel
4. A lesion that has induced a large haemorrhage
5. A lesion with intense inflammatory reaction or severe vitreous haze.
6. Extensive lesion irrespective of location.
7. Congenital toxoplasma retinochoroiditis within one year of life.
8. A newborn diagnosed with congenital toxoplasmosis
9. Any lesion in an immunocompromised host

Treatment regimens during pregnancy are:

**First trimester** – Spiramycin, sulphadiazine

**Second trimester** (>14 weeks) - Spiramycin, sulphadiazine, pyrimethamine and folinic acid

**Third trimester** - Spiramycin, pyrimethamine and folinic acid

Prophylactic treatment for ocular toxoplasmosis in immunocompetent patients was studied by Silveira et al and they showed a significant reduction in the recurrence from 24% to 7% in patients given trimethoprim-sulphamethoxazole over a period of 20 months. Randomized controlled trials have shown prophylaxis with antibiotics to be effective against disseminated toxoplasmosis in immunocompromised patients. Also Bosch – Driessen et al recommended a prophylactic treatment with antitoxoplasma drugs in all patients with inactive toxoplasmic retinochoroiditis undergoing cataract surgery.
**Conclusion**

Toxoplasmosis is a recurrent and progressively destructive disease with potentially blinding and even fatal consequences. Undercooked meat and contaminated water or food contaminated by oocysts from cat faeces are the sources of infection. It has been shown in recent studies that postnatal acquired infection is more common than congenital infection. However, disease transmission can be prevented by following strict food hygiene, hand washing, and environmental measures. There is no treatment available to eradicate the encysted tissue form. Recurrence occurs in 79% of patients despite the use of antiparasitic drugs and visual prognosis is not affected by use of multiple antiparasitic medications. As there is no consensus among uveitis specialists for treatment of ocular toxoplasmosis, randomized controlled prospective studies are necessary to formulate the management.

**References**